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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-079517-00004-0000

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Art. 444 RESPUESTA A SOLIC. F.Nos: 46

Ref: Expediente No. 03.079.617

Solicitud de patente de invención titulada: "DERIVADOS DE PIRAZOL."

Solicitante: PFIZER INC.

RESPUESTA AL OFICIO No. 7341 NOTIFICADO POR FIJACIÓN EN LISTA

No. 202, DE FECHA 15 DE JUNIO DE 2007.

(REQUERIMIENTO ARTÍCULO 46)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa de los siguientes documentos exigidos por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

1)

SMODIS J ET AL: "The Synthesis and Transformations of Substituted 2-Hydroxy-3-dimethylaminopropenoates. The Preparation of Condensed 3-Hydroxypyran-2-ones" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 33, 13 August 1998 (1998-08-13), pages 9799-9810, XP004127445 ISSN: 0040-4020

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2)

LIPINSKI ET AL: "Bronchodilator and
antiulcer Phenoxypyrimidinones"
JOURNAL OF MEDICINAL CHEMISTRY.,
vol. 23, 1980, pages 1026-1031,
XP002201971
AMERICAN CHEMICAL SOCIETY. WASHINGTON., US
ISSN: 0022-2623

3)

REGITZ; SCHÄFER: "Stabile enole von
alpha-Aryl(alkyl)oxydibenzoylmethanen"
LIEBIGS ANNALEN DER CHEMIE.,
vol. 7, 1981, pages 1172-1185, XP002201972
VERLAG CHEMIE GMBH. WEINHEIM., DE
ISSN: 0170-2041

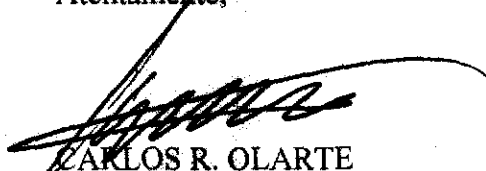
4)

MUNCH; HAUSER: "Acylation of certain
alpha-alkoxy and alpha-aryloxy ketones and
esters"
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY.,
vol. 71, 1949, pages 770-773, XP002201973
AMERICAN CHEMICAL SOCIETY, WASHINGTON,
DC., US
ISSN: 0002-7863

5)

ORAZIO ET AL: "Reaction of some
1,2-diaza-1,3-butadienes with activated
methine compounds"
JOURNAL OF ORGANIC CHEMISTRY.,
vol. 63, 1998, pages 9880-9887,
XP002201974
AMERICAN CHEMICAL SOCIETY. EASTON., US
ISSN: 0022-3263

Atentamente,


CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Artículos mencionados.



Tetrahedron 54 (1998) 9799-9810

TETRAHEDRON

The Synthesis and Transformations of Substituted 2-Hydroxy-3-dimethylaminopropenoates. The Preparation of Condensed 3-Hydroxypyran-2-ones

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Dedicated to Professor Alan R. Katritzky, University of Florida, Gainesville, USA, on the occasion of his 70th birthday

Received 6 March 1998; revised 24 April 1998; accepted 29 May 1998

Abstract: A convenient synthesis of substituted 2-hydroxy-3-dimethylaminopropenoates is reported. They react with cyclic 1,3-diketones, with aromatic and heteroaromatic hydroxy compounds to afford the corresponding 3-substituted hydroxytetrahydro-2H-1-benzopyran-2-ones, benzo- and naphthopyran-2-ones and azolo- and azinopyrin-2-ones, respectively. Catalytic debenzoylation of 3-benzoyloxy substituted fused pyran-2-ones gives free 3-hydroxy derivatives.
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2H-Pyran-2-ones and fused pyran-2-ones are important biologically active compounds.^{1,a,b} Among condensed 2H-pyran-2-ones derivatives, 2H-1-benzopyran-2-one (coumarin) plays an important role. Derivatives of this ring system can be found in numerous plants as metabolites.^c They exhibit various pharmacological activities as hypnotics, insecticides, antimicrobial agents, diuretics,^{1,d,e} and anticoagulants.^{1,f}

Rapid progress in the field of 2H-pyran-2-ones and condensed systems in recent years is due to the introduction of several drug receptor binding models leading to novel inhibitors of various enzymes, such as HIV protease,^{2,g} and α -chymotrypsin. 3,4-Dihydroxy-2H-benzopyran-2-ones and their hexahydro diastereomers show anti-lipidemic and platelet antiaggregatory properties.^{1,g}

However, from the synthetic point of view, the basic idea of construction of the coumarin system from the corresponding aromatic compound and C₂ or C₃ synthon has remained unchanged for many decades.^{1,a,j} Recently, substituted alkyl 2-acylamino-3-dimethylaminopropenoates and alkyl 2-(2,2-disubstituted)ethenylaminopropenoates, masked α -formyl- α -amino acid derivatives, have been used for the preparation of many heterocyclic systems, including 2H-pyran-2-ones and fused pyran-2-ones with a protected amino group attached at position 3 of the pyranone ring.⁴

The synthesis of substituted 3-dimethylamino-2-hydroxypropenoates

It has been reported that 2-methoxy- and 2-ethoxy- 3-dimethylaminopropenoates have been prepared from 2-methoxy- or 2-ethoxy- acetoacetate and t-butoxy-bis(dimethylamino)methane. They have been used for the synthesis of derivatives of oxaloacetic acid in α -substituted tetrone acids.⁵

We now report, the synthesis of substituted 3-amino-2-hydroxypropenoates (2), α -formyl- α -hydroxy acid derivatives, as reagents for construction of fused pyran-2-ones with a hydroxy or substituted hydroxy group attached at position 3 in the newly formed ring. They were prepared from substituted 2-hydroxyacetic acid esters and t-butoxy-bis(dimethylamino)methane in 73-90% yield (Scheme 1). The structure of compounds 2a-d were determined by ¹H NMR spectra, which show a singlet at δ = 6.95-7.25 ppm for H₃, indicating that only one isomer exists in solution. It was shown by X-ray analysis that methyl 2-benzoyloxy-3-dimethylaminopropenoate (2a) exists in the solid state in the (Z)-form.⁴

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PII: S0040-4020(98)00534-1

Scheme 1

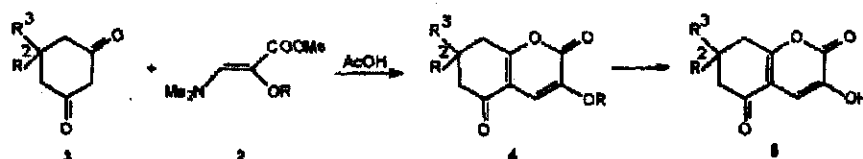


1, 2	R	R ¹
a	COPh	Me
b	CH ₂ Ph	Me
c	Ph	Me
d	COPh	Et

Reactions of 3-aminopropenoates with 1,3-dicarbonyl compounds

Cyclic diones, such as cyclohexane-1,3-dione (3a) and dimedone (3b) react with 2-benzoyloxy- 3-dimethylaminopropenoate (2b) when heated in acetic acid at 130°C for 2 hours to give 3-benzoyloxy-5-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-2-one (4a) and its 3-benzoyloxy derivative (4b) in 26% and 45% yield, respectively (Scheme 2).

Scheme 2



3	R ²	R ³	4	R	R ²	R ³	5	R ²	R ³
a	H	H	a	COPh	H	H	c	H	H
b	Me	H	b	COPh	Me	Me	e	Me	Me
c	Me	Me	c	CH ₂ Ph	H	H			
			d	CH ₂ Ph	Me	H			
			e	CH ₂ Ph	Me	Me			

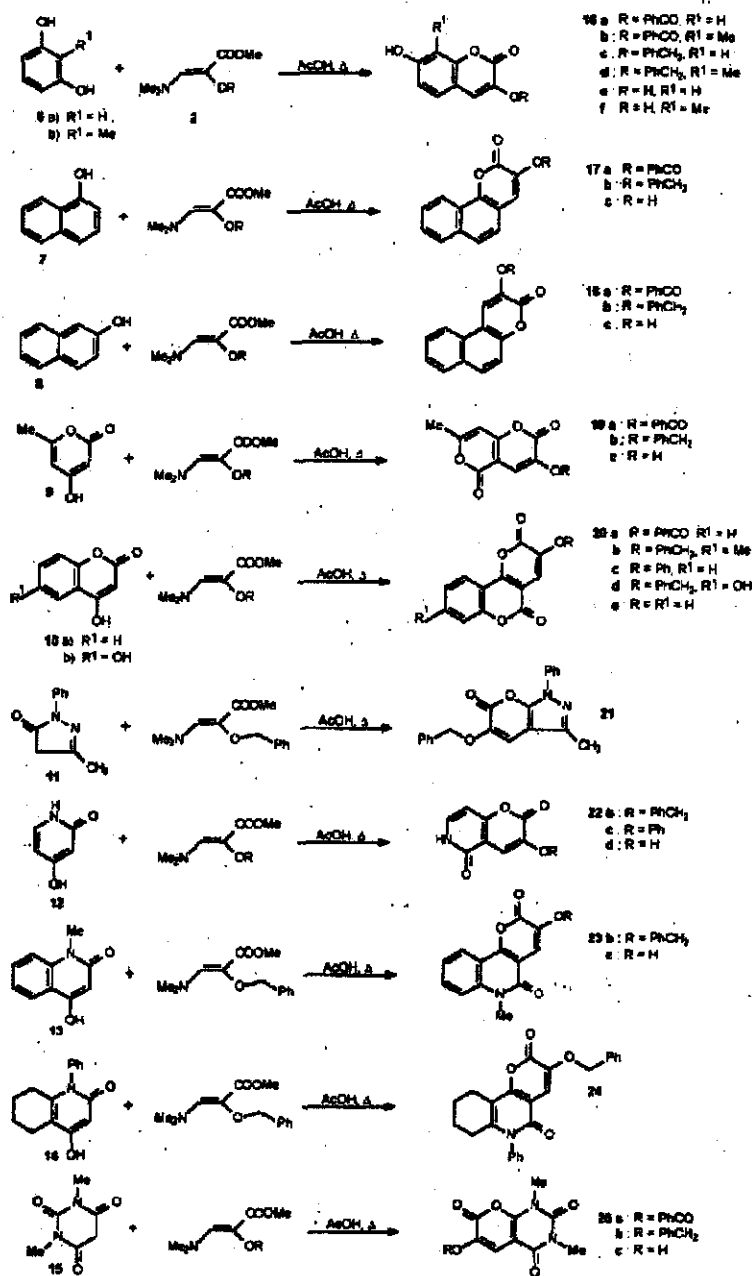
Reactions of 3-aminopropenoates with aromatic and heteroaromatic hydroxy compounds

Condensed 3-hydroxypyranones have been prepared from 3-amino or substituted 3-amino derivatives by hydrolysis,⁷ while 3-phenoxy substituted coumarins have been prepared from acetamides and salicylaldehyde in the presence of phosphorous oxychloride.⁸ 3-Hydroxycoumarins have been found among metabolites.¹¹ They are chemically interesting compounds because of activation of the 4-position towards electrophilic substitution⁹ and sigmatropic rearrangements.¹⁰

Activated aromatic and heteroaromatic hydroxy or potential hydroxy compounds react with compounds 2a-d to form 3-substituted hydroxypyran-2-one systems fused to aromatic or heteroaromatic ring. The reactions were carried out in glacial acetic acid at reflux temperature. The following compounds were selected: 6a,b, 7-9,

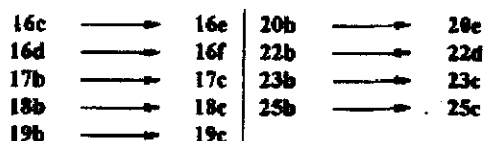
10a,b, 11-15 to give the following compounds 16a-d, 17a,b, 18a,b, 19a,b, 20a-d, 21, 22b,c, 23b, 24, and 25a,b, respectively (Scheme 3).

Scheme 3



Fused pyran-2-ones containing a 3-benzyloxy group, such as 16c,f, 17c, 18c, 19c, 20b, 22b, 23b, 25b, were catalytically debenzylated with hydrogen over Pd/C at 3 atm in a mixture of DMF and dioxane as solvent. The reaction was complete in 2-4 hours to give the products 16e,f, 17c, 18c, 19c, 20b, 22c, 23c, and 25c, respectively, with free hydroxy group at position 3, in 80-98% yield (Scheme 4).

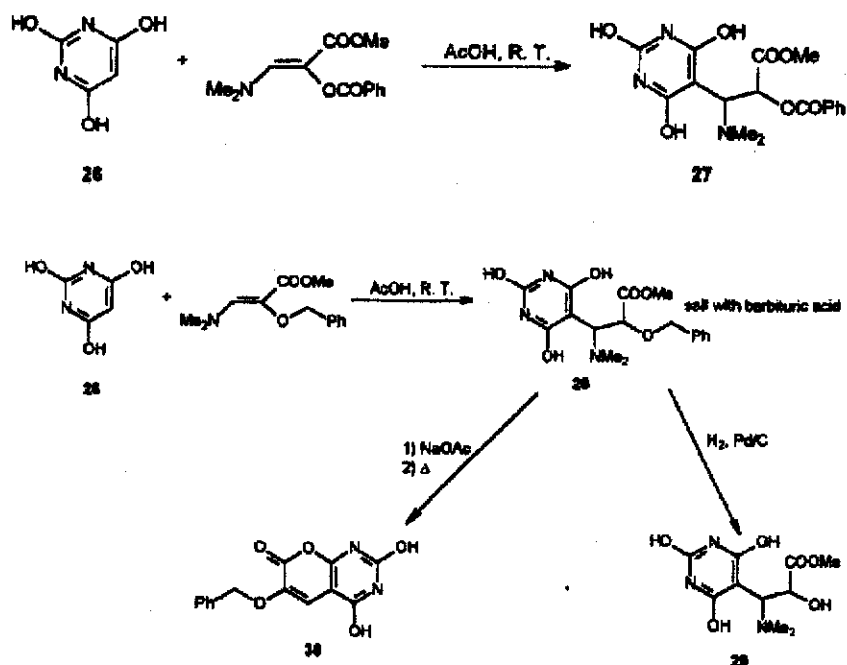
Scheme 4



Reactions of 3-aminopropenoates with barbituric acid and aminouracil

Barbituric acid (26) is insoluble in organic solvents, but it is soluble in acetic acid at boiling point. However, on reaction with 2-benzyloxy-3-dimethylaminopropenoate (2a) a mixture of products was formed. When the reaction was carried out at room temperature only one product was formed in 24 hours.

Scheme 5

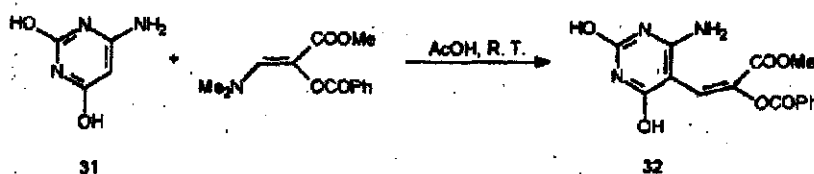


It was concluded on the basis of the ^1H NMR spectrum that nucleophilic addition of a C-nucleophile to the double bond of 2a occurred to give methyl 2-benzoyloxy-3-dimethylamino-3-(2,4,6-trihydroxy-5-pyrimidin-yl)propanoate (27) in 70% yield. Similarly, 26 reacts with methyl 2-benzoyloxy-3-dimethylaminopropenoate (2b) to give methyl 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (28), from which dimethylamine was eliminated, allowing cyclization to 6-benzoyloxy-2,4-dihydroxy-7H-pyrano[2,3-d]pyrimidin-7-one (30). However, 28 is in fact a salt formed between the adduct and barbituric acid, from which the benzyl group can be easily removed to give 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (29). (Scheme 5).

6-Aminouracil (31) is less soluble in acetic acid. At higher temperature a complex mixture of products was formed from reaction with 2a. However, when the reaction mixture was stirred at room temperature for 14 days, the C-substituted product 2-benzoyloxy-3-(6-amino-3H-dihydroxypyrimidin-5-yl)propanoate (32) was formed, indicating that addition to C₅ occurs in preference to addition-elimination of the 6-amino group. This is in agreement with other observations, that C₅ is more nucleophilic than group at the 6-position^{11,12} (Scheme 6).

The structure of 32 was confirmed by the ^1H NMR spectrum which shows a singlet at $\delta = 7.2$ ppm for the olefinic proton (H3), two singlets at $\delta = 10.4$ ppm and $\delta = 10.55$ ppm for the 2- and 4- hydroxy groups at positions 2 and 6, and a broad singlet at $\delta = 6.75$ ppm, integrating for two protons, assigned to the 6-amino group. After addition of deuterated water the last three peaks disappear.

Scheme 6



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H nmr spectra were obtained on a Varian EM 360 L and Bruker Avance 300 DPX spectrometers, mass spectra on an Autospeck Q spectrometer, and microanalyses for C, H, and N on a Perkin-Elmer Analyse 2400.

The following compounds were prepared according to the procedures described in the literature: methyl benzoyloxyacetate (1a),¹³ methyl benzoyloxyacetate (1b),¹⁴ and methyl phenyloxyacetate (1c).¹⁵

General procedure for the synthesis of 2-hydroxy substituted-3-dimethylaminopropenoates. A mixture of 2-hydroxy substituted acetates (1; 10 mmole) and t-butoxy-bis(dimethylamino)methane (12.5 mmole) was stirred at 90°C in an argon atmosphere for 2 hours. t-Butanol and dimethylamine formed during the reaction were distilled off. After cooling, water (50 ml) was added and the suspension was extracted with dichloromethane (3x, 50 ml). The solvent was removed from the dried (Na_2SO_4) organic layer and the residue was purified by crystallization or distillation.

The following compounds were prepared in this manner:

Methyl 2-benzoyloxy-3-dimethylaminopropenoate (2a): from methyl benzoyloxyacetate (1a); yield 73%, mp 104–106°C (methanol). NMR (CDCl_3) δ : 2.95 (6H, s, NMe_2), 3.65 (3H, s, COOMe), 7.15 (1H, s, 3-H), 7.40–7.65 (3H, m, 3H(Ph)), 8.05–8.30 (2H, m, 2H(Ph)). Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.87; H, 6.04; N, 5.75.

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Methyl 2-benzoyloxy-3-dimethylaminopropenoate (2b): from methyl benzoyloxyacetate (1b); yield 90%, bp *ca.* 140°C. NMR (CDCl₃) δ : 3.0 (6H, s, NMe₂), 3.75 (3H, s, COOMe), 4.75 (2H, s, CH₂), 6.95 (1H, s, 3-H), 7.30-7.65 (5H, m, Ph). Anal. Calcd. for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.91; N, 5.94.

Methyl 3-dimethylamino-2-phenyloxyacetate (2c): from methyl phenyloxyacetate (1c); yield 84%, mp 82-84°C (cyclohexane/petroleter 2:1). NMR (CDCl₃) δ : 2.95 (6H, s, NMe₂), 3.6 (3H, s, COOMe), 6.90-7.40 (6H, m, Ph, =CH-). Anal. Calcd. for C₁₂H₁₅NO₃: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.94; H, 6.87; N, 6.41.

Ethyl 2-benzoyloxy-3-dimethylaminopropenoate (2d): from ethyl benzoyloxyacetate (1d); yield 74%, mp 100-104°C (diisopropylether/n-hexane 2:1). NMR (CDCl₃) δ : 1.2 (3H, t, MeCH₂, J_{MeCH₂} = 7.0 Hz), 3.0 (6H, s, NMe₂), 4.2 (2H, q, MeCH₂), 7.25 (1H, s, =CH-), 7.5-7.7 (3H, m, 3H(Ph)), 8.15-8.35 (2H, m, 2H(Ph)). Anal. Calcd. for C₁₄H₁₇NO₃: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.75; H, 6.50; N, 5.27.

Reactions of cyclohexane-1,3-diones with 2. General procedure: A mixture of cyclohexane-1,3-dione derivative (3, 1 mmole) and 2 (1 mmole) in glacial acetic acid (5 ml) was heated in an oil bath at 130°C in an argon atmosphere for two hours. The residue obtained after evaporation of volatile components under reduced pressure was recrystallized from appropriate solvent.

The following compounds were prepared in this manner:

3-Benzoyloxy-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (4a): from methyl 2-benzoyloxy-3-dimethylaminopropenoate (2a) and cyclohexane-1,3-dione (3a); yield 26%, mp 125-127°C (ethanol/water 1:1). NMR (CDCl₃) δ : 2.25 (2H, t, 7-CH₂, J_{6,7}=J_{7,8}=6.0 Hz), 2.7 and 2.95 (2x2H, 2xt, 6-CH₂ and 8-CH₂), 7.50-7.80 (3H, m, 3H(Ph)), 7.80 (1H, s, 4-H), 8.10-8.35 (2H, m, 2H(Ph)). Anal. Calcd. for C₁₆H₁₂O₅: C, 67.60; H, 4.25. Found: C, 67.45; H, 4.17.

3-Benzoyloxy-7,7-dimethyl-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (4b): from ethyl 2-benzoyloxy-3-dimethylaminopropenoate (2d) and 5,5-dimethylcyclohexane-1,3-dione (3c); yield 34%, mp 135-136°C (diisopropyl ether). NMR (CDCl₃) δ : 1.20 (6H, s, 2x7-Me), 2.45 (2H, s, 6-CH₂), 2.75 (2H, s, 8-CH₂), 7.40-7.70 (3H, m, 3H(Ph)), 7.75 (1H, s, 4-H), 8.10-8.30 (2H, m, 2H(Ph)). Anal. Calcd. for C₁₈H₁₆O₅: C, 69.22; H, 5.16. Found: C, 69.28; H, 4.97.

3-Benzoyloxy-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (4c): from methyl 2-benzoyloxy-3-dimethylaminopropenoate (2b) and cyclohexane-1,3-dione (3a); yield 45%, mp 135-137°C (ethanol). NMR (CDCl₃) δ : 2.15 (2H, t, 7-CH₂, J_{6,7}=J_{7,8}=6.0 Hz), 2.65 and 2.85 (2x2H, 2xt, 6-CH₂ and 8-CH₂), 5.20 (2H, s, PhCH₂), 7.10 (1H, s, 4-H), 7.45 (5H, brs, Ph). Anal. Calcd. for C₁₆H₁₄O₄: C, 71.10; H, 5.22. Found: C, 70.90; H, 5.19.

3-Benzoyloxy-7-methyl-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (4d): from methyl 2-benzoyloxy-3-dimethylaminopropenoate (2b) and 5-methylcyclohexane-1,3-dione (3d); yield 51%, mp 128-131°C (ethanol). NMR (DMSO-d₆) δ : 1.00-1.20 (3H, d, 7-Me, J_{MeCH} = 4.0 Hz), 2.30-2.85 (5H, m, 7-H, 6-CH₂, 8-CH₂), 5.15 (2H, s, PhCH₂), 7.15 (1H, s, 4-H), 7.50 (5H, brs, Ph). Anal. Calcd. for C₁₇H₁₆O₄: C, 71.82; H, 5.67. Found: C, 71.95; H, 5.70.

3-Benzoyloxy-7,7-dimethyl-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-one (4e): from methyl 2-benzoyloxy-3-dimethylaminopropenoate (2b) and 5,5-dimethylcyclohexane-1,3-dione (3c); yield 52%, mp 149-152°C (ethanol). NMR (CDCl₃) δ : 1.10 (6H, s, 2x7-Me), 2.40 (2H, s, 6-CH₂), 2.65 (2H, s, 8-CH₂), 5.1 (2H, s, PhCH₂), 7.05 (1H, s, 4-H), 7.45 (5H, brs, Ph). Anal. Calcd. for C₁₈H₁₈O₄: C, 72.47; H, 6.08. Found: C, 72.29; H, 5.93.

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Reactions of 2 with aromatic and heterocyclic hydroxy compounds. General procedure: To a solution of aromatic or heteroaromatic hydroxy compound (2 mmole) in glacial acetic acid (10 ml), propenoate 2 (2 mmole) was added. The mixture was heated on an oil bath at 130°C for two hours in an argon atmosphere. The volatile components were evaporated *in vacuo* and the residue recrystallized from an appropriate solvent.

In this manner, the following compounds were prepared:

3-Benzoyloxy-7-hydroxy-2H-1-benzopyran-2-one (16a): from 2a and 1,3-dihydroxybenzene (6a); yield 20%, mp 220-221°C (ethanol/water 5:1). NMR (DMSO- d_6) δ : 6.85 (1H, d, 8-H, $J_{6,8}$ = 2.0 Hz), 6.95 (1H, dd, 6-H, $J_{5,6}$ = 6.5 Hz), 7.6 (1H, d, 5-H), 7.6-7.9 (3H, m, 3H(*Ph*)), 8.1 (1H, s, 4-H), 8.05-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{10}O_5$: C, 68.09; H, 3.57. Found: C, 68.38; H, 3.36.

3-Benzoyloxy-7-hydroxy-8-methyl-2H-1-benzopyran-2-one (16b): from 2a and 1,3-dihydroxy-2-methylbenzene (6b); yield 42%, mp 260-262°C (DMF/ethanol 1:2). NMR (DMSO- d_6) δ : 2.25 (3H, s, 8-Me), 3.20-4.50 (1H, brs, OH), 7.00 (1H, d, 6-H, $J_{5,6}$ = 8.5 Hz), 7.5 (1H, d, 5-H), 7.65-7.95 (3H, m, 3H(*Ph*)), 8.1 (1H, s, 4-H), 8.10-8.35 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 68.84; H, 4.25.

3-Benzoyloxy-7-hydroxy-2H-1-benzopyran-2-one (16c): from 2b and 1,3-dihydroxybenzene (6a); yield 13%, mp 242-245°C (ethanol). NMR (DMSO- d_6) δ : 5.15 (2H, s, $PhCH_2$), 6.75 (1H, s, 8-H), 6.85 (1H, dd, 6-H, $J_{5,6}$ = 8 Hz, $J_{6,8}$ = 1.5 Hz), 7.30-7.70 (7H, brs, *Ph*, 4-H, 5-H). *Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.11; H, 4.40.

3-Benzoyloxy-7-hydroxy-8-methyl-2H-1-benzopyran-2-one (16d): from 2b and 1,3-dihydroxy-2-methylbenzene (6b); yield 44%, mp 232-238°C (ethanol). NMR (DMSO- d_6) δ : 2.20 (3H, s, 8-Me), 5.15 (2H, s, $PhCH_2$), 6.90 (1H, d, 6-H, $J_{5,6}$ = 8.5 Hz), 7.30 (1H, d, 5-H), 7.50 (1H, s, 4-H), 7.50 (5H, brs, *Ph*), 9.00-10.00 (1H, brs, OH). *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.54; H, 4.96.

3-Benzoyloxy-2H-naphtho[1,2-b]pyran-2-one (17a): from 2a and 1-hydroxynaphthalene (7); yield 12%, mp 203-205°C (ethanol). NMR ($CDCl_3$) δ : 7.35-8.05 (9H, m, 3H(*Ph*), 4,5,6,7,8,9-H), 8.15-8.40 (2H, m, 2H(*Ph*)), 8.45-8.75 (1H, m, 10-H). *Anal.* Calcd. for $C_{20}H_{12}O_4$: C, 75.95; H, 3.82. Found: C, 75.90; H, 4.01.

3-Benzoyloxy-2H-naphtho[1,2-b]pyran-2-one (17b): from 2b and 1-hydroxynaphthalene (7); yield 23%, mp 164-166°C (ethanol). NMR ($CDCl_3$) δ : 5.25 (2H, s, $PhCH_2$), 7.05 (1H, s, 4-H), 7.40 (1H, d, 5-H, $J_{5,6}$ = 9 Hz), 7.7 (1H, d, 6-H), 7.25-8.00 (8H, m, 5H(*Ph*), 7,8,9-H), 8.35-8.65 (1H, m, 10-H). *Anal.* Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.26; H, 4.63.

2-Benzoyloxy-3H-naphtho[2,1-b]pyran-2-one (18a): from 2a and 2-hydroxynaphthalene (8); yield 47%, mp 175-178°C (n-propanol). NMR ($CDCl_3$) δ : 7.40-7.95 (7H, 3H(*Ph*), 7,8,9,10-H), 7.50 (1H, d, 5-H, $J_{5,6}$ = 9.0 Hz), 8.05 (1H, d, 6-H), 8.20-8.40 (2H, m, 2H(*Ph*)), 8.50 (1H, s, 1-H). *Anal.* Calcd. for $C_{20}H_{12}O_4$: C, 75.94; H, 3.82. Found: C, 75.79; H, 3.88.

2-Benzoyloxy-3H-naphtho[2,1-b]pyran-2-one (18b): from 2b and 2-hydroxynaphthalene (8); yield 41%, mp 190-192°C (ethanol). NMR ($CDCl_3$) δ : 5.3 (2H, s, $PhCH_2$), 7.30-8.20 (9H, m, 5H(*Ph*), 7,8,9,10-H), 7.40 (1H, d, 5-H, $J_{5,6}$ = 9.0 Hz), 7.65 (1H, s, 1-H), 7.85 (1H, d, 6-H). *Anal.* Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.66.

3-Benzoyloxy-7-methyl-2H,5H-pyrano[4,3-b]pyran-2,5-dione (19a): from 2a and 4-hydroxy-6-methyl-2H-pyran-2-one (9); yield 28%, mp 200-202°C (n-propanol). NMR (DMSO- d_6) δ : 2.35 (3H, s, 7-Me), 6.75 (1H, s, 8-H), 7.40-7.90 (3H, m, 3H(*Ph*)), 8.05 (1H, s, 4-H), 8.00-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.63; H, 3.07.

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3-Benzoyloxy-7-methyl-2H,5H-pyrano[4,3-b]pyran-2,5-dione (19b): from 2b and 4-hydroxy-6-methyl-2H-pyran-2-one (9); yield 91%, mp 223-225°C (ethanol). NMR (DMSO- d_6) δ : 2.30 (3H, s, 7-Me), 5.2 (2H, s, PhCH₂), 6.65 (1H, s, 8-H), 7.15 (1H, s, 4-H), 7.50 (5H, brs, 5H(Ph)). Anal. Calcd. for C₁₆H₁₂O₆: C, 67.60; H, 4.25. Found: C, 67.56; H, 4.15.

3-Benzoyloxy-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (20a): from 2a and 4-hydroxycoumarin (10a); yield 16%, mp 234-236°C (DMF/ethanol 1:2). NMR (DMSO- d_6) δ : 7.50-8.00 (6H, m, 3H(Ph), 7,8,9-H), 8.00-8.30 (4H, m, 2H(Ph), 4,10-H). Anal. Calcd. for C₁₉H₁₄O₆: C, 68.27; H, 3.02. Found: C, 68.05; H, 2.87.

3-Benzoyloxy-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (20b): from 2b and 4-hydroxycoumarin (10a); yield 22%, mp 239-243°C (DMF/ethanol 1:3). NMR (DMSO- d_6) δ : 5.25 (2H, s, PhCH₂), 7.30 (1H, s, 4-H), 7.40-7.80 (8H, m, 5H(Ph), 7,8,9-H), 7.85-8.20 (1H, m, 10-H). Anal. Calcd. for C₁₉H₁₂O₆: C, 71.25; H, 3.87. Found: C, 71.05; H, 3.66.

3-Phenylloxy-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (20c): from 2c and 4-hydroxycoumarin (10a); yield 32%, mp 230-231°C (DMF/ethanol 1:1). NMR (DMSO- d_6) δ : 7.10-8.20 (10H, m, 5H(Ph), 4,7,8,9,10-H). Anal. Calcd. for C₁₈H₁₀O₅: C, 70.59; H, 3.29. Found: C, 70.80; H, 3.05.

3-Benzoyloxy-9-hydroxy-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (20d): from 2b and 4,6-dihydroxycoumarin (10b); yield 29%, mp 297-300°C (DMF/ethanol 2:5). NMR (DMSO- d_6) δ : 5.25 (2H, s, PhCH₂), 6.90 (1H, d, 10-H, $J_{10,9}$ =2.0 Hz), 6.95 (1H, dd, 8-H, $J_{7,8}$ =2.0 Hz), 7.55 (5H, s, Ph), 7.80 (1H, d, 7-H), 10.40-11.40 (1H, brs, 9-OH). Anal. Calcd. for C₁₉H₁₂O₆: C, 67.86; H, 3.60. Found: C, 67.70; H, 3.24.

5-Benzoyloxy-3-methyl-1-phenyl-1H,6H-pyrazolo[3,4-b]pyran-6-one (21): from 3-methyl-1-phenylpyrazol-5(4H)-one (11) and 2b; yield 15%, mp 226-230°C (ethanol). NMR (DMSO- d_6) δ : 2.20 (3H, s, 3-Me), 4.20 (2H, s, PhCH₂), 7.20-7.95 (11H, m, 2xPh, 4-H). Anal. Calcd. for C₂₀H₁₆N₂O₃: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.41; H, 4.86; N, 8.47.

3-Benzoyloxy-5,6-dihydro-2H-pyrano[2,3-c]pyridine-2,5-dione (22b): from 2b and 4-hydroxypyridin-2(1H)-one (12); yield 72%, mp 285-287°C (ethanol). NMR (DMSO- d_6) δ : 5.2 (2H, s, PhCH₂), 6.4 (1H, s, 8-H, $J_{7,8}$ =7.5 Hz), 7.3 (1H, s, 4-H), 7.50 (5H, brs, Ph), 7.50 (1H, d, 7-H), 11.60-12.30 (1H, brs, NH). Anal. Calcd. for C₁₇H₁₁NO₄: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.51; H, 3.99; N, 5.29.

3-Phenylloxy-5,6-dihydro-2H-pyrano[2,3-c]pyridine-2,5-dione (22c): from 2c and 4-hydroxypyridin-2(1H)-one (12); yield 62%, mp 228-230°C (ethanol). NMR (DMSO- d_6) δ : 6.45 (1H, s, 8-H, $J_{7,8}$ =7.0 Hz), 7.10-7.70 (6H, m, 5H(Ph), 4-H), 7.65 (1H, d, 7-H), 11.40-12.70 (1H, brs, NH). Anal. Calcd. for C₁₆H₉NO₄: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.70; H, 3.37; N, 5.40.

3-Benzoyloxy-6-methyl-5,6-dihydro-2H-pyrano[3,2-c]quinoline-2,5-dione (23b): from 2b and 4-hydroxy-1-methylquinolin-2(1H)-one (13); yield 63%, mp 186-189°C (ethanol). NMR (DMSO- d_6) δ : 3.65 (3H, s, 6-Me), 5.20 (2H, s, PhCH₂), 7.30 (1H, s, 4-H), 7.20-7.80 (8H, m, 5H(Ph), 7,8,9-H), 7.95 (1H, dd, 10-H, $J_{8,10}$ =1.5 Hz, $J_{9,10}$ =8.0 Hz). Anal. Calcd. for C₂₀H₁₅NO₄: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.29; H, 4.44; N, 4.20.

3-Benzoyloxy-6-phenyl-5,6,7,8,9,10-hexahydro-2H-pyrano[3,2-c]quinoline-2,5-dione (24): from 2b and 4-hydroxy-1-phenyl-6,7,8,9-tetrahydroquinolin-2(1H)-one (14); yield 38%, mp 273-275°C (DMF/n-propanol 2:5). NMR (DMSO- d_6) δ : 1.50-1.85 (4H, m, 8,9-CH₂), 2.00-2.25 (2H, m, 7-CH₂), 2.55-2.80 (2H, m, 10-CH₂), 5.20 (2H, s, PhCH₂), 7.20-7.65 (11H, m, 2xPh, 4-H). Anal. Calcd. for C₂₂H₂₁NO₄: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.02; H, 5.22; N, 3.43.

6-Benzoyloxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7H-pyrano[2,3-d]pyrimidin-7-one (25a): from 2a and 1,3-dimethylbarbituric acid (15); yield 17%, mp 194°C (n-propanol). NMR (CDCl₃) δ : 3.45 and 3.60 (2x3H,

2xs, 1-Me, 3-Me), 7.50-7.85 (3H, m, 3H(Ph)), 7.90 (1H, s, 5-H), 8.10-8.35 (2H, m, 2H(Ph)). Anal. Calcd. for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.13; H, 3.40; N, 8.40.

6-Benzoyloxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7H-pyrano[2,3-d]pyrimidin-7-one (25b): from 2b and 1,3-dimethylbarbituric acid (15); yield 39%, mp 185-186°C (n-propanol). NMR ($CDCl_3$) δ : 3.40 and 3.55 (2x3H, 2xs, 1-Me, 3-Me), 5.10 (2H, s, $PhCH_2$), 7.25 (1H, s, 5-H), 7.45 (5H, brs, Ph). Anal. Calcd. for $C_{16}H_{12}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.82; H, 4.50; N, 8.83.

General procedure for debenzoylation. To a solution of benzyloxy derivative (2 mmole) in a mixture of DMF and dioxane (1:1, 30 ml), Pd/C (10%, 100 mg) was added and the mixture was hydrogenated in a Parr autoclave at 3 atm. The reaction was finished in 4 hours. The catalyst was removed by filtration, the solvent was evaporated *in vacuo*, and the solid residue recrystallized from an appropriate solvent. In this manner, the following compounds were prepared:

3-Hydroxy-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (5c): from 4c; yield 86%, mp 155-162°C (toluene/cyclohexane 4:1). NMR ($DMSO-d_6$) δ : 2.10 (2H, tt, 7- CH_2 , $J_{6,7}=J_{7,8}=6.0$ Hz), 2.5 (2H, t, 6- CH_2), 2.8 (2H, t, 8- CH_2), 6.9 (1H, s, 4-H), 10.1 (1H, brs, OH). Anal. Calcd. for $C_9H_6O_4$: C, 60.00; H, 4.48. Found: C, 59.89; H, 4.37.

3-Hydroxy-7,7-dimethyl-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (5e): from 4e; yield 92%, mp 138-140°C. NMR ($DMSO-d_6$) δ : 1.50 (6H, s, 2x7-Me), 2.45 (2H, s, 6- CH_2), 2.7 (2H, s, 8- CH_2), 7.2 (1H, s, 4-H). Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.24; H, 5.85.

3,7-Dihydroxy-2H-1-benzopyran-2-one (16c): from 16c; yield 80%, mp 285-290°C (toluene/cyclohexane 1:2). NMR ($DMSO-d_6$) δ : 6.75 (1H, d, 8-H, $J_{6,7}=1.5$ Hz), 6.80 (1H, dd, 6-H, $J_{5,6}=9.5$ Hz), 7.15 (1H, s, 4-H), 7.40 (1H, d, 5-H), 10.00 (2H, brs, 3,7-OH). Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.39; H, 3.43.

3,7-Dihydroxy-8-methyl-2H-1-benzopyran-2-one (16f): from 16d; yield 88%, mp 250-254°C (toluene). NMR ($DMSO-d_6$) δ : 2.20 (3H, s, 8-Me), 6.85 (1H, d, 6-H, $J_{5,6}=8.5$ Hz), 7.10 (1H, s, 4-H), 7.25 (1H, d, 5-H), 9.70-10.20 (2H, brs, 3,7-OH). Anal. Calcd. for $C_{10}H_6O_4$: C, 62.50; H, 4.20. Found: C, 62.67; H, 4.17.

3-Hydroxy-2H-naphtho[1,2-b]pyran-2-one (17c): from 17b; yield 95%, mp 248-250°C (dioxane/n-propanol 1:5). NMR ($DMSO-d_6$) δ : 7.35 (1H, s, 4-H), 7.50-8.20 (5H, m, 5,6,7,8,9-H), 8.20-8.50 (1H, m, 10-H), 10.60 (1H, brs, 3-OH). Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.17; H, 3.70.

2-Hydroxy-3H-naphtho[2,1-b]pyran-2-one (18c): from 18b; yield 59%, mp 241-243°C (ethanol). NMR ($DMSO-d_6$) δ : 5.80-7.30 (1H, brs, 2-OH), 8.55 (1H, d, 5-H, $J_{5,6}=9.0$ Hz), 8.55-8.80 (2H, m, 8,9-H), 8.90-9.20 (1H, m, 7-H), 9.00 (1H, s, 1-H), 9.30-9.55 (1H, m, 10-H). Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.61; H, 3.58.

3-Hydroxy-7-methyl-2H,5H-pyrano[4,3-b]pyran-2,5-dione (19c): from 19b; yield 80%, mp 277-279°C (ethanol). NMR ($DMSO-d_6$) δ : 2.20 (3H, s, 7-Me), 6.60 (1H, s, 8-H), 6.90 (1H, s, 4-H). Anal. Calcd. for $C_9H_6O_5$: C, 55.68; H, 3.12. Found: C, 55.79; H, 2.85.

3-Hydroxy-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (20e): from 20b; yield 88%, mp 319-320°C (n-propanol). NMR ($DMSO-d_6$) δ : 7.00 (1H, s, 4-H), 7.30-7.80 (3H, m, 7,8,9-H), 7.80-8.05 (1H, m, 10-H). Anal. Calcd. for $C_{12}H_6O_5$: C, 62.62; H, 2.63. Found: C, 62.64; H, 2.44.

3-Hydroxy-5,6-dihydro-2H-pyrano[2,3-c]pyridine-2,5-dione (22d): from 22b; yield 73%, mp >350°C (DMF). NMR ($DMSO-d_6$) δ : 6.35 (1H, d, 8-H, $J_{7,8}=5.5$ Hz), 7.05 (1H, s, 4-H), 7.40 (1H, d, 7-H), 9.80-11.80 (2H, brs, NH, OH). Anal. Calcd. for $C_8H_7NO_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.39; H, 2.91; N, 7.92.

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3-Hydroxy-6-methyl-5,6-dihydro-2H-pyran[3,2-c]quinoline-2,5-dione (23c): from 23b; yield 84%, mp 310–313°C (DMF). NMR (DMSO- d_6) δ : 3.65 (3H, s, 6-Me), 7.5 (1H, s, 4-H), 7.20–7.80 (3H, m, 7,8,9-H), 7.95 (1H, dd, 10-H, $J_{9,10}$ = 8.0 Hz, $J_{8,10}$ = 1.5 Hz), 10.40–11.30 (1H, brs, 3-OH). Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 63.97; H, 3.59; N, 5.73.

1,3-Dimethyl-7-hydroxy-1,2,3,4-tetrahydro-7H-pyrano[2,3-d]pyrimidin-2,4,7-trione (25c): from 25b; yield 98%, mp 195–197°C (toluene). NMR (DMSO- d_6) δ : 3.25 and 3.35 (2x3H, 2xs, 1,3-Me), 7.05 (1H, s, 5-H), 10.15 (1H, s, OH). MS: m/z = 224 (M^+ , 100%). Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 58.22; H, 3.60; N, 12.50. Found: C, 48.22; H, 3.93; N, 12.73.

Methyl 2-benzoyloxy-3-dimethylamino-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (27): A mixture of 2a (1 mmol) and barbituric acid (24, 1 mmole) in acetic acid (5 ml) was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* at 40°C. The residue was suspended in ethanol (10 ml) and the solid was collected by filtration to give 27 in 70% yield, mp 270°C (decomp). NMR (DMSO- d_6) δ : 2.55 (6H, s, NMe_2), 3.20–3.60 (2H, m, 2,3-H), 3.60 (3H, s, COOMe), 7.40–7.60 (3H, m, 3H(Ph)), 7.85–8.20 (2H, m, 2H(Ph)), 8.30–9.2 (1H, brs, OH), 9.8–10.3 (1H, brs, OH). Anal. Calcd. for $C_{17}H_{19}N_5O_7$: C, 54.11; H, 5.08; N, 11.14. Found: C, 54.01; H, 4.96; N, 11.43.

Methyl 2-benzoyloxy-3-dimethylamino-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate salt with barbituric acid (28): A mixture of 2b (1 mmole) and barbituric acid (1 mmole) in acetic acid (5 ml) was stirred at room temperature for 6 hours. The solvent was removed *in vacuo* at 40°C. The residue was suspended in ethanol (5 ml) and the solid collected by filtration to give 28 in 45% yield, mp 197–200°C (water). NMR (DMSO- d_6) δ : 2.55 (6H, s, NMe_2), 3.55 (3H, s, COOMe), 3.20–3.60 (1H, brs, 3-H), 4.35 (1H, brs, 2-H), 4.80 (2H, s, $PhCH_2$), 7.15 (1H, s, 5-H of barbituric acid), 7.25 (5H, s, Ph), 7.35 (1H, brs, OH), 7.8–8.5 (2H, brs, 2xOH), 9.45 (1H, brs, OH), 9.95 (1H, brs, OH), 10.05 (1H, brs, OH). Anal. Calcd. for $C_{21}H_{23}N_5O_9$: C, 51.32; H, 5.13; N, 14.23. Found: C, 51.08; H, 5.12; N, 13.98.

Methyl 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (29): To a solution of 28 (700 mg) in a mixture of dioxane (7 ml) and water (15 ml), Pd/C (10%, 120 mg) was added and the mixture was hydrogenated (3 atm) in a Parr autoclave for three days. The catalyst was removed by filtration, the solvent evaporated to dryness. Ethanol (10 ml) was added to the residue and filtered to give 29 in 71% yield, mp 260°C (decomp). NMR (DMSO- d_6) δ : 2.60 (6H, s, NMe_2), 3.30–4.10 (m, COOMe, 2,3-H, H_2O), 8.0–10.0 (3H, brs, 3xOH), 12.20 (1H, brs, OH). Anal. Calcd. for $C_{10}H_{15}N_5O_6$: C, 43.96; H, 5.53; N, 15.38. Found: C, 43.80; H, 5.26; N, 15.09.

6-Benzoyloxy-2,4-dihydroxy-7H-pyrano[2,3-d]pyrimidin-7-one (30): To a solution of 28 (1 mmole) in acetic acid (5 ml), sodium acetate (1 mmol) was added and the mixture stirred in an argon atmosphere at room temperature for 24 hours, then the mixture was heated at reflux temperature for 2 hours. The precipitate was, after cooling, collected by filtration to give 30 in 63% yield, mp 325°C (decomp). NMR (DMSO- d_6) δ : 3.70–4.80 (1H, brs, OH), 5.12 (2H, s, $PhCH_2$), 7.25 (1H, s, 5-H), 7.55 (5H, s, Ph), 11.25 (1H, brs, OH). MS: m/z 286 (M^+ , 14%), MS: calcd. for $C_{14}H_{10}N_2O_7$: m/z = 286.0590. Found: m/z = 286.0600. Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 58.75; H, 3.52; N, 9.79. Found: C, 58.90; H, 2.87; N, 9.67.

Methyl 2-benzoyloxy-3-(6-amine-2,4-dihydroxypyrimidin-5-yl)propanoate (32): A suspension of 6-aminouracil (31, 1 mmole) and 2a (1 mmole) in acetic acid (10 ml) was stirred at room temperature for 14 days. The solid was collected by filtration to give 32 in 69% yield, mp >300°C (acetic acid). NMR (DMSO- d_6) δ : 3.75 (3H, s, COOMe), 6.75 (2H, brs, 4- NH_2), 7.20 (1H, s, 3-H), 7.50–7.80 (3H, m, 3H(Ph)), 8.00–8.25 (2H, m, 2H(Ph)), 10.40 and 10.55 (2x1H, 2xbrs, 2', 6'-OH). Anal. Calcd. for $C_{15}H_{13}N_5O_6$: C, 54.38; H, 3.96; N, 12.68. Found: C, 54.26; H, 3.99; N, 12.36.

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- The X-ray analysis of compound 2a will be reported elsewhere.

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rotenone oxime (5), acetylrotenone oxime (6), carbethoxyrotenone oxime (7), dehydrorotenone (9), acetylrotenolone (10), and darric acid (11) were prepared using the procedures documented under "Chemistry Section". Verification and purity of these compounds were established by combustion analysis and spectral data, using the instrumentation described above.

6a,12a-Dihydro-8,9-dimethoxy-2-(1-methylethyl)[1]benzopyrano[3,4-b]furo[2,3-h][1]benzopyran-6(12H)-one (Isorotenone; 3). A slurry of 1 (25.0 g, 63.4 mmol) in 300 mL of concentrated HCl was heated at reflux for 20 min. Gas evolution (HCl) was copious. The mixture was cooled and the precipitate was collected. TLC (silica gel; 9:1 CHCl₃-CH₃OH) indicated mostly 1, with a minor amount of 3 which displayed an *R_f* slightly higher than 1. The solid was suspended in 400 mL of concentrated HCl and 100 mL of water and heated at reflux. After 60 h, TLC indicated mainly 3, with some 1 present. After an additional week at reflux, TLC indicated the absence of 1. The mixture was cooled and the solid was collected and recrystallized from methanol (600 mL) to yield 8.50 g (34%) of 3 as white prisms: mp 174-176 °C, lit.²⁹ mp 177-178 °C; IR (Nujol) 1780 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.27 [d, *J* = 7 Hz, 6 H, CH(CH₃)₂]. Anal. (C₂₃H₂₂O₆) C, H, N.

Isolation of Dequalin (12) and Tephrosin (13). The powdered root of *Lonchocarpus nicou*³⁰ (384 g) was exhaustively extracted with 500 mL of ether using a Soxhlet apparatus. On cooling, the solution deposited crystals of rotenone which were collected (20 g). The filtrate was concentrated and the dark residue was reconstituted in 200 mL of CCl₄, whereupon another crop of rotenone (12 g) was deposited. The CCl₄ filtrate was concentrated to leave 68 g of syrup, which was dissolved in 200 mL of ethanol. Sodium acetate (8 g) was added and reflux was maintained for 2 h. The ethanol was removed by evaporation, and the residue was suspended in CH₂Cl₂ and filtered. The filtrate was concentrated and the residue was dissolved in 100 mL of acetone. The resulting yellow crystals which formed were collected (6.7 g) and successively crystallized from ether, ethyl acetate, and acetonitrile. The resulting white crystals were shown by high-performance LC to be a mixture of 12 and 13. A Varian Model 8500 high-performance LC system was used for this and subsequent composition determinations. A two-column system was employed; a 4 × 1/8 in. o.d. precolumn packed with C₁₈ Porasil (Waters Associates; 37-50 μm) was followed by a 30 cm × 4 mm i.d. column of μBondapak C₁₈ (Waters Associates). Elution was

accomplished with 3:2 CH₃CN-H₂O.

A portion of the mixture of 12 and 13 (1.4 g) was chromatographed on a silicic acid column. Elution with 9:1 CH₂Cl₂-CHCl₃ yielded 12 (457 mg), mp 169-173 °C, lit.²⁷ mp 171 °C. Subsequent elution with 4:1 CH₂Cl₂-CHCl₃ initially afforded mixtures of 12 and 13 and then pure 13 (446 mg), mp 197-198 °C, lit.²⁷ mp 197-198 °C.

Pharmacological Methods. Measurement of SRS-A Antagonism. The SRS-A used in the present study was obtained by collection of peritoneal shock fluid from rats subjected to passive peritoneal anaphylaxis as described previously.⁴¹ The material was assayed on a strip of guinea pig ileum suspended in a tissue bath containing Tyrode's solution, maintained at 37 °C, and continuously aerated with 95% O₂-5% CO₂. Responses were checked in the presence of atropine (5 × 10⁻⁷ M) and mepyramine maleate (10⁻⁶ M),⁴² as well as the selective SRS-A antagonist FPL 55712, to assure pharmacological activity and selectivity.

A dose-response study allowed us to select a dose of SRS-A which produced a contraction which was ca. 60% of the maximum. This dose was employed in the evaluation of all antagonists. All antagonists were added to the tissue bath 2 min prior to challenge with SRS-A. Activity was recorded by calculating the percent inhibition induced by the antagonist.

In vivo measurement of inhibition of allergic reactions was done using the method of Greig and Griffin.⁴³ Guinea pigs were immunized to ovalbumin with a 1-mL subcutaneous and a 1-mL intraperitoneal administration of a 10% solution of ovalbumin. After sensitization developed (ca. 4 weeks), the animals were challenged with aerosolized antigen (ovalbumin). Time of collapse was the end point. Failure to collapse within a 6-min exposure to the antigen was considered maximal protection. The collapse times for animals receiving the antagonists were compared with collapse times of control animals. Bartlett's test was employed to delineate the homogeneity of variances among the treatment groups. Since the variances were homogeneous, a one-way analysis of variance and a Dunnett's test were utilized to determine any significant differences between experimental and control groups.

Acknowledgment. The authors are grateful to Fisons Pharmaceutical Ltd., Loughborough, Leics., for supplying a sample of FPL 55712. We also thank Ben J. Cerimele for statistical analyses.

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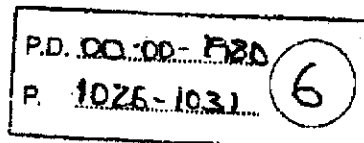
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Bronchodilator and Antiulcer Phenoxypyrimidinones¹

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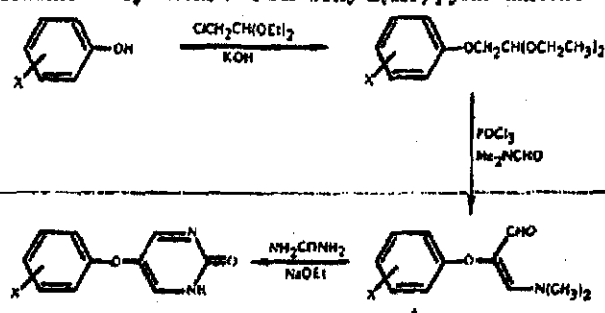
Central Research, Pfizer Inc., Groton, Connecticut 06340. Received December 6, 1979

Series of 5-phenoxy-2(1*H*)-pyrimidinones, 5-phenoxy-4(3*H*)-pyrimidinones, and related compounds were prepared in a follow-up of a lead prepared as a potential cyclic nucleotide regulating agent. Compounds were evaluated for bronchodilator activity in histamine-challenged guinea pigs and for antiulcer activity in a cold-restraint, stressed rat ulcer model. Bronchodilator activity comparable to, or greater than, that of theophylline was found in both the 2(1*H*)- and 4(3*H*)-pyrimidinone series and was most prominent in analogues containing either an electron-withdrawing or -donating substituent in the para position of the phenoxy ring. Significant antiulcer activity was observed only in the 2(1*H*)-pyrimidinone series among three closely related analogues. One of these, 5-(*m*-methoxyphenoxy)-2(1*H*)-pyrimidinone (3), exhibited more potent antiulcer effects than the clinically useful antiulcer agent carbamazepine, without demonstrating bronchodilator activity.

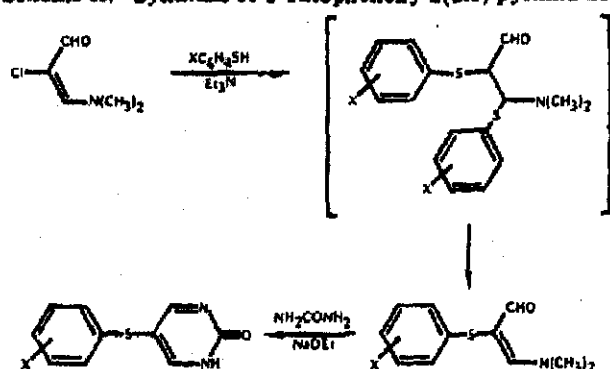
Series of chemical prototypes having certain structural features in common with the clinically useful bronchodi-

lator theophylline were prepared as potential cyclic nucleotide regulating agents. One of these, 5-phenoxy-2-

Scheme I. Synthesis of 5-Phenoxy-2(1H)-pyrimidinones



Scheme II. Synthesis of 5-Thiophenoxy-2(1H)-pyrimidinones

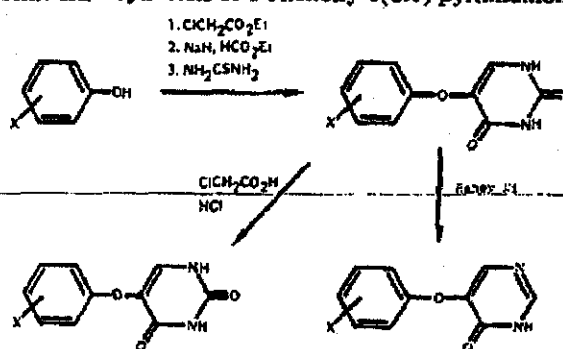


(1H)-pyrimidinone (compound 1, Table I), prevented bronchoconstriction in guinea pigs challenged with histamine and protected cold-restraint, stressed rats from gastric ulceration. This compound provided the basis for a structure-activity study reported here, which was aimed at optimizing antiulcer and bronchodilator activity.

Chemistry. The 5-phenoxy-2(1H)-pyrimidinones (1-21, Table I) were synthesized as illustrated in Scheme I by cyclization of an acrolein precursor with urea in the presence of sodium ethoxide. The 2-substituted 3-(dimethylamino)acrolein precursors (Table II) were obtained by Vilsmeier reaction of phenoxyacetaldehyde diethyl acetals using a modification of the method of Arnold.³ The required acetals, in turn, were prepared by reaction of phenolate anion with chloroacetaldehyde diethyl acetal.⁴ Phenoxyacetic acids were inferior substrates to phenoxyacetaldehyde diethyl acetals in the Vilsmeier reaction. Thus, while phenoxyacetic acid gave acrolein 1a in only 11% yield, an 81% yield of 1a was obtained using phenoxyacetaldehyde diethyl acetal as the substrate.

The 5-(thiophenoxy)-2(1H)-pyrimidinones (32-35, Table I) were prepared according to Scheme II by cyclization of the appropriate 2-(thiophenoxy)-3-(dimethylamino)acroleins with urea in the presence of sodium ethoxide. Attempted preparation of the latter intermediates by Vilsmeier reaction with (thiophenoxy)acetaldehyde diethyl acetals was unsuccessful. The only products isolated from this reaction were disulfides. The 2-(thiophenoxy)-3-(dimethylamino)acroleins were prepared instead by reaction

Scheme III. Synthesis of 5-Phenoxy-4(3H)-pyrimidinones



of the appropriate thiophenols with 2-chloro-3-(dimethylamino)acrolein⁵ in the presence of triethylamine. As shown in Scheme II, it seems likely that the mechanism of this reaction involves initial Michael addition of thiophenol to the acrolein double bond, followed by displacement of the activated α -chloro group by a second equivalent of thiophenol; the bis(thiophenol) adduct then loses thiophenol to generate the acrolein.

The 5-phenoxy-4(3H)-pyrimidinones (22-31, Table I) were prepared as illustrated in Scheme III by Raney nickel desulfurization⁶ of the corresponding 5-phenoxy-pyrimidines-2(1H)-thiones, most of which were readily available by known procedures.^{6,7} Hydrolysis of these pyrimidine-2(1H)-thiones with chloroacetic acid in concentrated HCl afforded the 5-phenoxyuracils (36-39, Table I).^{6,8}

Biological Results and Discussion

Bronchodilator Activity. Theophylline, a clinically useful bronchodilator, served as a positive standard in the guinea pig bronchodilator test, giving 20 to 30% protection against histamine-induced bronchoconstriction. Both series of pyrimidinones exhibited potent activity, with some compounds producing protection equal to theophylline at ten times lower doses, while at high doses producing greater protection. The degree of protection elicited by the parent compounds (1 and 22, Table I) was comparable to that of theophylline; however, bronchodilator activity was markedly enhanced by para substitution of the phenoxy moiety with either electron-withdrawing or electron-donating groups. Thus, *p*-methyl (4), ethyl (9), chloro (12), and bromo (16) derivatives in the 2(1H)-pyrimidinone series and *p*-methyl (24) and *p*-chloro (26) derivatives in the 4(3H)-pyrimidinone series were all highly potent, nearly completely blocking the histamine effect. By comparison, meta-substituted derivatives generally had significantly reduced activity, in the range of theophylline (7, 11, 21, and 23), or were inactive (3, 8, 13, and 25). Ortho-substituted derivatives (2 and 27) lacked significant bronchodilator activity, as did the 4-isopropyl derivative 10. Replacement of the phenolic ether bridge (1, 4, and 12) by a thioether bridge (32, 34, and 35) led to a diminution of bronchodilator activity.

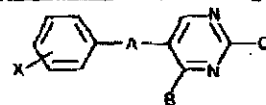
Bronchodilator activity was also observed with the uracils 36, 38, and 39. Substituent effects among these compounds paralleled those found in the 2(1H)- and 4(3H)-pyrimidinone series. Although uracils were generally

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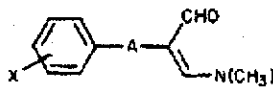
Table I. Bronchodilator and Antiulcer Pyrimidinones^a



no.	X	A	B	C	mp, °C	solvent	formula	anal.	yield	broncho- dilator act.: % protec- tion ^b	antiulcer act.: % decrease in total no. of lesions (p value) ^c	
											10, mg/kg po	100 mg/kg ip
1	H	O	H	OH	180-181	CH ₃ COCH ₃	C ₁₀ H ₈ N ₂ O ₂	C, H, N	49	28	37 (+)	81 (+)
2	2-CH ₃	O	H	OH	208-209	CH ₃ CO ₂ H	C ₁₁ H ₈ N ₂ O ₂	C, H, N	67	6	0 (-)	25 (-)
3	3-CH ₃	O	H	OH	163-164	C ₆ H ₅ OH	C ₁₁ H ₈ N ₂ O ₂	C, H, N	46	3	38 (+)	70 (+)
4	4-CH ₃	O	H	OH	186-187	CH ₃ COCH ₃	C ₁₁ H ₈ N ₂ O ₂	C, H, N	15	86	57 (+)	0 (-)
5	2-CH ₃ , 4-CH ₃	O	H	OH	187-188	CH ₃ CO ₂ C ₆ H ₅	C ₁₂ H ₈ N ₂ O ₂	C, H, N	69		6 (-)	0 (-)
6	3-CH ₃ , 4-CH ₃	O	H	OH	124-126	(i-C ₄ H ₉) ₂ O	C ₁₁ H ₈ N ₂ O ₂	C, H, N	48	14	54 (-)	53 (-)
7	3-CH ₃ , 5-CH ₃	O	H	OH	209-210	CH ₃ CO ₂ C ₆ H ₅	C ₁₂ H ₈ N ₂ O ₂	C, H, N	85	38	50 (-)	53 (+) ^d
8	3-C ₆ H ₅	O	H	OH	152-153	CH ₃ CO ₂ C ₆ H ₅	C ₁₃ H ₈ N ₂ O ₂	C, H, N	37	3	23 (-)	53 (+) ^d
9	4-C ₆ H ₅	O	H	OH	158-159	CH ₃ COCH ₃	C ₁₁ H ₈ N ₂ O ₂	C, H, N	37	98	0 (-)	27 (-)
10	4-(C ₆ H ₅) ₂	O	H	OH	176-177	C ₆ H ₅ OH	C ₁₂ H ₈ N ₂ O ₂	C, H, N	11	0	0 (-)	9 (-)
11	3-Cl	O	H	OH	177-178	CH ₃ COCH ₃	C ₁₀ H ₇ ClN ₂ O ₂	C, H, N, Cl	29	22	22 (-)	0 (-)
12	4-Cl	O	H	OH	218-220	C ₆ H ₅ -CH ₂ CO ₂ H	C ₁₁ H ₇ ClN ₂ O ₂	C, H, N	84	92	7 ^e (-)	0 (-)
13	3-OCH ₃	O	H	OH	163-165	CH ₃ CO ₂ H-H ₂ O	C ₁₁ H ₈ N ₂ O ₂	C, H, N	3	3	55 (-)	82 (+) ^d
14	4-OCH ₃	O	H	OH	169-170	CH ₃ CO ₂ H-H ₂ O	C ₁₁ H ₈ N ₂ O ₂	C, H, N	42	45	0 (-)	0 (-)
15	4-F	O	H	OH	220-221	CHCl ₃ -CH ₃ OH	C ₁₀ H ₇ FN ₂ O ₂	C, H, N, F	6	66	0 (-)	0 (-)
16	4-Br	O	H	OH	211-213	C ₆ H ₅ OH	C ₁₁ H ₇ BrN ₂ O ₂	C, H, N, Br	65	90	0 (-)	0 (-)
17	4-SCH ₃	O	H	OH	197-199	CH ₃ OH	C ₁₁ H ₈ N ₂ O ₂ S	C, H, N	40	55	0 (-)	0 (-)
18	4-SOCH ₃	O	H	OH	259-260	CH ₃ OH	C ₁₁ H ₈ N ₂ O ₂ S	C, H, N	72	10	50 (-)	0 (-)
19	2-Cl, 4-Cl	O	H	OH	210-211	CH ₃ COCH ₃ -H ₂ O	C ₁₀ H ₇ Cl ₂ N ₂ O ₂	C, H, N, Cl	50	47	22 (-)	19 ^e (-)
20	3-CH ₃ , 4-Cl	O	H	OH	224-225	CH ₃ CO ₂ C ₆ H ₅ -CH ₃ OH	C ₁₁ H ₇ ClN ₂ O ₂	C, H, N	40	6	0 (-)	14 (-)
21	3-CF ₃	O	H	OH	191-192	CH ₃ CO ₂ H-H ₂ O	C ₁₀ H ₆ F ₃ N ₂ O ₂	C, H, N ^f	16	26	39 (-)	0 (-)
22	H	O	OH	H	189-191	CH ₃ CO ₂ H-H ₂ O	C ₁₀ H ₇ N ₂ O ₂	C, H, N	82	23	0 (-)	0 (-)
23	3-CH ₃	O	OH	H	143-145	CH ₃ COCH ₃ -hexane	C ₁₁ H ₈ N ₂ O ₂	C, H, N	54	28	0 (-)	0 (-)
24	4-CH ₃	O	OH	H	122-124	CH ₃ COCH ₃ -CH ₃ COC ₂ H ₅	C ₁₁ H ₈ N ₂ O ₂	C, H, N	49	92	27 (-)	0 (-)
25	3-Cl	O	OH	H	158-161	CH ₃ COCH ₃ -hexane	C ₁₀ H ₇ ClN ₂ O ₂	H, N ^g	50	18		18 ^e (-)
26	4-Cl	O	OH	H	163-164	pptd from base	C ₁₀ H ₇ ClN ₂ O ₂	C, H, N	49	92		0 (-)
27	2-Cl	O	OH	H	163-165	CH ₃ COCH ₃	C ₁₀ H ₇ ClN ₂ O ₂	C, H, N, Cl	50	13		
28	4-F	O	OH	H	146-147	CH ₃ CO ₂ C ₆ H ₅ -hexane	C ₁₁ H ₇ FN ₂ O ₂	C, H, N	27	80	28 (-)	
29	3-Cl, 4-Cl	O	OH	H	165-166	CHCl ₃ -hexane	C ₁₀ H ₆ Cl ₂ N ₂ O ₂	C, H, N ^h	74	45		
30	3-OCH ₃	O	OH	H	150-152	CH ₃ CO ₂ C ₆ H ₅ -hexane	C ₁₁ H ₇ N ₂ O ₂	C, H, N	57	7	0 (-)	
31	4-OCH ₃	O	OH	H	172-174	CH ₃ CO ₂ C ₆ H ₅ -CHCl ₃ -CH ₃ OH	C ₁₁ H ₇ N ₂ O ₂	C, H, N	39	26	0 (-)	
32	H	S	H	OH	213-215	C ₆ H ₅ OH	C ₁₀ H ₇ N ₂ OS	C, H, N	38	23	45 (-)	47 (-)
33	3-CH ₃	S	H	OH	208-210	CH ₃ CO ₂ C ₆ H ₅	C ₁₁ H ₇ N ₂ OS	C, H, N	25		0 (-)	78 (+)
34	4-CH ₃	S	H	OH	222-224	CH ₃ CO ₂ H-H ₂ O	C ₁₁ H ₇ N ₂ OS	C, H, N	30	26	18 (-)	64 (+)
35	4-Cl	S	H	OH	218-220	CH ₃ CO ₂ H-H ₂ O	C ₁₀ H ₆ ClN ₂ OS	C, H, N, S, Cl	53	63		
36	H	O	OH	OH	297-298	C ₆ H ₅ OH-H ₂ O	C ₁₀ H ₇ N ₂ O ₂	k	60	25	22 (-)	
37	3-CH ₃	O	OH	OH	291-295	pptd from reaction	C ₁₁ H ₇ N ₂ O ₂	C, H, N	92	7	0 (-)	67 ^e (+)
38	4-CH ₃	O	OH	OH	>300	C ₆ H ₅ OH	C ₁₁ H ₇ N ₂ O ₂	k	87	35	0 (-)	
39	4-Cl	O	OH	OH	>300	CH ₃ CO ₂ H	C ₁₀ H ₆ ClN ₂ O ₂	C, H, N	40	50	35 (-)	88 (+)

^a Structures drawn in enolic form for clearness of presentation. ^b Respiratory status of guinea pigs exposed to histamine aerosol expressed as percent protection. Control = 0; complete protection = 100. Drugs given 60 mg/kg po 1 h prior to histamine challenge. ^c Ulcer status expressed as percent decrease in total number of lesions in cold-restraint, stressed rats. Active: $p < 0.05$ (+); inactive: $p > 0.10$ (-). Drugs 10 mg/kg po or 100 mg/kg ip given 3 h before stress. ^d $p > 0.05$, $p < 0.10$. ^e Tested 60 mg/kg po. ^f Tested 32 mg/kg po. ^g Tested 32 mg/kg ip. ^h F: calcd, 22.25; found, 22.83. ⁱ C: calcd, 53.95; found 54.99. m/e ³⁵Cl isotope: calcd, 222.0196; found, 222.0198. ^j Cl: calcd, 27.59; found, 27.15. ^k Reference 6.

Table II. 2-Phenoxy- and 2-Thiophenoxy-3-(dimethylamino)acroleins



no.	X	A	mp, °C	solvent	formula	anal.	% yield
1a	H	O	115-117	C ₆ H ₆ -hexane	C ₁₁ H ₁₁ NO ₂	C, H, N	81
2a	2-CH ₃	O	141-143	subl 125°C (0.1 mm)	C ₁₂ H ₁₃ NO ₂	C, H, N	88
3a	3-CH ₃	O	103-105	CH ₂ CO ₂ C ₆ H ₅ -hexane	C ₁₇ H ₁₇ NO ₂	C, H, N	61
4a	4-CH ₃	O	87-89	subl 125°C (0.1 mm)	C ₁₂ H ₁₃ NO ₂	C, H, N	22
5a	2-CH ₃ , 4-CH ₃	O	137-138	CH ₂ CO ₂ C ₆ H ₅	C ₁₈ H ₁₉ NO ₂	C, H, N	69
6a	3-CH ₃ , 4-CH ₃	O	124-126	(i-C ₄ H ₉) ₂ O	C ₁₇ H ₁₉ NO ₂	C, H, N	48
7a	3-CH ₃ , 5-CH ₃	O	135-136	C ₆ H ₅ OH-hexane	C ₁₇ H ₁₉ NO ₂	C, H, N	34
8a	3-C ₂ H ₅	O	65-66	(C ₆ H ₅) ₂ O-cyclohexane	C ₁₉ H ₂₁ NO ₂	C, H, N	44
9a	4-C ₂ H ₅	O	45-48	(C ₆ H ₅) ₂ O-pet. ether	C ₁₉ H ₂₁ NO ₂	C, H, N	15
10a	4-i-C ₄ H ₉	O	79-80	(C ₆ H ₅) ₂ O-hexane	C ₂₁ H ₂₃ NO ₂	C, H, N	36
11a	3-Cl	O	125-126	C ₆ H ₆ -hexane	C ₁₁ H ₉ ClNO ₂	C, H, N, Cl	42
12a	4-Cl	O	125-126	CH ₂ COCH ₃ -hexane	C ₁₁ H ₉ ClNO ₂	C, H, N, Cl	48
13a	3-OCH ₃	O	78-79	CH ₂ CO ₂ C ₆ H ₅ -hexane	C ₁₇ H ₁₇ NO ₃	C, H, N	4
14a	4-OCH ₃	O	103-104	(C ₆ H ₅) ₂ O	C ₁₇ H ₁₇ NO ₃	C, H, N	26
15a	4-F	O	98-100	hexane-CH ₂ CO ₂ C ₆ H ₅	C ₁₇ H ₁₅ FNO ₂	C, H, N, F	59
16a	4-Br	O	131-133	hexane-CH ₂ CO ₂ C ₆ H ₅	C ₁₇ H ₁₅ BrNO ₂	C, H, N, Br	70
17a	4-SCH ₃	O	75-77	hexane-CH ₂ CO ₂ C ₆ H ₅	C ₁₇ H ₁₇ NO ₂ S	C, H, N, S	16
19a	2-Cl, 4-Cl	O	114-116	hexane-CH ₂ CO ₂ C ₆ H ₅	C ₁₁ H ₉ Cl ₂ NO ₂	C, H, N, Cl	3 ^a
20a	3-CH ₃ , 4-Cl	O	142-143	CH ₂ CO ₂ C ₆ H ₅	C ₁₇ H ₁₇ ClNO ₂	C, H, N, Cl	53
21a	3-CF ₃	O	108-110	hexane-CH ₂ CO ₂ C ₆ H ₅	C ₁₇ H ₁₃ F ₃ NO ₂	C, H, N, F	44
32a	H	S	90-92	(i-C ₄ H ₉) ₂ O	C ₁₁ H ₁₁ NOS	C, H, N	36
34a	4-CH ₃	S	88-90	(i-C ₄ H ₉) ₂ O	C ₁₂ H ₁₃ NOS	C, H, N	29
35a	4-Cl	S	96-97	(C ₆ H ₅) ₂ O	C ₁₁ H ₉ ClNOS	C, H, N, S ^b	23

^a Prepared from 2,4-dichlorophenoxyacetic acid. See Experimental Section. ^b Cl: calcd, 14.67; found, 15.09.

Table III. Activity in Histamine Aerosol Test. Percent Protection and Duration of Action^a

no.	dose, mg/kg po				duration, h, at 80 mg/kg po			
	3	10	30	60	1	2	4	8
4	2	18	81	86	86	86	8	10
12	22	37	71	92	92	94	94	88

^a Respiratory status of guinea pigs exposed to histamine aerosol expressed as percent protection. Control = 0; complete protection = 100. Duration (h) refers to the time between dosing and initiation of histamine challenge.

less active than the corresponding 2(1*H*)- and 4(3*H*)-pyrimidinones, their activity is believed to contribute to that of the pyrimidinones, since both 2(1*H*)-pyrimidinones and 4(3*H*)-pyrimidinones are metabolized to uracils.⁹

Marked differences, which may be related to rates of metabolism, were observed in duration of action of the pyrimidinones. Thus, pyrimidinones 4 and 12 were equiefficacious when given 1 h before histamine challenge (Table I). However, pyrimidinone 12 was still highly active when given 8 h before challenge, in contrast to 4 which was inactive (Table III). A quantitative structure-activity study was not attempted, since dose-response curves of members of the pyrimidinones were not parallel (compounds 4 and 12, Table III).

Although the pyrimidinones and especially the uracils bear a structural resemblance to theophylline, it is uncertain whether bronchodilator activity is related to elevation of cyclic AMP levels.

Antiulcer Activity. Antiulcer activity was assessed in rats using carbenoxolone, a clinically useful ulcer-healing agent, as a positive standard. This drug, which is not active orally in rats because of hydrolysis of the hemisuccinate ester moiety by the intestinal microflora in this species,¹⁰ demonstrated significant antiulcer activity by intraperi-

toneal administration at doses of 30 mg/kg.

Some members of the 2(1*H*)-pyrimidinones, but not the 4(3*H*)-pyrimidinones, exhibited significant antiulcer activity. Within the 2(1*H*)-pyrimidinone series, significant oral activity was confined to three closely related analogues, the parent compound (1) and the *m*- and *p*-methyl derivatives (3 and 4). These compounds provided significant protection from stress-induced ulceration at doses of 10 mg/kg, po. Several other meta-substituted derivatives, 7, 8, and 13, also demonstrated antiulcer activity but only by intraperitoneal administration at higher doses (100 mg/kg). Replacement of the phenolic ether bridge in 1, 3, and 4 by a thioether bridge (32, 33, and 34) resulted in a decrease or loss of antiulcer activity. The uracils 36 and 38, which are related to pyrimidinones 1 and 4, were inactive. However, uracil 37, which is a metabolite of pyrimidinone 3 in rat, rhesus monkey, and man,¹¹ exhibited activity at 32 mg/kg, po.

In more detailed studies, compound 3 was shown to stimulate gastric mucus secretion in vivo over the same dose range that prevents experimentally induced gastric ulceration in rats and to display mucotropic effects in vitro in a system employing segments of rat gastric glandular mucosa.¹¹ A direct correlation between the mucotropic and antiulcer effects suggests that stimulation of mucus secretion, presumably mediated by increased cyclic AMP production, underlies the antiulcer activity of this agent. Following administration of 3 (50 mg/kg, ip) to rats, cyclic AMP levels increased by 50% in the glandular region of the stomach and, although compound 3 had no significant effects on rat gastric mucosal cyclic AMP phosphodiesterase, its metabolite 37 had the same inhibitory effect as theophylline (*I*₅₀ = 100 μM).¹² Compound 3 is rapidly orally absorbed in the rat,⁹ and the greater oral activity of 2(1*H*)-pyrimidinone (3) over uracil 37 may be due to less favorable absorption of the very insoluble uracil. Inhibition

(9) H. D. Doohan, Pfizer Inc., unpublished work.

(10) P. Iverson, W. E. Lindup, D. V. Parks, and R. T. Williams, *Xenobiotica*, 1, 79 (1971).

(11) J. N. Pereira, G. A. Mears, J. P. Leader, and L. A. Hohnke, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 37(2), A484 (1978).

(12) J. P. Leader, Pfizer Inc., unpublished work.

of gastric acid secretion does not appear to contribute significantly to the antiulcer activity of 3.¹¹

Dose-response comparisons established that 3 administered orally is approximately three times as potent as carbenoxolone administered intraperitoneally in protecting rats from gastric ulceration. Furthermore, in contrast to carbenoxolone, 3 elicits its protective effects in rats without fluid retention or altering urinary electrolyte output. Compound 3 has been assigned the nonproprietary (USAN) name tolimidone.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Analytical Department of Pfizer Inc. Where analyses are indicated only by symbols of the elements, analytical values were within $\pm 0.4\%$ of theoretical values. NMR and/or mass spectra were obtained on all compounds and were consistent with structures and assignments. NMR spectra were recorded on either a Varian A-60 or T-60 spectrometer, and the mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Representative procedures for the preparation of compounds 1-21 (Scheme I), 32-35 (Scheme II), and 22-31 (Scheme III) are illustrated below.

Phenoxyacetaldehyde Diethyl Acetals. The crude intermediates were prepared by literature procedures¹⁴ and were used without extensive purification for the preparation of the 2-(substituted phenoxy)-3-(dimethylamino)acroleins. A typical procedure is illustrated below.

3-Methylphenoxyacetaldehyde Diethyl Acetal. Into a 3-L. three-neck flask equipped with a pressure-compensating dropping funnel, overhead stirrer, and condenser with solvent takeoff was added 99.1 g (1.5 mol) of 85% KOH pellets. The dry flask was heated, and to the stirred hot KOH pellets was added 170.0 g (1.5 mol) of *m*-cresol. The flask was maintained at such a temperature that the contents were at 90–100 °C so that the phenolate anion did not precipitate. A clear solution of molten potassium *m*-cresolate and H₂O resulted. To the stirred molten solution, 375 g (2.46 mol) of chloroacetaldehyde diethyl acetal (bp 152–156 °C) was added at such a rate that the mixture remained at 90 to 100 °C. The mixture (two phases) was stirred rapidly and heated, and an azeotrope of the acetal and H₂O was removed via the takeoff on the condenser. Distillation was continued until the distilling vapor was at 140 to 150 °C. On cooling, the azeotrope separated into an aqueous and acetal layer and the acetal could be readded to the reaction mixture. The mixture was stirred vigorously and heated for 6 h, during which time KCl precipitated. The crude cooled mixture was poured into a stirred solution of ice-H₂O and ether. The layers were separated and the aqueous layer was washed with two more portions of ether. The combined ether solutions were washed with cold 2 N NaOH solution and then dried over anhydrous Na₂SO₄, treated with activated charcoal and concentrated on a steam bath to a mobile amber oil weighing 424 g. The residual traces of ether were removed by distillation at atmospheric pressure, and then excess chloroacetaldehyde diethyl acetal was removed by distillation at H₂O aspirator pressure (20 mm). Final distillation under high vacuum at 0.2 to 0.3 mmHg at 90–95 °C gave 291.7 g (85%) of 3-methylphenoxyacetaldehyde diethyl acetal as a clear colorless oil: NMR (CDCl₃) δ 7.35–8.7 (4 H, m), 4.8 (1 H, t), 3.96 (2 H, d), 3.68 (4 H, m), 2.3 (3 H, s), 1.21 (6 H, t). Anal. (C₁₃H₂₀O₂) C, H.

2-(3-Methylphenoxy)-3-(dimethylamino)acrolein (3a). To 175 g (2.4 mol) of DMF was added 358 g (2.4 mol) of POCl₃, maintaining the temperature at 25 °C by an external ice bath. Upon completion of the addition, the resultant amber heavy oil was warmed to 50 °C for 45 min and then cooled to 25 °C. CHCl₃ (700 mL) was added and the resultant solution was brought to reflux. While reflux continued, 190 g (0.8 mol) of 3-methylphenoxyacetaldehyde diethyl acetal was added over a 30-min

period. Provision was made to trap the large amount of HCl that evolved during the addition. After a 8-h reflux following the addition, the cooled CHCl₃ solution was cautiously added to a stirred mixture of 2.3 kg of K₂CO₃, 2 L of ice-H₂O, and 2 L of a 9:1 benzene-ethanol solution. The organic layer was separated, concentrated to a dark oil, and taken up in CHCl₃ to remove inorganic salts. The CHCl₃ was removed in vacuo to give a dark red oil. Isopropyl ether was added to precipitate 87 g (61%) of a granular light yellow solid, mp 99–101 °C. Recrystallization from ethyl acetate-hexane gave an analytical sample: mp 103–105 °C; NMR (CDCl₃) δ 9.23 (1 H, s), 7.33–8.5 (4 H, m), 6.60 (1 H, s), 3.05 (6 H, s), 2.32 (3 H, s). Anal. (C₁₂H₁₃NO₂) C, H, N.

2-(2,4-Dichlorophenoxy)-3-(dimethylamino)acrolein (19a). To the reagent prepared from 640 g (8.75 mol) of DMF and 908 g (5.93 mol) of POCl₃ was added 442 g (2.0 mol) of 2,4-dichlorophenoxyacetic acid using the procedure of Arnold⁵ to give 13.7 g (3%) of needle-shaped crystals. Recrystallization from hexane-ethyl acetate (1:2) gave needles, mp 114–116 °C. Anal. (C₁₁H₁₁Cl₂NO₂) C, H, N, Cl.

2-(4-Methylthiophenoxy)-3-(dimethylamino)acrolein (34a). A solution of 4.06 g (0.03 mol) of 2-chloro-3-(dimethylamino)-acrolein, 6.06 g (0.06 mol) of triethylamine, and 3.72 g (0.03 mol) of *p*-toluenethiol in 50 mL of ethanol was heated at reflux for 2.5 h. The cooled reaction solution was poured over H₂O and extracted with ether. The ether extracts were dried over anhydrous MgSO₄ and concentrated in vacuo to a 100-mL volume. Isopropyl ether (50 mL) was added and the total volume was reduced to 100 mL on a steam bath. Cooling resulted in crystallization of 1.9 g (29%) of 34a: mp 88–90 °C; NMR (CDCl₃) δ 9.06 (1 H, s), 7.53 (1 H, s), 7.05 (4 H, s), 3.25 (6 H, s), 2.28 (3 H, s). Anal. (C₁₁H₁₃NOS) C, H, N.

2-(3-Methylthiophenoxy)-3-(dimethylamino)acrolein (33a). The crude intermediate was prepared from a commercially available mixture (K&K Labs) of ~70% *m*-toluenethiol and 30% *p*-toluenethiol, utilizing the procedure for the preparation of compound 34a.

5-(3-Methylphenoxy)-2(1H)-pyrimidinone (3). To a solution of 39.2 g (0.576 mol) of NaOEt in 150 mL of EtOH was added 59.3 g (0.288 mol) of 2-(3-methylphenoxy)-3-(dimethylamino)-acrolein (3a) and 34.6 g (0.576 mol) of urea. The mixture was heated at reflux for 4 h, 10 mL of H₂O was added, and refluxed was continued for another 2 h. When the mixture was cooled, 30.3 g of a crude tan solid (mp >300 °C) precipitated and was collected by filtration and dried. The crude sodium salt was dissolved in 1200 mL of hot H₂O and filtered from a small quantity of insoluble material. Glacial acetic acid was added to pH 6.0, resulting in crystallization of 21.4 g (46%) of a tan solid, mp 182–183 °C. Recrystallization from ethanol gave an analytical sample: mp 163–164 °C; NMR (Me₂SO) δ 12.0 (N-H, exchange), 8.25 (2 H, s), 7.4–8.5 (4 H, m), 2.26 (3 H, s). Anal. (C₁₁H₁₀N₂O₂) C, H, N.

5-(Thiophenoxy)-2(1H)-pyrimidinones 32–35. These compounds were prepared from the (thiophenoxy)(dimethylamino)acroleins 32a–35a using the procedure for compound 3.

5-(3-Methylthiophenoxy)-2(1H)-pyrimidinone (33). Crude product containing 34 was prepared from 33a using the procedure described for 3. Fractional crystallization of the crude product from ethyl acetate resulted in isolation of the 3-methylthiophenoxy isomer (33), mp 208–210 °C, uncontaminated by the 4-methylthiophenoxy isomer (34), mp 222–224 °C. The isomeric purity of 33 could be readily determined by the position of the NMR absorption of the tolythio methyl group: NMR (Me₂SO) for 33, δ 2.4 (3 H, s); for 34, 2.27 (3 H, s). Anal. (C₁₁H₁₀N₂OS) C, H, N.

5-Phenoxy-4-hydroxypyrimidine (22). To a solution of 22.0 g (0.55 mol) of NaOH in 700 mL of H₂O was dissolved 121 g (0.55 mol) of 2-thio-4-hydroxy-5-phenoxy-pyrimidine. To the stirred solution was added slowly 1250 g of wet Raney nickel at such a rate that the resultant foaming remained under control. The mixture was stirred well and heated at reflux for 2 h. The suspension was filtered while still hot, and the Raney nickel residue was washed with 1.5 L of boiling water, with care being taken that the catalyst remained wet. The combined aqueous solutions were concentrated to 700 mL and acidified with acetic acid to precipitate a white solid. This was collected by filtration and dried to give 85.5 g (82.5%) of 22, mp 188–189 °C. Recrystallization

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(14) M. Creland, French Patent 1 026 008 (1953); *Chem. Abstr.*, 52P, 5466g.

from aqueous acetic acid gave 22: mp 189-191 °C; NMR (M_e_2SO) δ 8.13 (1 H, s), 7.88 (1 H, s), 7.58-6.38 (5 H, m). Anal. ($C_{10}H_9N_2O_2$) C, H, N.

5-[4-(Methylsulfinyl)phenoxy]-2(1H)-pyrimidinone (18). To a slurry of 1.17 g (0.005 mol) of 17 in 20 mL of methanol at 0 °C was added 1.175 g (0.0055 mol) of $NaIO_4$ in 10 mL of H_2O , and the slurry was stirred at 0 °C for 8 h and then for 20 h at 25 °C. The resultant slurry was diluted with H_2O and the methanol was removed in vacuo. Filtration gave 0.917 g (73%) of a white solid, mp 259-260 °C. Anal. ($C_{11}H_9N_2O_3S$) C, H, N.

Pharmacological Procedures. Guinea Pig Histamine Aerosol. Bronchodilator activity was evaluated according to the method of Van Arman, Miller, and O'Malley¹² in conscious female Reed-Willet guinea pigs (200-250 g) fasted overnight. One hour following no administration of vehicle, or the test drug dissolved in 1 N HCl or suspended in vehicle, each animal was challenged with histamine aerosol as follows: a 0.4% aqueous solution of histamine was placed in a Vaponephrine standard nebulizer (Vaponephrine Co., Edison, N.J.) and sprayed under an air pressure of 6 psi into a closed 8 x 8 x 12 in. transparent plastic container for 1 min. Immediately thereafter, the guinea pig was placed in the container. The respiratory status (a reflection of bronchoconstriction) of the guinea pig after 1 min in the container was scored as follows: 0, normal breathing; 1, slightly deepened breathing; 2, labored breathing; 3, severely labored breathing and ataxia; 4, unconsciousness.

The percent inhibition values were derived by comparing the total score of a group of eight treated animals with that of a similar control group to generate a single value with no standard deviation.

In order to assess the significance of a result, data on 11 groups of eight animals were recalculated by assigning a percent inhibition value to each animal (based on the score 0 = 100% inhibition, 1 = 75%, 2 = 50%, 3 = 25%, and 4 = 0) and where more than 90% of control scores were 4. Based on this calculation, the standard deviation of the mean value for eight animals was 5.33. As a result, it is likely that any two values differing by more than 11% would be significantly different based on the premise that values differing by more than 2 standard deviations represent different populations.

Cold-Restraint, Stress-Induced Gastric Ulceration. Ulcer protective effects were determined in rats using a modification of the method of Perkins.¹⁵ Cold-restraint, stress-induced gastric ulceration was produced by immobilizing nonfasted, female, 80-120 g Sprague-Dawley rats in a supine position and placing them in a refrigerator at 12 °C for 3 h. Experimental drugs suspended in saline containing 10 g/L carboxymethylcellulose and 1 g/L Tween 80 were administered 3 h before the initiation of the stress period. At the conclusion of the ulcerogenic stress, the rats were sacrificed by cervical dislocation, their stomachs were removed, and the degree of gastric ulceration was determined. Differences in number of ulcers per animal were compared with Wilcoxon rank sum tests in order to calculate a *p* value. Compounds were considered active (+) if the decrease in number of ulcers per animal compared to control were significant at the *p* ≤ 0.05 level.

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Synthesis of α -Methylene- γ -butyrolactones: A Structure-Activity Relationship Study of Their Allergenic Power

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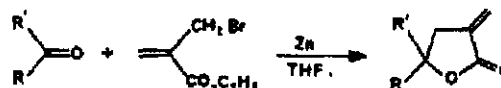
Laboratoire de Dermato-Chimie, Associé au CNRS, Université Louis Pasteur de Strasbourg, Clinique Dermatologique, CHR de Strasbourg, 67081 Strasbourg, France. Received February 27, 1980

Thirty-five α -methylene- γ -butyrolactones have been prepared and their allergenic properties tested on the skin of guinea pigs experimentally sensitized to (a) alantolactone (1), (b) isovalantolactone (2), and (c) α -methylene- γ -butyrolactone (3). The two first groups of animals cross-react to lactones containing 9 to 18 carbon atoms but not to smaller α -methylene- γ -butyrolactones. Conversely, animals sensitized to α -methylene- γ -butyrolactone react only with α -methylene- γ -butyrolactones containing 6 and 7 carbon atoms. These results are discussed in relation with the allergic contact dermatitis mechanism.

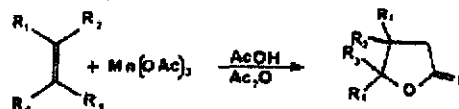
The biological properties of compounds containing the α -methylene- γ -butyrolactone moiety have been the focus of a considerable amount of work. Research has been focussed mainly on their cytotoxic, antitumoral,^{1,2} antibacterial,³ and plant growth inhibition activities.⁴ These compounds, which occur naturally in many plants⁵ (such as compositae, frullaniaceae, magnoliaceae, etc.), can also cause severe allergic contact dermatitis (ACD) in man.⁶

We have been interested in this last property for some time. The mechanism of ACD has not been completely elucidated.⁷ It is generally believed that an allergen

Scheme I. Reformatsky Synthesis of γ -Substituted α -Methylene- γ -butyrolactone



Scheme II. Synthesis of Butyrolactones from Manganese Triacetate and Olefins



(hapten), in order to become a true antigen, must bind to a protein (or another carrier). Why are some compounds allergenic while other are not? To approach the answer to this fundamental question, we have prepared a series of γ -monosubstituted and β,γ - and γ,γ -disubstituted α -methylene- γ -butyrolactones and tested their allergenic

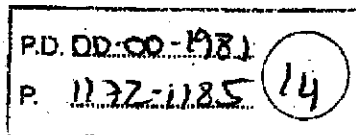
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Stabile Enole von α -[Aryl(Alkyl)oxy]dibenzoylmethanen

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Die Enole **13a–m** von α -(Aryloxy)- und α -(Alkylloxy)dibenzoylmethanen **4a–m** werden durch Zerlegung der Kupferchelate **11a–m** mit Schwefelsäure erhalten. Zu den Kupferverbindungen gelangt man entweder durch Esterkondensation der Acetophenone **6h–m** mit Benzoesäurephenylester (**7**) oder durch nukleophile Substitution von α -Bromdibenzoylmethan (**9**) mit den Phenolen **10a–g**. Die in Gegenwart von Natriumhydrid bzw. Triethylamin zunächst gebildeten Enolate **8** lassen sich direkt mit Kupfer(II)-acetat in die Chelate **11** umwandeln. Die Enole **13** sind durch Isomerisierung zu den β -Diketonen **4** sowie durch die Bromierung zu **12** charakterisiert.

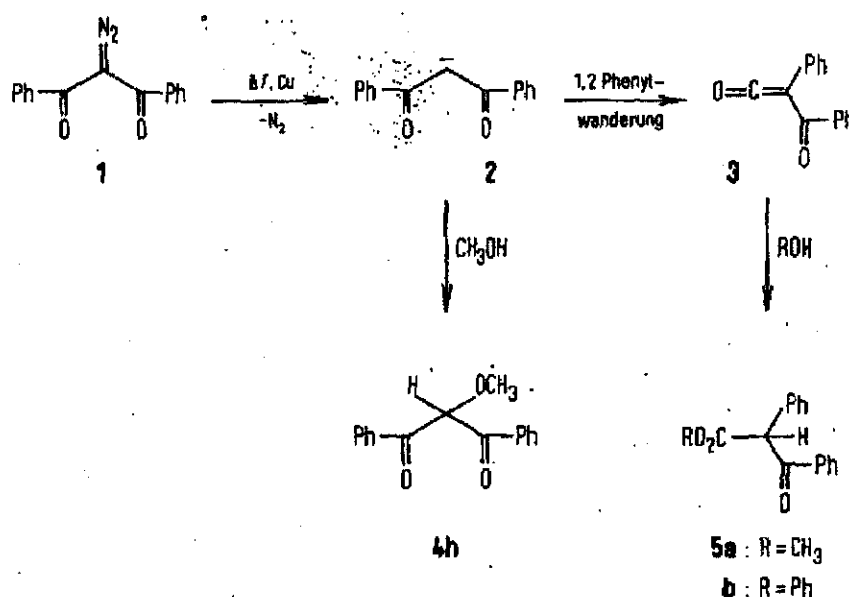
Stable Enols of α -[Aryl(Alkyl)oxy]dibenzoylmethanes

The enols **13a–m** of α -(aryloxy)- and α -(alkyloxy)dibenzoylmethanes **4a–m** are obtained by decomposition of the copper chelates **11a–m** with sulfuric acid. The copper compounds are synthesized either by ester condensation of the acetophenones **6h–m** with phenyl benzoate (**7**) or by nucleophilic substitution of α -bromodibenzoylmethane (**9**) with the phenols **10a–g**. The enolates **8**, primarily formed in the presence of sodium hydride or triethylamine, respectively, are directly converted into the chelates **11** with copper(II) acetate. The enols **13** are characterized by isomerization to the β -diketones **4** as well as by bromination to **12**.

Die quantitative Bestimmung der Keto/Enol-Gleichgewichte von β -Dicarbonylverbindungen nach Meyer¹⁾ beruht darauf, daß man deren Enolgehalt durch bromometrische Titration ermittelt. Hierbei muß man die äußeren Bedingungen so wählen, daß die Nachenolisierung „vernachlässigbar“ ist und die Bromierung selbst „momentan“ erfolgt, was in Methanol als Solvens und bei -20°C i. a. gegeben ist. Zahlreiche Anwendung dieser Technik²⁾ oder auch der hieraus entwickelten automatisierten coulometrischen Bromtitration^{3,4)} stehen naturgemäß nur wenige Arbeiten über die Kinetik des Bromierungsablaufes selbst gegenüber^{5,6,7)}. Hierbei wurde gefunden, daß die Enole halogenierter β -Dicarbonylverbindungen bei 25°C in Methanol etwa 100mal langsamer bromiert werden als die Grundverbindung selbst⁶⁾. Diese Tendenz setzt sich – wie wir fanden⁸⁾ – in beeindruckender Weise bei den Enolen von α -(Aryloxy)- bzw. α -(Alkylloxy)dibenzoylmethan (**13**) fort. Um nun den sterischen und elektronischen Substituenteneinfluß auf die Bromierungskinetik zu untersuchen, haben wir uns zunächst mit der Synthese eines repräsentativen Spektrums derartiger Enole befaßt, über die im folgenden berichtet wird.

Verkochung von (Diazo)dibenzoylmethan (1)

Aus dem α -Diazo- β -diketon 1, das durch Diazogruppen-Übertragung bequem zugänglich^{9,10)} ist, entstehen die α -[Alkyl(Aryl)oxy]dibenzoylmethane 4 durch Verköchung in Gegenwart von Alkoholen bzw. Phenolen; für die Isomerisierung zu den β -Diketonenolen 13 bot sich u. a. der Weg über die entsprechenden Enolate an. Literaturbekannt ist z. B. die kupferkatalysierte Umwandlung von α -Diazoacetessigsäure-methylester in α -Methoxyacetessigsäure-methylester¹¹⁾ oder auch die Bortrifluorid-katalysierte Herstellung von α -Methoxyacetylaceton aus α -Diazoacetylaceton¹²⁾.



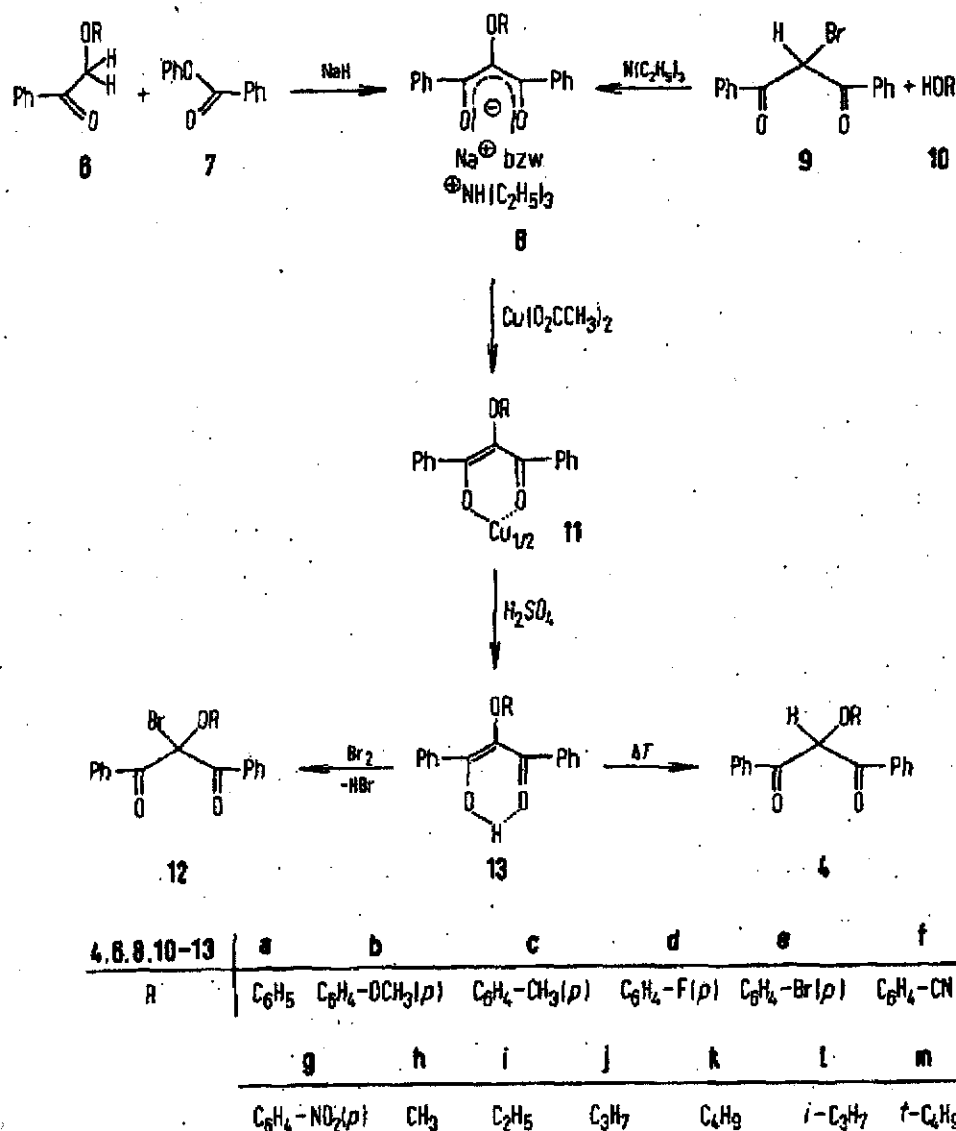
Eigene orientierende Versuche mit 1 zeigten aber sehr schnell, daß diesem Syntheseweg für die Herstellung von 4 bzw. 13 doch sehr enge Grenzen gesetzt sind, da sich die mit der Insertion konkurrierende Wolff-Umlagerung von 1 nur schwer unterdrücken läßt¹³⁾. So liefert zwar die kupferkatalysierte Thermolyse von 1 in Methanol bei Gegenwart von Perchlorsäure mit 42proz. Ausbeute das gesuchte α -Methoxy- β -diketon 4h, doch führt bereits die Schwefelsäure-katalysierte Umsetzung der gleichen Reaktanden nur noch zur Wolff-Umlagerung (5a, 39%). Entsprechend ist das Ergebnis der thermischen Zersetzung von 1 mit Phenol in Gegenwart von Kupferpulver (5b, 77%). Die Konstitution der beiden β -Ketoester ist zusätzlich abgesichert durch saure Hydrolyse und Decarboxylierung zu Desoxybenzoin.

Kupferchelat 11a – m

Als Methode der Wahl zur Herstellung einer breiten Palette von α -[Aryl(Alkyl)oxy]dibenzoylmethan-Enolen (13a – m) hat sich die später beschriebene Zerlegung der Kupferchelat 11a – m erwiesen. Die letzteren werden auf zwei Wegen erhalten.

Einerseits kondensiert man – in Anlehnung an Erfahrungen von Munch-Petersen und Hauser¹⁴⁾ über die Acylierung von α -Alkoxy-carbonylverbindungen – die Acetophenone 6h – m mit Benzoesäure-phenylester (7) in Gegenwart von Natriumhydrid (anstelle von Natriumamid) und wandelt die Natriumenolate 8h – m durch Zusatz von

Kupfer(II)-acetat unmittelbar in die Kupferchelate **11h – m** um (41 – 53%). Bis auf **6j** und **k**, die durch Kupferacetylacetonat-katalysierte Zersetzung von ω -Diazoacetophenon hergestellt wurden¹⁵⁾, sind die anderen ω -Alkoxyacetophenone literaturbekannt.



Andererseits läßt sich in **9** das Brom glatt durch nukleophile Substitution mit Phenolen (**10a – g**) in Anwesenheit von Triethylamin in Aceton austauschen, wobei zunächst vermutlich wieder die Enolate **8** gebildet werden, die erneut mit Kupfer(II)-acetat in die entsprechenden Kupferchelate **11a – g** übergeführt werden. Eventuell nicht umgesetztes **9** stört hierbei nicht, da es selbst keinen Kupferkomplex bildet¹⁶⁾. Die Umsetzung von **9** mit Alkanolaten führt offenbar schon deshalb nicht zum Ziel, weil sie von der Spaltung des β -Diketonsystems begleitet ist. So wird bei der Umsetzung von **9** mit Natriummethanolat in Methanol Benzoesäure-methylester neben ω -Methoxyacetophenon (**6h**) erhalten¹⁷⁾.

Alle Kupferkomplexe **11a – m** geben exakte Elementaranalysen. In den IR-Spektren (KBr) fehlt zunächst als Folge der Chelatisierung die CO-Absorption im üblichen Be-

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reich, was für die Metallchelate von β -Dicarbonylverbindungen charakteristisch ist¹⁸⁾. Innerhalb recht enger Grenzen zeigen alle Chelate intensive Absorptionsbanden bei 1600 ± 10 , 1545 ± 15 , 1500 ± 10 , 1450 ± 15 , 1335 ± 20 und $1225 \pm 15 \text{ cm}^{-1}$, wobei die energiereichste Schwingung den Phenylresten zukommen sollte. Starke Absorptionen im 1500-cm^{-1} -Bereich treten auch bei anderen Metallkomplexen von β -Diketonen auf^{19,20)}.

Die 70-eV-Massenspektren von **11a** – **m** zeigen keine Molpeaks, doch treten diese – mit Ausnahme von **11m** – bei verminderter Elektronenenergie auf und zeigen das geforderte Isotopenverhältnis. In allen Massenspektren tritt ein Fragment $m/e = [(M\text{-Cu})/2] + 1$ auf, das dem Molpeak der relevanten Enole **13a** – **m** entspricht. Von dieser Beobachtung ausgehend wird verständlich, daß sich das weitere Fragmentierungsmuster von dem der Enole nicht mehr unterscheidet (s. unten).

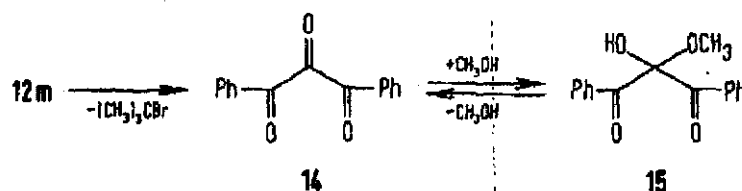
Enole **13a** – **m**

Aus den Kupferchelaten **11a** – **m** setzt man die Enole **13a** – **m** mit halbkonzentrierter Schwefelsäure frei. Genügend schnelle Aufarbeitung bei Vermeidung allzu hoher Temperaturen liefert diese mit einem durch coulometrische Bromtitration ermittelten Reinheitsgrad von $\geq 99.5\%$; sie stellen gelbe, kristalline Verbindungen dar, die nach einigem Stehen an der Luft zerfließen. Das Enol **13a** ist bereits bekannt, wurde aber fälschlicherweise als das tautomere β -Diketon **4a** angesehen¹⁴⁾.

Keto/Enol-Gleichgewichte offenkettiger β -Dicarbonylverbindungen sind temperatur- und lösungsmittelabhängig; hohe Temperaturen und polare, protische Solventien begünstigen die Ketoform. Unter diesen Aspekten wird es verständlich, daß die Enole **13a** – **m** beim mehrstündigen Erhitzen in Methanol/Wasser zu den β -Diketonen **4a** – **m** tautomerisieren. Letztere sind farblos und zeigen – ausgenommen **4i** – höhere Schmelzpunkte als die Enoltautomeren (s. Tabelle 4); die gelben Schmelzen enthalten vermutlich wieder mehr oder minder große Enolanteile (vgl. auch Lit.¹³⁾).

Alle Enole reagieren mit äquimolaren Mengen Brom im Einklang mit ihrer Konstitution zu den α -Aryl(Alkyl)oxy- α -brom- β -diketonen **12a** – **m**, wobei die Reaktion im Falle von **13m** allerdings nicht auf der Bromierungsstufe **12m** stehen bleibt (s. unten).

In den IR-Spektren (KBr) der Bromverbindungen **12a** – **l** treten intensive Banden im C/O- und C/C-Doppelbindungsbereich auf (1715 ± 5 , 1680 ± 10 , 1600 ± 5 und $1585 \pm 10 \text{ cm}^{-1}$). In den Massenspektren (70 eV) der Bromverbindungen **12** findet man ebenso wie bei den zuvor erwähnten Kupferkomplexen **11** – bis auf **12b** – selbst bei verminderter Elektronenenergie keine Molpeaks, wofür die leichte Bromabspaltung verantwortlich ist; der weitere Fragmentierungsablauf gleicht dann wieder dem der Ketone **4** bzw. der Enole **13** (s. unten).



Zu erwähnen ist noch die „ungewöhnliche“ Bromierung von **13m**, bei der primär zunächst **12m** entsteht. Dieses geht aber unmittelbar unter der Abspaltung von *tert*-Butyl-

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640
28

bromid in Diphenyltriketon (14) über und addiert dann noch das Solvens Methanol zum Halbketal 15. Für die Richtigkeit der hier gegebenen Interpretation der Reaktion $13m \rightarrow 14$ gibt es einen unabhängigen Hinweis: α -Diazo- β -dicarbonylverbindungen reagieren mit *tert*-Butylhypochlorit unter Stickstoffabspaltung und O/Cl-Insertion, wobei primär Zwischenprodukte des Typs 12m entstehen; diese zerfallen spontan in *tert*-Butylchlorid und vicinale Tricarbonylverbindungen²¹⁾. Das ^1H -NMR-Spektrum (CDCl_3) von 15 zeigt die erwarteten Signale (s. Experimenteller Teil), nach vier Stunden hat sich aber ein Gleichgewicht mit dem gelben 14 und Methanol ($\delta = 3.43$, OCH_3) eingestellt (ca. 2:1).

Spektren der Tautomeren 4 und 13

Die Enole 13a–m zeigen im IR-Spektrum (KBr) eine breite, mehrfach aufgespaltene Absorption, wobei die Banden bei 1605 ± 5 , 1305 ± 10 und $1175 \pm 15 \text{ cm}^{-1}$ besonders deutlich hervortreten (s. Tabelle 1); zusätzliche Absorptionen (1495 – 1510 sowie 1215 – 1245 cm^{-1}) treten nur bei den Aryloxyderivaten 13a–g auf. Daß in den chelatisierten Enolen *cis*-konfigurierter β -Diketone aufgrund eines weitgehenden Bindungsausgleichs sowie der Wasserstoffbrücke keine Carbonylfrequenz im üblichen Bereich und auch keine deutlich sichtbare OH-Absorption in den IR-Spektren (KBr) erscheint, ist bekannt²²⁾; ebenso kennt man das Auftreten starker Absorptionen im 1600-cm^{-1} -Bereich, die einer stark abgeschwächten CO-Frequenz zugeschrieben wird^{20, 23, 24)}.

Im Gegensatz hierzu findet man bei den isomeren β -Diketonen 4a–m die typische, aufgespaltene Carbonylabsorption (1705 ± 5 sowie $1685 \pm 10 \text{ cm}^{-1}$)^{25, 26)} neben weiteren in Tabelle 1 aufgeführten Absorptionsbanden. Die Frequenzaufspaltung resultiert offenbar aus der mechanischen Kopplung der beiden CO-Gruppen und nicht aus dem Vorliegen von Rotationsisomeren²⁷⁾.

Beweisend für die Konstitution der Enolchelate ist das in den ^1H -NMR-Spektren (CDCl_3) von 13a–m auftretende, tieffeldverschobene und konzentrationsunabhängige OH-Signal ($\delta = 15.27$ – 16.05 ; s. Tabelle 1); relativ zum unsubstituierten Dibenzoylmethan-Enol ($\delta = 16.9^{28)}$ bedeutet dies eine Abschwächung der Wasserstoffbrücke in den RO-substituierten Enolen^{29, 30)}, was vorrangig auf dem –I-Effekt der Substituenten beruhen sollte. Das gleiche Phänomen tritt auch im System α -Methoxyacetylaceton ($\delta = 14.1$)³¹⁾/Acetylaceton ($\delta = 15.6$)³²⁾ auf.

In den ^1H -NMR-Spektren (CDCl_3) der β -Diketone 4a–m tritt folgerichtig ein Methinproton auf (s. Tabelle 1), wobei dieses in den aryloxysubstituierten Verbindungen 4a–g bei deutlich tieferem Feld liegt ($\delta = 6.32$ – 6.60) als in den alkoxysubstituierten Systemen 4h–m ($\delta = 5.65$ – 5.86). Es sei noch vermerkt, daß sich das Keto/Enol-Gleichgewicht $4 \rightleftharpoons 13$ so langsam einstellt, daß bei der Aufnahme der ^1H -NMR-Spektren keine wechselseitigen Tautomerenanteile gefunden wurden.

Die Massenspektren (70 eV) der Enole 13a–m sowie der β -Diketone 4a–m zeigen frappierende Ähnlichkeit, was vermutlich entweder auf einseitiger oder auch auf gegenseitiger Isomerisierung unter der thermischen Belastung beruht. Außer bei 13m und 4m findet man schwache Molpeaks, die bei den Enolen 13 intensiver sind (5–29%) als bei den β -Diketonisomeren 4 (1–9%).

Das Molekölion zeigt eine Reihe einfacher Bindungsbrüche, die weitgehend substituentenunabhängig sind. Die Spaltung einer C/C-Bindung des β -Diketonensystems selbst

Tabelle 1. IR- und ^1H -NMR-Daten der Enole 13 a–m sowie der β -Diketone 4 a–m

Enol bzw. Keton	IR (KBr) [cm ⁻¹]									¹ H-NMR (CDCl ₃ ; δ-Werte, J in Hz)	
	13 (Doppelbindungsbereich)					4 (Doppelbindungsbereich)				13 (=C-OH)	4 (CO-CH)
a	1600	1495	1315	1220	1170	1705/1695	1595/1570	1485	1450	16.05	6.47
b	1610	1510	1315	1215	1190	1705/1695	1605/1590	1515	1455	15.93	6.32
c	1600	1495	1305	1225	1180	1700/1685	1605/1590	1510	1450	15.98	6.39
d	1600	1495	1305	1225	1180	1705/1690	1605/1590	1515	1460	16.00	6.37
e	1600	1485	1295	1215	1160	1705/1690	1605/1590	1495	1460	15.97	6.39
f	1610	1505	1315	1245	1175	1700/1685	1605/1590	1510	1455	15.97	6.53
g	1600	1495	1315	1230	1175	1700/1685	1600/1585	1500	1455	15.98	6.60
h	1605		1305		1175	1700/1675	1595/1580		1450	15.78	5.65
i	1605		1310		1180	1710/1685	1605/1590		1560	15.78	5.71
j	1605		1305		1180	1710/1685	1605/1590		1460	15.73	5.68
k	1610		1305		1185	1705/1695	1605/1590		1460	15.70	5.67
l	1600		1300		1175	1705/1695	1605/1590		1460	15.62	5.78
m	1600		1300		1180	1705/1685	1600/1585		1455	15.27	5.86

Tabelle 2. Massenspektrometrische Fragmentierung der Enole 13a-m und der β -Diketone 4a-m.

Fragmente (m/e; % relative Intensität, in Klammern die entsprechenden Werte von 4a-m)												
Enol	$C_4H_3^+$	$O=C=CH-C=O^+$	Ph^+	$Ph-\overset{+}{C}=\overset{+}{O}H$	$Ph-\overset{+}{C}=CH-C=\overset{+}{O}$ OH				$Ph-\overset{+}{C}=\overset{+}{O}H$ R	R^+	$R-\overset{+}{O}H$	$R-C=\overset{+}{O}$
	51	69	77	106	147	223	224	240	M - 133	M - 239	R + 17	R + 28
13a	10 (8)		49 (40)	10 (10)		6 (5)	(7)		12 (7)	a)		b)
13b	6 (8)	(8)	39 (36)	10 (9)	(5)	5 (27)	(7)		32 (9)	6	15 (7)	6
13c	18 (33)	5 (57)	52 (73)	10 (11)	(32)	(43)	(37)		6 (4)	4 (8)	18	
13d	8 (14)		43 (60)	10 (10)		3 (4)			13 (5)	3 (7)		6 (4)
13e	7 (4)		38 (32)	10 (9)		(4)			5 (3)			
13f	13 (8)	26	48 (42)	10 (10)	14	23	16		4 (5)		3	
13g	7 (5)		43 (35)	9 (9)		(3)			5 (3)			
13h	10 (5)		42 (34)	10 (9)								
13i	9 (6)		39 (36)	12 (10)						3		
13j	12 (7)		48 (38)	19 (11)				5		6 (6)		
13k	7 (6)		32 (28)	11 (12)				5 (3)		4 (5)		
13l	10 (5)		42 (28)	24 (9)				29 (3)		5 (5)		
13m	5 (8)		28 (32)	14 (11)				10 (3)		18 (11)		

^{a)} Identisch mit Ph^+ aus der Spaltung der Ph/CO -Bindung. — ^{b)} Identisch mit dem Basispeak $PhCO^+$.

0.3
6.4
2.8

liefert das Benzoylkation ($m/e = 105$), das zugleich den Basispeak darstellt; in dessen Gefolge treten die Fragmente $m/e = 51$ und 77 auf (s. Tabelle 2). Die Bildung des ebenfalls durchgängig auftretenden Bruchstücks $m/e = 106$ könnte unmittelbar von den Enolen **13a–m** ausgehen. Der R^+ -Peak tritt verständlicherweise umso deutlicher hervor, je stabiler das betreffende Carbeniumion ist; am markantesten ist er naturgemäß bei **13m** bzw. **4m** (s. Tabelle 2). Die völlige Abspaltung des RO-Restes gibt Anlaß zur Bildung von $m/e = 223$; sie wird nur bei Aryloxysubstitution beobachtet. Im Falle von **13b** und **c** bzw. **4b** und **c** ist sie von dem Entstehen des Molekülions von Dibenzoylmethan ($m/e = 224$) begleitet, das von den für diese Verbindung charakteristischen Fragmentationen $m/e = 147$ bzw. 69 begleitet wird³³⁾ (s. Tabelle 2). – Ferner treten in einigen Fällen (**b**, **c** und **f**) Bruchstücke der Massenzahlen $R + 17$ sowie 240 (bei **j–m**) auf; sie sind mit Wasserstoffwanderungen verknüpft. Umlagerungen unter der Beteiligung von Kohlenwasserstoffresten sind für das Auftreten der Fragmente $M - 133$ sowie $R + 28$ verantwortlich, die beide nur bei Aryloxysubstitution von **13** und **4** auftreten (s. Tabelle 2).

Dem Fonds der Chemischen Industrie danken wir für finanzielle Unterstützung. Frau M. Alester schulden wir Dank für die Durchführung der Elementaranalysen, Herrn G. Haage für die Aufnahme der ^1H -NMR- und MS-Spektren.

Experimenteller Teil

Die Schmelzpunkte wurden im Kupfer-Heizblock bestimmt und sind unkorrigiert. – Die Elementaranalysen wurde nach dem Verfahren von Merz und Pfab³⁴⁾ durchgeführt. – IR-Spektren: Gerät Beckman IR 20 A; ^1H -NMR-Spektren: Gerät Varian NV 14 (Tetramethylsilan als innerer Standard); Massenspektren: Gerät Varian MAT 311. – Bei allen Umsetzungen wurden wasserfreie Lösungsmittel eingesetzt.

Versuche mit 2-Diazo-1,3-diphenylpropan-1,3-dion (**1**)

2-Methoxy-1,3-diphenylpropan-1,3-dion (4h) aus **1**: Die Lösung von $12.5\text{ g } 1^{\text{g})}$ in 150 ml Methanol wird nach Zusatz von 1 g Kupferpulver und 5 Tropfen 70proz. Perchlorsäure 1 h unter Rückfluß erhitzt (100% Stickstoff). Nach Filtrieren wird bei 30°C i. Vak. eingedampft, der Rückstand in 200 ml Ether gelöst, zweimal mit je 50 ml Wasser gewaschen und über Natriumsulfat getrocknet. Nach erneutem Eindampfen, Aufnehmen des zurückbleibenden Öles in wenig Methanol und Kühlen auf Trockeneis erhält man 5.3 g (42%) farbloses **4h** vom Schmp. 77°C (aus Methanol) (Lit.¹⁴⁾: $77 - 78^\circ\text{C}$). – Analytische und spektroskopische Daten s. Tabellen 1, 2 und 4.

2-Oxo-2,3-diphenylpropansäure-methylester (5a): $10.0\text{ g } 1^{\text{g})}$ in 500 ml Methanol/Schwefelsäure $2:1$ werden 40 h bei Raumtemp. gerührt, mit 21 Wasser verdünnt und zweimal mit je 500 ml Ether ausgeschüttelt. Nach Trocknen über Natriumsulfat und Eindampfen i. Vak. wird der ölige Rückstand in wenig Methanol gelöst und bei -20°C gekühlt, wobei man 4.0 g (39%) farbloses **5a** vom Schmp. $73 - 74^\circ\text{C}$ (aus Methanol) erhält (Lit.³⁵⁾: $74 - 75^\circ\text{C}$). – IR (KBr): $1679, 1748\text{ cm}^{-1}$ (CO). – ^1H -NMR (CDCl_3): $\delta = 3.72$ (s, OCH_3), 5.63 (s, *tert*-CH). – Erhitzen von **5a** in halbkonzentrierter Salzsäure (6 h) liefert Desoxybenzoin vom Schmp. 55°C (Lit.³⁶⁾: $55 - 56^\circ\text{C}$). IR-Vergleich mit authentischer Probe.

2-Oxo-2,3-diphenylpropansäure-phenylester (5b): Zu 150 ml Phenol gibt man $12.5\text{ g } 1^{\text{g})}$ sowie 1.0 g Kupferpulver und erhitzt 30 min auf $90 - 100^\circ\text{C}$ (100% Stickstoff). Man filtriert heiß und

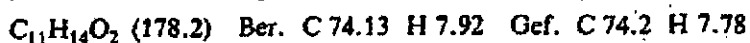
destilliert das überschüssige Phenol bei 85°C/12 Torr ab, wobei 12.2 g (77%) farbloses 5b vom Schmp. 121°C (aus Methanol) zurückbleiben. – IR (KBr): 1675, 1772 cm⁻¹ (CO). – ¹H-NMR (CDCl₃): δ = 5.85 (s, *tert*-CH). – Die saure Hydrolyse gemäß der von 5a liefert ebenfalls Desoxybenzoin.

Kupferchelate 11a – m

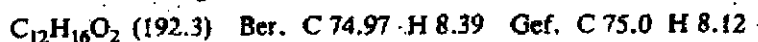
2-Brom-1,3-diphenylpropan-1,3-dion (9): Die 40–45°C warme Lösung von 56.1 g (0.25 mol) 1,3-Diphenylpropan-1,3-dion und 25.3 g (0.25 mol) Triethylamin in 800 ml Methanol läßt man unter Rühren zu der Lösung von 40.0 g (0.25 mol) Brom und 51.7 g (0.3 mol) 47proz. Bromwasserstoffsäure in 200 ml Methanol fließen. Die fast farblose Lösung wird mit 1 l Wasser verdünnt und das ausgeschiedene 9 ohne Trocknen aus 500 ml Methanol umkristallisiert. Kühlen auf 0°C liefert 65.1 g (86%) farblose Kristalle vom Schmp. 92°C (Lit.¹⁶: 92–93°C).

ω-Alkoxyacetophenone 6h – m: Die Synthese von 6h, l, i und m ist in Lit.¹⁵ beschrieben.

ω-Propoxyacetophenon (6j): Die Lösung von 146.2 g (1.0 mol) ω-Diazoacetophenon³⁷ in 1.5 l Propylalkohol wird mit 0.2 g Kupfer(II)-acetylacetonat unter Rühren im Wasserbad erwärmt. Bei 50–60°C kommt es zu heftiger Stickstoffentwicklung, nach deren Beendigung noch 2 h unter Rückfluß erhitzt wird. Nach Eindampfen i. Vak. wird der dunkelbraune Rückstand fraktionierend destilliert. Ausb. 74.1 g (42%) fast farbloses 6j vom Sdp. 67–69°C/0.04 Torr. – IR (Film): 1710 cm⁻¹ (CO). – ¹H-NMR (CDCl₃): δ = 4.68 (s, CO–CH₂).



ω-Butoxyacetophenon (6k): Aus 146.2 g (1.0 mol) ω-Diazoacetophenon³⁷, 1.5 l Butylalkohol und 0.2 g Kupfer(II)-acetylacetonat erhält man gemäß voranstehender Vorschrift 102.3 g (53%) fast farbloses 6k vom Sdp. 100°C/0.007 Torr. – IR (KBr): 1710 cm⁻¹ (CO). – ¹H-NMR (CDCl₃): δ = 4.67 (s, CO–CH₂).



Kupferchelate 11h – m durch Kondensation. – *Allgemeine Vorschrift:* Zu der Suspension aus 2.2 g einer 55proz. Natriumhydridpaste (50 mmol) in 50 ml Ether tropft man unter Stickstoff und bei Rühren 25 mmol Acetophenon 6h–l in 100 ml Ether innerhalb von 30 min. Zu dem Reaktionsgemisch tropft man anschließend 5.0 g (25 mmol) Benzoesäure-phenylester³⁸ in 50 ml Ether im Laufe von 60 min und erhitzt dann 5 h unter Rückfluß. Im Falle von 11m werden Benzoesäure-phenylester und 6m in 150 ml Ether zusammen zur Natriumhydridsuspension getropft und 60 h bei Raumtemp. gerührt. Man gießt auf 100 ml Eis/Wasser, schüttelt die Etherphase zweimal mit je 50 ml Wasser aus und tropft die vereinigten wäßrigen Phasen unter Rühren zu einer heißen Kupfer(II)-acetat-Lösung [0.6 g (10 mmol) Eisessig und 0.8 g (10 mmol) Natriumacetat in 100 ml Wasser werden mit 4.5 g (25 mmol) Kupfer(II)-acetat versetzt, kurz zum Sieden erhitzt und filtriert]. Die olivgrünen Kupferchelate 11h – m werden abgesaugt, mit viel heißem Wasser gewaschen und im Luftstrom getrocknet. – Ausbeuten, Zersetzungspunkte und analytische Daten in Tabelle 3.

Kupferchelate 11a – g durch nukleophile Substitution. – *Allgemeine Vorschrift:* Die Lösung von 6.1 g (20 mmol) 9, 4.2 g (42 mmol) Triethylamin und 21 mmol Phenol 10 in 30 ml Aceton wird kräftig gerührt, wobei es nach wenigen Minuten zur Abscheidung von Triethylammoniumbromid kommt. Man erhitzt 90 min unter Rückfluß, verdünnt nach Abkühlen mit 100 ml Methanol, wobei sich das Salz auflöst und fügt 1.8 g (10 mmol) Kupfer(II)-acetat in 50 ml Methanol zu. Die olivgrünen Kupferchelate 11a – g werden abgesaugt, zweimal mit je 100 ml Methanol ausgekocht und bei 40°C/0.1 Torr getrocknet. – Ausbeuten, Zersetzungspunkte und analytische Daten in Tabelle 3.

Tabelle 3. Analytische Daten der Kupferchelate 11a – m

11	-1,3-propandionato]kupfer(II)	% Ausb.	Zers.-P. [°C] ^{a)}	Summenformel (Molmasse)	Analyse		
					C	H	
a	Bis[2-phenoxy-1,3-diphenyl-	74	220	C ₄₂ H ₃₀ O ₆ Cu (694.2)	Ber. 72.66 Gef. 72.5	4.36 4.39	
b	Bis[2-(<i>p</i> -methoxyphenoxy)-1,3-diphenyl-	64	200	C ₄₄ H ₃₄ O ₈ Cu (754.3)	Ber. 70.06 Gef. 70.0	4.54 4.51	
c	Bis[2-(<i>p</i> -methylphenoxy)-1,3-diphenyl-	67	220	C ₄₄ H ₃₄ O ₆ Cu (722.3)	Ber. 73.17 Gef. 72.9	4.74 4.74	
d	Bis[2-(<i>p</i> -fluorphenoxy)-1,3-diphenyl-	66	230	C ₄₂ H ₂₈ F ₂ O ₆ Cu (730.2)	Ber. 69.08 Gef. 68.9	3.86 3.92	
e	Bis[2-(<i>p</i> -Bromphenoxy)-1,3-diphenyl-	73	230	C ₄₂ H ₂₈ BrO ₆ Cu (852.1)	Ber. 59.21 Gef. 59.0	3.31 3.38	
f	Bis[2-(<i>p</i> -Cyanphenoxy)-1,3-diphenyl-	74	240	C ₄₄ H ₂₈ N ₂ O ₆ Cu (744.3)	Ber. 71.01 Gef. 71.3	3.79 ^{b)} 3.87	
g	Bis[2-(<i>p</i> -nitrophenoxy)-1,3-diphenyl-	77	210	C ₄₂ H ₂₈ N ₂ O ₁₀ Cu (784.2)	Ber. 64.33 Gef. 64.1	3.60 ^{c)} 3.65	
h	Bis[2-methoxy-1,3-diphenyl-	53	200	C ₃₂ H ₂₆ O ₆ Cu (570.1)	Ber. 67.42 Gef. 67.6	4.60 4.56	
i	Bis[2-ethoxy-1,3-diphenyl-	50	200	C ₃₄ H ₃₀ O ₆ Cu (598.2)	Ber. 68.27 Gef. 68.3	5.06 5.11	
j	Bis[1,3-diphenyl-2-propoxy-	42	190	C ₃₆ H ₃₄ O ₆ Cu (626.2)	Ber. 69.05 Gef. 68.9	5.47 5.36	
k	Bis[2-butoxy-1,3-diphenyl-	41	180	C ₃₈ H ₃₈ O ₆ Cu (654.3)	Ber. 69.76 Gef. 69.5	5.85 5.81	
l	Bis[2-isopropoxy-1,3-diphenyl-	45	190	C ₃₆ H ₃₄ O ₆ Cu (626.2)	Ber. 69.05 Gef. 69.0	5.47 5.53	
m	Bis[2-(<i>tert</i> -butoxy)-1,3-diphenyl-	46	190	C ₃₈ H ₃₈ O ₆ Cu (654.3)	Ber. 69.76 Gef. 69.9	5.85 5.78	

^{a)} Genaue Angaben sind nicht möglich, da sich die Verbindungen über einen größeren Temperaturbereich nur langsam zersetzen. – ^{b)} Ber. N 3.76, gef. N 3.6. – ^{c)} Ber. N 3.57, gef. N 3.5.

Enole 13a – m

Enole 13a – m durch Zersetzung der Kupferchelate 11a – m. – Allgemeine Vorschrift: Die Suspension von 1.0 g 11a – m in 100 ml Ether wird im Scheidetrichter mit 50 ml eiskalter 50proz. Schwefelsäure unterschichtet und kräftig geschüttelt. Die wäßrige Phase wird abgetrennt, mit 100 ml Ether gewaschen, und die vereinigten Etherphasen werden über Natriumsulfat getrocknet. Entfernen des Lösungsmittels bei 25°C/12 Torr, Lösen des Rückstandes in 5 – 10 ml Methanol und Kühlen im Trockeneis/Methanol-Bad liefert die Enole 13a – m als gelbe Kristalle. Die α -alkoxysubstituierten Enole 13h – m zeigen nach nochmaliger Rekristallisation aus Methanol einen Reinheitsgrad von mindestens 99.5%³⁹⁾. Die α -aryloxysubstituierten Enole 13a – g werden folgendermaßen weitergereinigt: Man nimmt das Rohprodukt in 50 ml 0.1 N Kaliumhydroxid auf, filtriert, gießt die alkalische Lösung unter kräftigem Rühren auf 500 ml 0.1 N Schwefelsäure und extrahiert die Emulsion mit 100 ml Ether. Nach Trocknen über Natriumsulfat, Eindampfen und Umkristallisieren aus 5 ml Methanol werden die Enole 13a – g mit einem Reinheitsgrad von mindestens 99.8%³⁹⁾ erhalten. – Ausbeuten, Schmelzpunkte und analytische Daten in Tabelle 4.

Isomerisierung der Enole 13a – m zu den β -Diketonen 4a – m. – Allgemeine Vorschrift: 1.0 g Enol 13a – m in 50 ml Methanol/Wasser 1:1 wird 5 h unter Rückfluß erhitzt, nach Abkühlen mit 500 ml Wasser versetzt und mit 200 ml Ether extrahiert. Die wäßrige Phase wird nochmals mit

Tabelle 4. Analytische Daten der Enole 13a – m und der β -Diketone 4a – m

-1-propen-2-on (13) -propan-1,3-dion (4)	% Ausb.	Schmp. [°C]	Summenformel (Molmasse)	Analyse		
					C	H
1-Hydroxy-2-phenoxy-1,3-diphenyl- (13a)	13a: 70	13a: 98 – 100 ^{a)}	$C_{21}H_{16}O_3$ (316.4)	Ber.	79.73	5.10
2-Phenoxy-1,3-diphenyl- (4a)	4a: 50	4a: 123		Gef. 13a:	79.8	5.13
				Gef. 4a:	79.8	5.07
1-Hydroxy-2-(p-methoxyphenoxy)- 1,3-diphenyl- (13b)	13b: 61	13b: 89 – 90	$C_{22}H_{18}O_4$ (346.4)	Ber.	76.24	5.24
2-(p-Methoxyphenoxy)-1,3-diphenyl- (4b)	4b: 49	4b: 123		Gef. 13b:	76.3	5.19
				Gef. 4b:	76.4	5.21
1-Hydroxy-2-(p-methylphenoxy)- 1,3-diphenyl- (13c)	13c: 55	13c: 84 – 85	$C_{22}H_{18}O_3$ (330.4)	Ber.	79.98	5.49
2-(p-Methylphenoxy)-1,3-diphenyl- (4c)	4c: 43	4c: 107		Gef. 13c:	79.8	5.45
				Gef. 4c:	79.7	5.48
1-Hydroxy-2-(p-fluorphenoxy)- 1,3-diphenyl- (13d)	13d: 67	13d: 109 – 110	$C_{21}H_{15}FO_3$ (334.4)	Ber.	75.44	4.52
2-(p-Fluorphenoxy)-1,3-diphenyl- (4d)	4d: 45	4d: 112		Gef. 13d:	75.5	4.57
				Gef. 4d:	75.6	4.58
2-(p-Bromphenoxy)-1-hydroxy-1,3- diphenyl- (13e)	13e: 53	13e: 122 – 123	$C_{21}H_{15}BrO_3$ (395.3)	Ber.	63.81	3.83
2-(p-Bromphenoxy)-1,3-diphenyl- (4e)	4e: 47	4e: 138		Gef. 13e:	63.8	3.87
				Gef. 4e:	63.7	3.86
2-(p-Cyanphenoxy)-1-hydroxy- 1,3-diphenyl- (13f)	13f: 56	13f: 108 – 109	$C_{22}H_{15}NO_3$ (341.4)	Ber.	77.41	4.43 ^{b)}
2-(p-Cyanphenoxy)-1,3-diphenyl- (4f)	4f: 59	4f: 127		Gef. 13f:	77.5	4.47
				Gef. 4f:	77.4	4.48
1-Hydroxy-2-(p-nitrophenoxy)- 1,3-diphenyl- (13g)	13g: 50	13g: 124	$C_{21}H_{15}NO_3$ (361.4)	Ber.	69.80	4.18 ^{c)}
2-(p-Nitrophenoxy)-1,3-diphenyl- (4g)	4g: 57	4g: 133		Gef. 13g:	69.6	4.21
				Gef. 4g:	70.1	4.16
1-Hydroxy-2-methoxy-1,3-di- phenyl- (13h)	13h: 50	13h: 61 – 63	$C_{16}H_{14}O_3$ (254.3)	Ber.	75.58	5.55
2-Methoxy-1,3-diphenyl- (4h)	4h: 59	4h: 77 ^{d)}		Gef. 13h:	75.4	5.52
				Gef. 4h:	75.4	5.51

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Tabelle 4 (Fortsetzung)

-1-propen-2-on (13) -propan-1,3-dion (4)	% Ausb.	Schmp. [°C]	Summenformel (Molmasse)	Analyse	
				C	H
2-Ethoxy-1-hydroxy-1,3-diphenyl- (13i)	13i: 54	13i: 57–59	$C_{17}H_{16}O_3$ (268.3)	Ber.	76.10 6.02
2-Ethoxy-1,3-diphenyl- (4i)	4i: 37	4i: 57		Gef. 13i: 76.1 6.05	
1-Hydroxy-1,3-diphenyl-2- propoxy- (13j)	13j: 80	13j: 55–56	$C_{18}H_{18}O_3$ (282.3)	Ber.	76.57 6.43
1,3-Diphenyl-2-propoxy- (4j)	4j: 53	4j: 60		Gef. 13j: 76.5 6.36	
2-Butoxy-1-hydroxy-1,3-di- phenyl- (13k)	13k: 64	13k: 48–49	$C_{19}H_{20}O_3$ (296.4)	Ber.	77.00 6.80
2-Butoxy-1,3-diphenyl- (4k)	4k: 44	4k: 72		Gef. 13k: 76.9 6.74	
1-Hydroxy-2-isopropoxy-1,3-di- phenyl- (13l)	13l: 78	13l: 65–66	$C_{18}H_{18}O_3$ (282.3)	Ber.	76.57 6.43
2-Isopropoxy-1,3-diphenyl- (4l)	4l: 37	4l: 78		Gef. 13l: 76.5 6.41	
2-(tert-Butoxy)-1-hydroxy-1,3-di- phenyl- (13m)	13m: 70	13m: 88–89	$C_{19}H_{20}O_3$ (296.4)	Ber.	77.00 6.80
2-(tert-Butoxy)-1,3-diphenyl- (4m)	4m: 57	4m: 112		Gef. 13m: 77.1 6.79	
				Gef. 4m: 76.7 6.78	

a) In Lit. ¹⁴⁾ fälschlicherweise für 4a angegeben. – b) Ber. N 4.10, gef. 13f: 4.0, gef. 4f: 4.1. – c) Ber. N 3.88, gef. 13g: 3.9, gef. 4g: 4.0. – d) Lit. ¹⁴⁾ 77–78°C.

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50 ml Ether ausgeschüttelt. Die vereinigten Etherextrakte werden über Natriumsulfat getrocknet, eingedampft und aus 5–10 ml Methanol umkristallisiert – ggf. unter Zusatz von Aktivkohle –, wobei man die farblosen β -Diketone 4a–m erhält. – Ausbeuten, Schmelzpunkte und analytische Daten in Tabelle 4.

α -Brom- β -diketone 12a–l. – *Allgemeine Vorschrift:* Die Lösung von 5 mmol Enol 13a–l in 10 ml warmem Methanol wird mit 0.8 g (5 mmol) Brom in 10 ml Methanol versetzt, wobei es zu rascher Entfärbung kommt. Eindampfen bei 30°C/12 Torr, Aufnehmen des Rückstandes in 100 ml Wasser, Ausschütteln mit 50 ml Ether, Trocknen über Natriumsulfat und Entfernen des Lösungsmittels i. Vak. liefert die farblosen α -Brom- β -diketone 12a–l, die noch aus Methanol umkristallisiert werden. – Ausbeuten, Schmelzpunkte und analytische Daten in Tabelle 5.

Tabelle 5. Analytische Daten der α -Brom- β -diketone 12a–l

12	-propan-1,3-dion	% Ausb.	Schmp. [°C]	Summenformel (Molmasse)	Analyse C N		
a	2-Brom-2-phenoxy-1,3-diphenyl-	69	101	C ₂₁ H ₁₅ BrO ₃ (395.3)	Ber. 63.81 Gef. 63.4	3.83 3.79	
b	2-Brom-2-(<i>p</i> -methoxyphenoxy)-1,3-diphenyl-	68	91	C ₂₂ H ₁₇ BrO ₄ (425.3)	Ber. 62.13 Gef. 62.1	4.03 3.97	
c	2-Brom-2-(<i>p</i> -methylphenoxy)-1,3-diphenyl-	71	107	C ₂₂ H ₁₇ BrO ₃ (409.3)	Ber. 64.56 Gef. 64.3	4.19 4.17	
d	2-Brom-2-(<i>p</i> -fluorphenoxy)-1,3-diphenyl-	82	110	C ₂₁ H ₁₄ BrFO ₃ (413.3)	Ber. 61.04 Gef. 61.1	3.41 3.40	
e	2-Brom-2-(<i>p</i> -bromphenoxy)-1,3-diphenyl-	67	106	C ₂₁ H ₁₄ Br ₂ O ₃ (474.2)	Ber. 53.20 Gef. 53.3	2.98 2.96	
f	2-Brom-2-(<i>p</i> -cyanphenoxy)-1,3-diphenyl-	73	128	C ₂₂ H ₁₄ BrNO ₃ (420.3)	Ber. 62.88 Gef. 63.1	3.36 ^{a)} 3.36	
g	2-Brom-2-(<i>p</i> -nitrophenoxy)-1,3-diphenyl-	72	144	C ₂₁ H ₁₄ BrNO ₃ (440.3)	Ber. 57.29 Gef. 57.5	3.21 ^{b)} 3.23	
h	2-Brom-2-methoxy-1,3-diphenyl-	69	79	C ₁₆ H ₁₃ BrO ₃ (333.2)	Ber. 57.68 Gef. 57.7	3.93 3.89	
i	2-Brom-2-ethoxy-1,3-diphenyl-	52	85	C ₁₇ H ₁₅ BrO ₃ (347.2)	Ber. 58.81 Gef. 58.8	4.35 4.43	
j	2-Brom-1,3-diphenyl-2-propoxy-	44	78	C ₁₈ H ₁₇ BrO ₃ (361.2)	Ber. 59.85 Gef. 60.0	4.74 4.72	
k	2-Brom-2-butoxy-1,3-diphenyl-	80	86	C ₁₉ H ₁₉ BrO ₃ (375.3)	Ber. 60.81 Gef. 60.8	5.10 5.17	
l	2-Brom-2-isopropoxy-1,3-diphenyl-	81	90	C ₁₈ H ₁₇ BrO ₃ (361.2)	Ber. 59.85 Gef. 60.3	4.74 4.83	

^{a)} Ber. N 3.33, gef. N 3.4. – ^{b)} Ber. N 3.18, gef. N 3.2.

2-Hydroxy-2-methoxy-1,3-diphenylpropan-1,3-dion (15): Bromiert man 1.5 g (5 mmol) 13m mit 0.8 g (5 mmol) Brom gemäß voranstehender allgemeiner Vorschrift und arbeitet entsprechend auf, so erhält man aus der Methanol-Lösung nach mehrtägigem Kühlen bei –20°C 1.0 g (75%) farbloses 15 vom Zers.-P. 103–104°C (aus Methanol) [Lit.⁴⁰⁾ 96°C]. – IR (KBr): 1690 (CO), 3420 cm^{–1} (OH). – ¹H-NMR (CDCl₃, frisch bereitete Lösung): δ = 3.32 (s, OCH₃), 5.93 (s, OH, verschwindet beim Deuterieren mit D₂O).

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alone and on admixture with the original 4(or 5)-methyl-2-nitramino-1,3-diazacyclohexene-2 (m. p. 147-148°). The recovery of original material was 6.2 g. (89% by weight).

and 2-alkylaminoimidazolines and -tetrahydropyrimidines is described. The formation of cyclic ureas, e. g., 1,3-diazacyclohexanone-2, as by-products in this reaction is discussed.

Summary

A new method of preparation of 2-alkylamino-

KINGSTON, ONTARIO

RECEIVED OCTOBER 4, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Acylation of Certain α -Alkoxy and α -Aryloxy Ketones and Esters¹

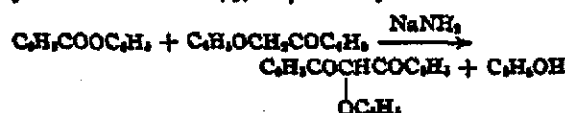
By JON MUNCH-PETERSEN² AND CHARLES R. HAUSER

Although many acylations of ketones³ and esters⁴ have been described in the literature, relatively few successful acylations of α -alkoxy and α -aryloxy ketones and esters have been reported previously. The present paper describes some new contributions to this field. Various condensing agents have been employed.

Acylation of α -Alkoxy and α -Aryloxy Ketones.—Apparently the only acylations of this type effected previously are those reported by Malkin and Robinson⁵ who acylated α -methoxy and α -4-dimethoxyacetophenone with ethyl formate using sodium ethoxide. The copper salts of the resulting β -ketoaldehydes (named as enols) were obtained in yields of 16 and 81%, respectively.⁶

We have found that, in contrast to acetophenone, α -methoxyacetophenone fails to be acylated with ethyl acetate, ethyl propionate, or ethyl benzoate, and α -phenoxyacetophenone fails to be acylated with ethyl acetate, employing sodium amide under the usual conditions.^{7a} Similarly α -methoxyacetophenone fails to be acylated with ethyl acetate employing potassium triphenylmethide⁷ in refluxing ether. In each of these cases, the methoxy or phenoxy ketone was largely recovered. However, both of these ketones may be acylated with phenyl benzoate or phenyl propionate by means of sodium amide. The benzoylations of α -methoxyacetophenone and α -

phenoxyacetophenone have been effected in yields of 26 and 59%, respectively.



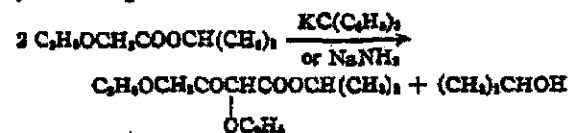
The benzoylation of α -methoxyacetophenone has also been effected with benzoyl chloride but the yield was only 11%. The propionylations of α -methoxyacetophenone and α -phenoxyacetophenone have been effected in yields of 26 and 50%, respectively; however, the latter yield is only for the copper salt.



Since some starting materials were recovered in these cases, the yields of acylation products could probably be improved.

The acylation of α -methoxyacetophenone with acetic anhydride has been effected in 10% yield by means of boron trifluoride.

Acylation of α -Alkoxy and α -Aryloxy Esters.—The self-condensation of ethyl ethoxyacetate was first reported by Conrad⁸ who used sodium, but no yield was given. Similarly, Pratt and Robinson⁹ effected the self-condensation of methyl and ethyl methoxyacetate in yields of 40-50% using sodium. Darzens and Meyer¹⁰ reported a 75% yield in the self-condensation of ethyl ethoxyacetate using sodium ethoxide. We have self-condensed isopropyl ethoxyacetate in 69% yield using potassium triphenylmethide and in 35% yield using sodium amide



The lower yield with the sodium amide may be accounted for on the basis that this reagent reacts

(8) Conrad, *Ber.*, 11, 53 (1878).

(9) Pratt and Robinson, *J. Chem. Soc.*, 183 (1925).

(10) Darzens and Meyer, *Compt. rend.*, 138, 478 (1904).

(1) Paper XLI on "Condensations"; paper XL, *This Journal*, 65, 9649 (1947).

(2) On leave of absence from the Department of Organic Chemistry, The Technical University of Denmark, Solvgade 82, Copenhagen, Denmark.

(3) See especially (a) Adams and Hauser, *This Journal*, 66, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, 67, 1510 (1945); (c) Hauser and Adams, *ibid.*, 66, 345 (1944); (d) Adams and Hauser, *ibid.*, 67, 384 (1945).

(4) See especially Hauser and Hudson, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., Vol. I, pp. 353-392.

(5) Malkin and Robinson, *J. Chem. Soc.*, 127, 1190 (1925).

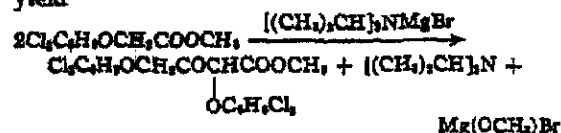
(6) We have verified this result with α -methoxyacetophenone, but the yield of the free β -ketoaldehyde was only 8%; most of the methoxy ketone was recovered. It should be pointed out that this reaction was carried out at 0° and that, when attempts were made to effect the formation of the sodium derivative of α -methoxyacetophenone (prepared with sodium amide or potassium triphenylmethide) in refluxing ether, only the methoxy ketone was recovered.

(7) Levine, Baumgarten and Hauser, *This Journal*, 66, 1220 (1944).

not only with the α -hydrogen of the ester leading to condensation but also with the carbonyl carbon resulting in the formation of ethoxyacetamide which was isolated from the reaction mixture in 35% yield. Since sodium amide self-condenses isopropyl acetate in better yield (57%)¹¹ and apparently produces little if any acetamide,¹² the substitution of an α -hydrogen of this ester by the ethoxy group evidently activates the carbonyl carbon¹³ relative to the α -hydrogen toward sodium amide.¹⁴

The self-condensation of ethyl α -ethoxypropionate could not be effected satisfactorily. With potassium triphenylmethide or sodium hydride only a small amount of product was obtained even though the ester anion appeared to be formed readily.¹⁵ With di-isopropylaminomagnesium bromide a product was obtained but it was apparently contaminated with some of the di-isopropyl amide, giving a positive test for nitrogen. Since di-isopropylaminomagnesium bromide self-condenses ethyl *n*-butyrate and ethyl isobutyrate to form a nitrogen free β -ketoester,¹⁶ the formation of some amide with the ethyl α -ethoxypropionate lends further support to the view expressed above, that the α -ethoxy group activates the carbonyl carbon relatively more than the α -hydrogen.

Ethyl phenoxyacetate was first self-condensed by Johnson and Hill¹⁷ using sodium; the yield of the sodium derivative of the β -ketoester was good, but the free β -ketoester was not isolated. We have similarly obtained a good yield (76%) of the sodium derivative of the β -ketoester using di-isopropylaminomagnesium bromide. We also self-condensed methyl 2,4-dichlorophenoxyacetate; the free β -ketoester was obtained in a 65% yield

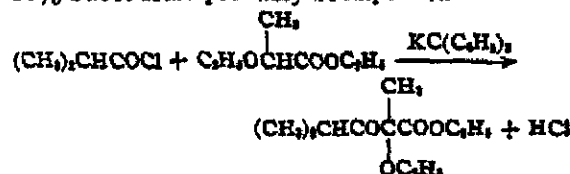


Ethyl α -phenoxypropionate and ethyl α -(2,4-dichlorophenoxy)-propionate apparently self-condensed in the presence of di-isopropylmagnesium

bromide, but the pure products were not isolated.

Apparently an alkoxy ester has not previously been acylated with a different ester. In an attempt to acylate isopropyl ethoxyacetate with phenyl benzoate using sodium amide¹¹ or potassium triphenylmethide⁷ we have obtained the self-condensation product of the ethoxyacetate (35%) even though the addition of the ethoxyacetate to the reagent was followed immediately by the addition of the phenyl benzoate.¹⁸ Since isopropyl acetate has been benzoylated with phenyl benzoate by means of sodium amide under similar conditions,¹¹ either the anion of isopropyl ethoxyacetate is acylated more slowly by phenyl benzoate than the anion of isopropyl acetate or, more likely, isopropyl ethoxyacetate undergoes self-condensation more rapidly than isopropyl acetate. This again is an indication of the above-mentioned effect of the ethoxy group.

However, we have succeeded in acylating ethyl α -ethoxypropionate with isobutyryl chloride using potassium triphenylmethide. The yield was only 15% but it could probably be improved



Koelsch and Whitney¹⁹ have acylated ethyl phenoxyacetate with ethyl oxalate and ethyl formate using sodium ethoxide. We have benzoylated ethyl α -phenoxypropionate with phenyl benzoate using sodium amide but, rather surprisingly, the β -ketoacid (13%) instead of the β -ketoester was obtained. Most of the ethyl α -phenoxypropionate was recovered.

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Experimental²⁰

α -Methoxyacetophenone²¹ and α -phenoxyacetophenone²² were prepared as described in the literature.

(18) In these experiments isopropyl benzoate was obtained in yields of 67 and 50%, respectively. This ester was identified by its boiling point and by hydrolysis to benzoic acid and isopropyl alcohol. In the experiment with sodium amide a 35% yield of ethoxyacetamide (m. p. 80°) was obtained. The isopropyl benzoate was formed, presumably, by reaction of the phenyl benzoate with the isopropoxide ion which was produced as a by-product in the self-condensation of isopropyl ethoxyacetate and, in the experiment with sodium amide, also in the formation of ethoxyacetamide.

(19) Koelsch and Whitney, *THIS JOURNAL*, 63, 1762 (1941).

(20) Boiling points and melting points are uncorrected; analyses are by Microchemical Laboratory, University of Pittsburgh, Pittsburgh, Pa.

(21) Moffett and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 31, 1941, p. 79.

(22) Mohr, *Ber.*, 15, 2428 (1882).

(11) Shivers, Dillon and Hauser, *THIS JOURNAL*, 69, 129 (1947).

(12) Hauser, Levine and Kibler, *ibid.*, 66, 36 (1946).

(13) That the carbonyl carbon is activated by the ethoxy group toward a basic anion is indicated by the six times larger rate of alkaline hydrolysis of methyl ethoxyacetate than methyl acetate. See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 312.

(14) In agreement with this, an attempt to carbonate isopropyl methoxyacetate after treatment with sodium amide failed; methoxyacetamide (m. p. 83-83°) was isolated in 70% yield. Under similar conditions isopropyl acetate gives the carbonation product (66%) and apparently none of the amide.¹¹

(15) With potassium triphenylmethide, the color of the reagent was discharged immediately, see ref. 7. With sodium hydride the calculated amount of hydrogen was evolved when equivalent amount of this reagent and the ester were refluxed in *n*-butyl ether (b. p. 140°). See Swamer and Hauser, *THIS JOURNAL*, 69, 2667 (1946).

(16) Hauser and Frostick, unpublished work from this Laboratory.

(17) Johnson and Hill, *Am. Chem. J.*, 46, 295 (1912); *THIS JOURNAL*, 34, 1026 (1912).

Isopropyl ethoxyacetate, b. p. 181°, was prepared according to the procedure for ethyl ethoxyacetate,²³ using isopropyl alcohol in the esterification of the ethoxyacetic acid.

Ethyl α -ethoxypropionate was prepared according to the same procedure,²³ using α -chloropropionic acid instead of chloroacetic acid; the ester boiled at 153–155° (reported b. p. 158°).²⁴ The over-all yield was 58%, the yield of α -ethoxypropionic acid, b. p. 80–83° at 10 mm., being 77%.

Ethyl phenoxycetate, b. p. 247–249° (reported b. p. 250°)²⁵ and ethyl α -phenoxypropionate, b. p. 242–244° and b. p. 96° at 4 mm., were obtained in 80% yields from the corresponding acids by the general method involving the saturation of an ethanolic solution of the acid with hydrogen chloride.

Ethyl α -(2,4-dichlorophenoxy)-propionate, b. p. 130–130° at 4 mm. (reported b. p. 173–176° at 12 mm.)²⁶ was prepared by esterification of α -(2,4-dichlorophenoxy)-propionic acid, m. p. 115–118° (reported m. p. 117–118°),²⁷ which was obtained in 31% yield following the procedure given by Pakorny²⁸ for 2,4-dichlorophenoxyacetic acid.

Acylations of α -Methoxy- and α -Phenoxyacetophenone by the Sodium Amide Method. Table I.—The general procedure described previously^{2,9} has been modified. To a stirred suspension of 0.2 mole of sodium amide was added an ether solution of 0.1 mole of the ketone. After ten minutes, an ether solution of the ester was added. The mixture was refluxed for two hours and then poured onto ice. The water layer, after washing with ether, was acidified and extracted with ether. The ether layer, after washing with saturated sodium bicarbonate solution and water, was dried and the solvent distilled. Treatment of the residue varied.

TABLE I

ACTYLATIONS OF ROCH ₂ COC ₂ H ₅ USING SODIUM AMIDE			
R	Acylating compound	β -Diketone	M. p. Yield, %
CH ₃	PhBz	α -Methoxydibenzoyl-methane ^a	77–78 26
C ₆ H ₅	PhBz	α -Phenoxydibenzoyl-methane ^b	97–100 50
CH ₃	BzCl	α -Methoxydibenzoyl-methane	77–78 11
CH ₃	PhPr	α -Methoxy- α -propionyl acetophenone ^c	B. p. 129–130 25 at 6 mm.
C ₆ H ₅	PhPr	α -Phenoxy- α -propionyl acetophenone	50 ^d

^a Anal. Calcd. for C₁₅H₁₄O₂: C, 75.57; H, 5.55. Found: C, 75.78; H, 5.20. ^b Anal. Calcd. for C₁₇H₁₄O₂: C, 79.73; H, 5.10. Found: C, 79.91; H, 4.90. ^c Anal. Calcd. for C₁₇H₁₆O₃: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.65. ^d Obtained as the copper salt.

In the benzoylation of α -methoxyacetophenone with phenyl benzoate the β -diketone was isolated by the copper salt method²⁹ and recrystallized from methanol.

In the benzoylation of α -phenoxyacetophenone most of the phenol was distilled off *in vacuo*. The residue, which crystallized, was brought into solution in 2 *N* sodium hydroxide. By acidifying, the β -diketone was precipitated, filtered, washed with water and a little ice-cold ethanol and finally recrystallized from ethanol.

(23) Fuson and Wojcik, "Organic Syntheses," John Wiley and Sons, Inc., N. Y., Coll. Vol. II, 1943, p. 260.

(24) Schreiner, *Ann.*, 197, 15 (1875); Furdie, *J. Chem. Soc.*, 78, 583 (1898).

(25) Morel, *Bull. soc. chim.*, [3] 21, 908 (1890).

(26) Sauerbach, *J. prakt. Chem.*, [3] 21, 142 (1880).

(27) Bloch, *Ber.*, 35, 1604 (1900).

(28) Pakorny, *Trans. J. Am. Chem. Soc.*, 65, 1708 (1941).

(29) Hauser, Rieger, Swamer and Thompson, *ibid.*, 66, 2848 (1947).

In the benzoylation of α -methoxyacetophenone with benzoyl chloride equivalent amounts of sodium amide, the ketone and benzoyl chloride were used; before adding the ketone, the ether suspension of sodium amide was refluxed for several hours.

In the propionylation of α -methoxyacetophenone with phenyl propionate the β -diketone was separated from the phenol by fractional distillation *in vacuo*.

In the propionylation of the α -phenoxyacetophenone with phenyl propionate most of the phenol was removed by heating *in vacuo* (4 mm.) in an oil-bath kept at 200° for thirty minutes. The residue, which gave a strong red enol test with ferric chloride, was treated with a saturated copper acetate solution and the copper salt³⁰ of the β -diketone crystallized by standing overnight. After washing, the yield of the copper salt was 50%. From the copper salt, the β -diketone was recovered as a brown oil, the over-all yield being 37%, but it did not crystallize.

Acetylation of α -Methoxyacetophenone by the Boron Trifluoride Method.—The general procedure described previously²⁹ has been modified. The reaction mixture of 0.2 mole of the ketone and 0.4 mole of acetic anhydride, after saturation with boron trifluoride at temperatures between –10 and 0°, was kept at 0° for one hour and at room temperature (29–30°) for another hour. The mixture was refluxed with sodium acetate for thirty minutes and cooled. After neutralization of most of the acetic acid with sodium hydroxide, the mixture was extracted with ether and the ether solution washed with sodium bicarbonate solution and water. α -Methoxybenzoyl acetone, isolated by the copper salt method, was obtained as a yellow liquid, boiling at 110–111° at 4 mm.

Anal. Calcd. for C₁₁H₁₂O₃: C, 68.78; H, 6.29. Found: C, 68.78; H, 6.12.

None of the ketone was recovered and a considerable amount of tar was obtained.

When the reaction mixture was worked up within twenty minutes after saturation below 0° as described for other ketones,²⁹ no β -diketone was obtained and the ketone was largely recovered.

Self-condensation of α -Alkoxy and α -Aryloxy Esters. Table II.—The self-condensation of isopropyl ethoxyacetate with potassium triphenylmethide was carried out according to the general procedure,¹ except that the reaction mixture was refluxed for three hours. The condensation was also effected by sodium amide³¹; in this experiment ethoxyacetamide (m. p. 80°) was isolated.

Ethyl phenoxycetate and methyl 2,4-dichlorophenoxyacetate (m. p. 39–40°)³² were self-condensed by diisopropylmagnesium bromide by adaptation of the procedure for the condensation of certain esters using diethylmagnesium bromide.³³ The reactions were generally carried out on a 0.1 or 0.2 mole scale.

To the stirred solution of ethylmagnesium bromide was added an ether solution of an equivalent of diisopropylamine, b. p. 83–84°,³⁴ and after twenty minutes an ether solution of an equivalent of the ester was added. After spontaneous refluxing ceased, the mixture was refluxed on the steam-bath for one and one-half hours. After cooling in an ice-salt-bath, crushed ice and concentrated hydrochloric acid were added and the mixture stirred until no solid was left. The ether phase, after combining with an ether extract of the aqueous phase, was stirred with 2 *N* sodium hydroxide. The white precipitate of the sodium derivative of the β -ketoester was filtered off, washed with water and dried in the air.

In the experiment with ethyl phenoxycetate the sodium derivative of the β -ketoester was a white powder, which melted under slight decomposition at 190°. It was converted into the free β -ketoester by shaking in a separatory funnel with ether and hydrochloric acid. The water layer was extracted with ether, the combined ether ex-

(30) We are indebted to J. T. Baker Chemical Company for a sample of this ester.

(31) Hauser and Walker, *Trans. J. Am. Chem. Soc.*, 69, 285 (1947).

(32) We are indebted to the Shell Chemical Corporation for a sample of this amine.

TABLE II
 SELF-CONDENSATION OF ALKOXY- AND ARYLOXYESTERS

Ester	Condensing agent	β -Ketoester	B. p. °C.	Mm.	Yield %
Isopropyl ethoxyacetate	NaNH ₂	Isopropyl α , γ -diethoxyacetoacetate	107-108	5	35
Isopropyl ethoxyacetate	KC(C ₆ H ₅) ₃	Isopropyl α , γ -diethoxyacetoacetate ^a	103-104	4	69
Ethyl phenoxyacetate	(<i>i</i> -Pr) ₂ NMgBr	Ethyl α , γ -diphenoxyacetoacetate ^a			63 ^a
Methyl 2,4-dichlorophenoxyacetate	(<i>i</i> -Pr) ₂ MgBr	Methyl α , γ -di-(2,4-dichlorophenoxy)- acetoacetate ^{b, c}	102-104 (m. p.)		65

^a Anal. Calcd. for C₁₁H₁₄O₄: C, 56.88; H, 5.68. Found: C, 56.59; H, 5.82. ^b No nitrogen was found by the sodium fusion test. ^c The sodium derivative was obtained in 78% yield. ^d Anal. Calcd. for C₁₇H₁₄O₄Cl₂: C, 46.80; H, 2.76; Cl, 32.37. Found: C, 46.82; H, 2.78; Cl, 32.10.

tracts washed with a saturated sodium bicarbonate solution and water, and dried. After evaporation of the solvent, the β -ketoester was obtained as a yellow oil, which, however, did not crystallize. Attempts to distill the β -ketoester *in vacuo* (3 mm.) resulted in decomposition. Attempts to effect ketonic cleavage in acid²³ and slightly alkaline²⁴ solution gave phenol and tar.

In the experiment with methyl 2,4-dichlorophenoxyacetate, the sodium derivative of the β -ketoester was similarly converted into the free keto ester, and this, after evaporation of the ether, crystallized, and was recrystallized from ethanol.

Acylation of Ethyl α -Ethoxypropionate with Isobutyryl Chloride.—To an ether suspension of 0.2 mole of potassium triphenylmethide (freed from ammonia by refluxing the mixture for four hours followed by purging the apparatus with nitrogen) was added 29.2 g. (0.2 mole) of ethyl α -ethoxypropionate. The red color disappeared immediately. After ten minutes, 21.2 g. (0.2 mole) of isobutyryl chloride was added. After refluxing on the steam-bath for three hours, the mixture was poured onto ice and 5 ml. of glacial acetic acid. The ether layer, after combining with an ethereal extract of the aqueous phase, was washed with saturated sodium bicarbonate solution, then with water, and dried. The solvent was distilled and the residue fractionated *in vacuo*, yielding 53% of the original ester and 10 g. of crude β -ketoester. Redistillation gave 6.5 g. (15%) of ethyl α -isobutyryl- α -ethoxypropionate, b. p. 75-76° at 4 mm.

Anal. Calcd. for C₁₁H₁₆O₄: C, 61.08; H, 9.22. Found: C, 61.31; H, 9.41.

Benzylation of Ethyl α -Phenoxypropionate with Phenyl Benzoate.—To the stirred suspension of 0.1 mole of sodium amide was added an ether solution of 19.4 g. (0.1 mole) of ethyl α -phenoxypropionate. After fifteen minutes, an ether solution of 19.8 g. (0.1 mole) of phenyl benzoate was added. The mixture was refluxed on the steam-bath for one hour and then poured onto ice and hydrochloric acid. The water layer was extracted with ether. The combined ether phase was extracted with sodium hy-

dride solution. From the ether phase there was recovered 70% of ethyl α -phenoxypropionate, b. p. 241-245° and 20% of the phenyl benzoate, m. p. 68°. Acidification of the alkaline extract yielded a precipitate from which, after fractional crystallization, there was obtained 0.3 g. of α -phenoxypropionic acid, m. p. 114-115° (reported m. p. 115-116°)²⁴ and 3.5 g. (13%) of α -benzoyl- α -phenoxypropionic acid, m. p. 135-137°, neutr. equiv.: Calcd. 270.3; found 270.3 and 270.8.

Anal. Calcd. for C₁₅H₁₄O₄: C, 71.10; H, 5.22. Found: C, 71.47; H, 5.35.

Summary

1. Although α -methoxy- and α -phenoxyacetophenone failed to be acylated with ethyl acetate, ethyl propionate, and ethyl benzoate by the sodium amide method, these ketones have been acylated with phenyl propionate and phenyl benzoate. α -Methoxyacetophenone has been acetylated by the boron trifluoride method.

2. Isopropyl ethoxyacetate has been self-condensed by potassium triphenylmethide and by sodium amide; ethyl phenoxyacetate and methyl 2,4-dichlorophenoxyacetate have been self-condensed by diisopropylaminomagnesium bromide.

3. Ethyl α -ethoxypropionate has been acylated with isobutyryl chloride by potassium triphenylmethide.

4. Certain related condensations have been studied. The effect of the α -ethoxy group on the relative reactivities of the carbonyl carbon and the α -hydrogen of esters has been considered.

DURHAM, N. C.

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(23) Hudson and Hauser, THIS JOURNAL, 66, 2168 (1941).

(24) Bischoff, Ber., 32, 926 (1903).

Reaction of Some 1,2-Diaza-1,3-butadienes with Activated Methine Compounds. A Straightforward Entry to 1,4-Dihydropyridazine, Pyridazine, and 4,5(4*H*,5*H*)-Cyclopropylpyrazole Derivatives

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1-Aminocarbonyl-1,2-diaza-1,3-butadienes with β -tri- or β -dicarbonyl compounds containing at least two keto functions give 1,4-dihydropyridazines, while hydrazone 1,4-adducts are obtained in the case of compounds containing one or no keto function. 1,4-Dihydropyridazines are transformed into pyridazines. The same substrates with 3-phenoxy-pentane-2,4-dione afford pyridazines. Surprisingly, 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes with methyl 2-acetylacetoacetate produce 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles deriving from 1-alkoxycarbonyl-1,2-dihydropyridazine intermediates by ring contraction. These pyrazole derivatives with acetic acid show ring expansion to 1-alkoxycarbonyl-1,4-dihydropyridazines that can be converted into 1,4-dihydropyridazines with sodium hydroxide. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles or 1-alkoxycarbonyl-1,4-dihydropyridazines with trifluoroacetic acid provide 1-aminopyrroles via 1-alkoxycarbonyl-1,4-dihydropyridazine intermediates in the case of pyrazoles. The X-ray crystal structure of 1-*tert*-butoxycarbonyl-3,5-dimethyl-4-methoxycarbonyl-4,5(4*H*,5*H*)-(methoxycarbonylcyclopropyl)-1*H*-pyrazole was determined.

Introduction

1,2-Diaza-1,3-butadienes have been demonstrated to be powerful tools in organic chemistry¹⁻³ and, in particular, in the construction of polyfunctionalized pyrrole, pyrazole, thiazole, and imidazole rings.³⁻⁵

In a previous paper, we preliminarily reported the first synthesis of some 1,4-dihydropyridazines and pyridazines by reaction of 1-aminocarbonyl-1,2-diaza-1,3-butadienes with β -tricarboxyl compounds.⁶ In fact, in the course of our activity in this field we have detected, with only one exception,⁷ that the reaction between 1,2-diaza-1,3-buta-

dienes and carbonyl compounds containing activated methylene or methine groups always generates pyrrole rather than dihydropyridazine nuclei,^{3,8} as erroneously reported by previous authors.^{9,10} This occurrence is a consequence of a domino 1,4-addition (Michael-type)-ring annulation reaction by a nucleophilic reagent bearing in the α -position to the attacking carbon atom a ketone, nitrile, or ester function on the azo-ene system of 1,2-diaza-1,3-butadienes,¹¹ concluding in a [3 + 2] instead of [4 + 2] cyclization process (Scheme 1).³ Indeed, [4 + 2] cycloadditions of Diels-Alder-type producing tetrahydropyridazine rings have been revealed when 1,2-diaza-

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(1) Schantl, J. C. 1-Azo-1-alkene. In *Houben-Weyl*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1990; Vol. E15; p 909. Schantl, J. C. *Il Farmaco* 1995, 50, 379 and the references therein.

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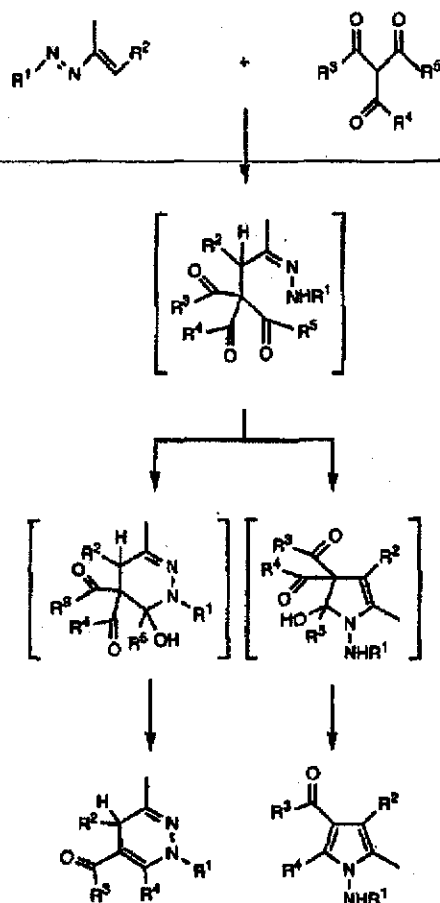
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Scheme 1



1,3-butadienes as heterodiene systems were reacted with electron-rich olefins as dienophiles.^{1,2,12,13}

The synthesis of pyridazine derivatives has recently received much attention because of their biological activity.¹⁴ In particular, South et al. (Monsanto Corp.) patented pyridazine products exhibiting "bleaching" herbicidal activity prepared from 1,2-diaza-1,3-butadienes.¹⁵

For these reasons, we decided to investigate more exhaustively the reaction of both 1-aminocarbonyl- and 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes with different β -tri- or β -dicarbonyl compounds containing activated methine groups in order to obtain pyridazine structures. Some interesting diversities in the pathway of these reactions have been observed.

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Results and Discussion

1-Aminocarbonyl-1,2-diaza-1,3-butadienes 1a-e easily react in tetrahydrofuran at room temperature with triacetyl methane 2a or methyl or ethyl 2-acetylacetoacetate 2b,c in the presence of sodium hydride or potassium carbonate to give in one flask 1-unsubstituted 1,4-dihydropyridazines 5a-m in good to excellent yields (Scheme 2 and Table 1). In most cases, potassium carbonate instead of sodium hydride as previously employed afforded less complicated reaction mixtures and better yields in final products.⁶ The mechanism proposed in Scheme 2 is the result of some mechanistic findings presented and discussed in detail below.

Under the same reaction conditions, 1a,b react with diethyl acetylmalonate 6a or triethyl methanetricarboxylate 6b, providing in high yields the hydrazones 7a,b by 1,4-addition of β -tricarbonyl derivatives to the azo-ene system (Scheme 3) and supporting the first step of the mechanism proposed in Scheme 2. Since the adducts 7a,b manifest no tendency to produce further reactions, it can be concluded that the presence of one or no keto function is not able to permit the ring closing owing to the elimination of an acetic acid molecule.

The reaction under usual conditions between 1a,d,e and ethyl 2-(2-furoyl)acetoacetate 2d or ethyl 2-(2-thenoyl)acetoacetate 2e produces a mixture of 1-unsubstituted 6-methyl- and 1-unsubstituted 6-(2-furoyl)-1,4-dihydropyridazines 5c,j,m or 1-unsubstituted 6-(2-thenoyl)-1,4-dihydropyridazines 5n-r in a similar ratio. This occurrence is likely due to the nearly equivalent possibility of ring closing on the two different keto groups of the hypothesized intermediates 3 (Scheme 4 and Table 1). The pathway A leads to the same compounds 5c,j,m depicted above (Scheme 2), while the pathway B leads to new compounds 5n-r with a furoyl or thenoyl ring as substituent.

The reaction of 1a,b,d,e with 3-phenylpentane-2,4-dione 2f or 3-(2-chloro-6-fluorobenzyl)pentane-2,4-dione 2g under the same conditions gives rise in one pot to 1-unsubstituted 1,4-dihydropyridazines 5s-v in good yields (Scheme 5 and Table 1). This behavior proves that this procedure can be successfully applicable also to compounds possessing an activated β -dicarbonyl methine group.

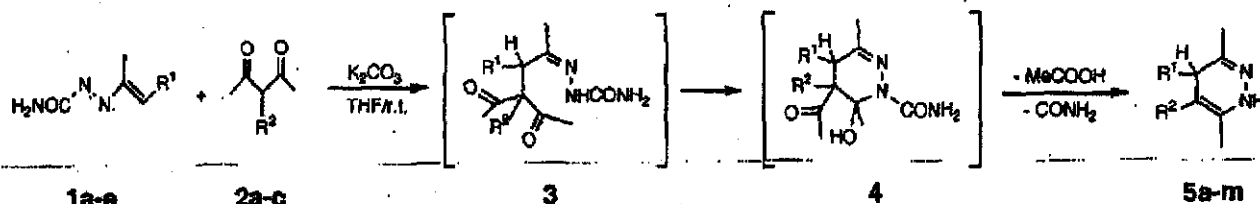
The conversion of 5a-v into the corresponding pyridazines 9a-v in nearly quantitative yields was achieved by bromination of the carbon atom in position 4 with tribromide on Amberlyst A-26 in methylene chloride at room temperature (Scheme 6 and Table 2). The use of this solid-phase brominating reagent implicated remarkable improvements with respect to phenyltrimethylammonium tribromide previously utilized by virtue of the minor presence of reaction byproducts,⁶ both in terms of regioselectivity and yields.¹⁶ Furthermore, this polymer-supported brominating agent is more convenient than phenyltrimethylammonium tribromide also due to its easy regeneration and the simpler manipulation of the reaction mixture (only filtration).¹⁷ The expected brominated intermediates 8 were not isolated because of the ready dehydrobromination process.⁶

Pyridazines 9a,d,f,h,k have been directly obtained as exclusive products when 1a-e were reacted in tetrahy-

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Scheme 2



- 1a: $R^1 = COOMe$ 2a: $R^2 = COMe$
 1b: $R^1 = COOEt$ 2b: $R^2 = COOMe$
 1c: $R^1 = COOt-Bu$ 2c: $R^2 = COOEt$
 1d: $R^1 = COO(CH_2)_2OMe$
 1e: $R^1 = COOCH_2Ph$

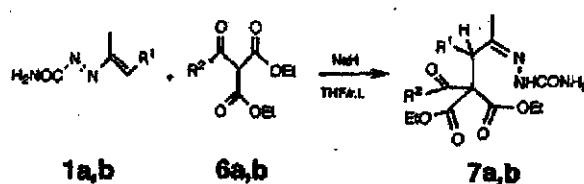
Table 1. Yields of 1-Unsubstituted-1,4-Dihydropyridazines 5a-v

Entry	R^1	R^2	Yield ^a (%)
5a	COOMe	COMe	84
5b	COOMe	COOMe	90
5c	COOMe	COOEt	58
5d	COOEt	COMe	87
5e	COOEt	COOMe	88
5f	COOt-Bu	COMe	69
5g	COOt-Bu	COOMe	83
5h	$COO(CH_2)_2OMe$	COMe	57
5i	$COO(CH_2)_2OMe$	COOMe	54
5j	$COO(CH_2)_2OMe$	COOEt	57
5k	$COOCH_2Ph$	COMe	75
5l	$COOCH_2Ph$	COOMe	74
5m	$COOCH_2Ph$	COOEt	87
5n	COOMe		43
5o	COOMe		33
5p	$COO(CH_2)_2OMe$		40
5q	$COO(CH_2)_2OMe$		34
5r	$COOCH_2Ph$		37
5s	COOMe	Ph	42
5t	COOEt		43
5u	$COO(CH_2)_2OMe$		57
5v	$COOCH_2Ph$		61

^aYield of pure isolated products.

dofuran at room temperature with 3-phenoxy-pentane-2,4-dione 2h in the presence of potassium carbonate. In this case, the intermediates 3 and 4, as well as the product 5, were not detected probably because of a rapid aromatization process due to the loss of phenol and carbamic acid residues (Scheme 7).

Scheme 3



- 1a: $R^1 = COOMe$ 6a: $R^2 = Me$
 1b: $R^1 = COOEt$ 6b: $R^2 = OEt$
 7a: $R^1 = COOMe, R^2 = Me$ (84 %)
 7b: $R^1 = COOEt, R^2 = OEt$ (91 %)

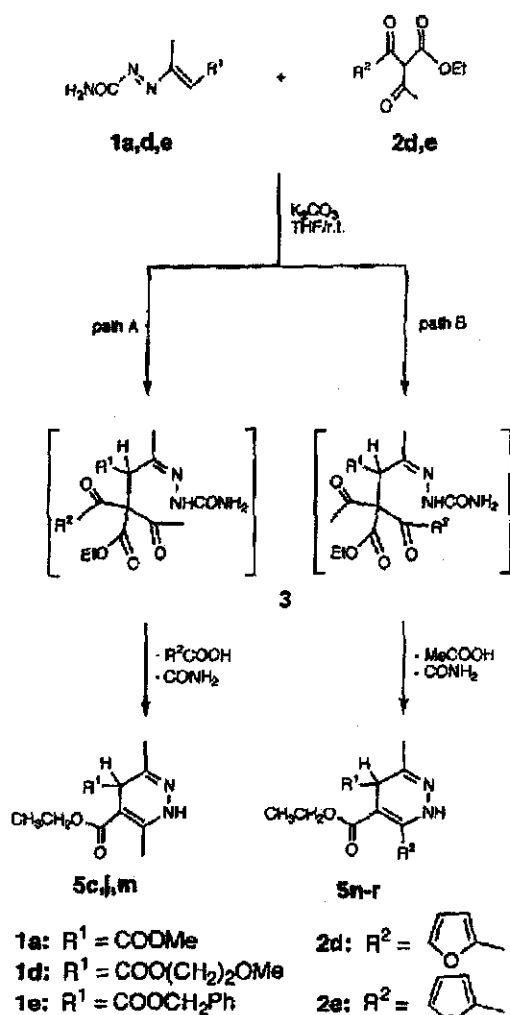
Surprisingly, the reaction between 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes 1f-h and methyl 2-acetylacetoacetate 2b in tetrahydrofuran at room temperature in the presence of potassium carbonate offered 1-alkoxycarbonyl-1,4-dihydropyridazines 14a-c and then 1-unsubstituted 1,4-dihydropyridazines 5b,e by means of a more complicated mechanism compared with that of analogous 1a-e. A detailed study of some reaction products and intermediates allowed us to obtain interesting mechanistic information.

Indeed, when the reaction was carried out under the usual conditions (Scheme 2) the isolated products were different from the expected 5b,e as well as from 14a-c. In fact, the spectroscopic data revealed that the substituent group linked to the nitrogen heteroatom of this product is still present, while in 5b,e the same group is absent. Moreover, 1H and ^{13}C NMR spectra exhibit similar resonances as for 14a-c but with some significant differences: (i) a large upfield shift of methine proton (from ~ 4.5 to ~ 2.8 ppm) in 1H NMR spectra; (ii) the presence of three $C-sp^3$ signals (~ 26.3 , ~ 50.1 , and ~ 59.0 ppm) instead of only one $C-sp^3$ resonance (~ 44.7 ppm) of compound 5b,e; (iii) the coupling constant value for the carbon that resonates at ~ 26.3 ppm is $J_{CH} = 165$ Hz, typical for a CH in a cyclopropane ring.

Therefore, all spectroscopical evidence should be fitted with molecules having the structure of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a-c. X-ray diffraction investigations were undertaken for 13c, as a model able to prove unambiguously the structure assigned to these compounds. The crystal parameters of such a molecular model unequivocally confirmed our hypothesis (Figure 1).

In particular, the TLC analysis of the reaction mixtures reveals two other spots with higher polarity than 13a-

Scheme 4



c. Attempts to isolate the more polar one were unsuccessful because of its quick transformation in the middle one followed by its conversion in **13a-c**. However, it was possible to isolate a small amount of pure middle products that demonstrated to be the 1-alkoxycarbonyl-1,2,5,6-tetrahydropyridazine derivatives **11a-c** by 1H NMR and MS spectroscopy, mainly due to the OH and NH signals at ~ 6.77 and ~ 12.84 ppm, respectively, as well as to the presence of two different methyl group signals at ~ 1.92 and ~ 2.45 ppm, respectively, attributable to two acetyl groups of the starting methyl 2-acetylacetoacetate. In tetrahydrofuran, this compound spontaneously generated exclusively **13a-c**. Thus, we suppose that the greatest polar spot corresponds to the transient hydrazone 1,4-adduct **10**.

On the basis of this evidence, it seems reasonable to conclude that the reaction takes place by means of a preliminary 1,4-addition of **2b** to the substrates **1f-h** as consequence of the nucleophilic attack by the activated methine group on the heterodiene system producing the hydrazone intermediate **10**. The subsequent intramolecular nucleophilic attack by the terminal hydrazone nitrogen atom to the carbonyl function determines the closing of **11a-c**. The elimination of an acetic acid molecule from this last intermediate furnishes **12**, which

affords **13a-c** owing to ring contraction of the six- to five-membered heterocycle (Scheme 8).

Further proof of the interconversion between these heterocyclic structures was furnished upon reaction of **13a-c** with acetic acid at room temperature, determining ring expansion to **14a-c** that in turn afforded **5b,e** by cleavage with sodium hydroxide in methanol at room temperature (Scheme 9).

In our opinion, the preliminary hydrazone intermediates **3** and **10** in the reactions both of **1a-e** and **1f-h** with activated methine compounds previously detected in similar circumstances³ and indirectly supported by the 1,4-adducts **7a,b** can be considered common for all these reactions. However, the absence of any detectable intermediate, as well as the concomitant loss of the $CONH_2$ group, in the case of **1a-e** hinder us to extend in toto or in part the remaining detailed mechanism established for the reactions of **1f-h** on the basis of isolable intermediates.

When **13a-c** were reacted with trifluoroacetic acid at room temperature (**13c**) or under reflux (**13a,b**), the corresponding 1-aminopyrroles **15a-c** were recovered. The same products were obtained when **14a-c** were submitted to the same reaction (Scheme 10). In both cases, **5b,e** were revealed as side products of these reactions.

Therefore, taking into account the reaction pathway depicted in Scheme 9, the formation of **15a-c** from **13a-c** involves **14a-c** as intermediates. In some cases, in fact, these intermediates can be isolated by column chromatography from the reaction mixtures when the reactions are interrupted before the complete conversion of **13a-c** into **15a-c**.

Conclusion

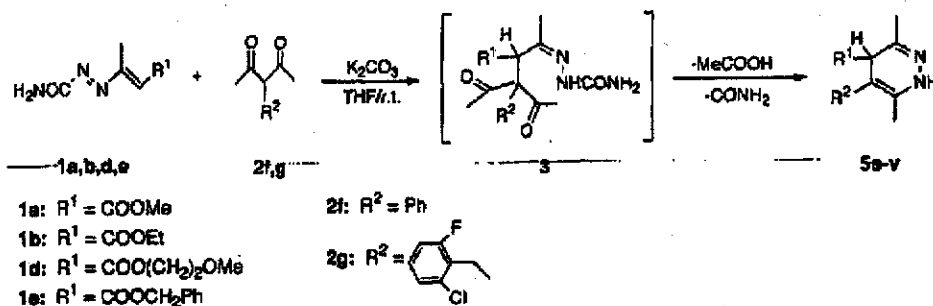
The reaction of 1-aminocarbonyl-1,2-diaza-1,3-butadienes with activated methine compounds represents a straightforward entry to 1,4-dihydropyridazine and pyridazine derivatives. Surprisingly, the analogous reaction between 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes and methyl 2-acetylacetoacetate produces 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles. A detailed investigation of the reaction pathway demonstrated that these compounds derive from 1-alkoxycarbonyl-1,2-dihydropyridazine intermediates by ring contraction. Ring expansion of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles leads to 1-alkoxycarbonyl-1,4-dihydropyridazines that can be converted into 1-unsubstituted 1,4-dihydropyridazines. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles and 1-alkoxycarbonyl-1,4-dihydropyridazines separately give 1-aminopyrroles via 1-alkoxycarbonyl-1,4-dihydropyridazine intermediates in the case of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles.

In conclusion, this paper reports not only useful access to new heterocyclic systems but also deals with some interesting interconversions of five-membered rings of pyrazole type into six-membered rings of the 1,4-dihydropyridazine type and then the last one into some five-membered rings of the pyrrole type by ring opening-closing mechanisms.

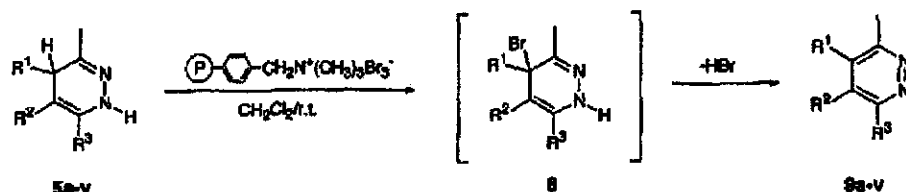
Experimental Section

General Methods. 1-Aminocarbonyl-1,2-diaza-1,3-butadienes **1a-e** and 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes **1f-h** were synthesized according to previously reported

Scheme 5



Scheme 6



procedures.^{18,19} Starting materials of the above-mentioned reagents, as well as triacetylmethane (2a), methyl (2b) and ethyl 2-acetylacetoacetates (2c), diethyl acetylmalonate (6a), triethyl methanetricarboxylate (6b), ethyl 2-(2-furoyl)acetoacetate (2d), ethyl 2-(2-thenoyl)acetoacetate (2e), 3-phenylpentane-2,4-dione (2f), 3-(2-chloro-6-fluorobenzyl)pentane-2,4-dione (2g), 3-phenoxy-pentane-2,4-dione (2h), tribromide on Amberlyst A-26, sodium hydride, sodium hydroxide, potassium carbonate, trifluoroacetic acid, acetic acid, and solvents are commercially available materials (Carlo Erba, Aldrich, Acros, Fluka, Lancaster, Avocado, and Maybridge) and were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. The products often decompose at the melting point. IR-FT spectra were performed in Nujol mull. MS spectra were made at an ionizing voltage of 70 eV. ¹H NMR spectra were recorded at 200 MHz, while ¹³C NMR were recorded spectra at 50.32 MHz. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) in Hz. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Precoated silica gel plates 0.25 mm were employed for analytical thin-layer chromatography and silica gel 35–70 μm for column chromatography.

Preparation of 1-Unsubstituted 1,4-Dihydropyridazines 5a–v. To a stirred solution of triacetylmethane (2a), methyl 2-acetylacetoacetate (2b), ethyl 2-acetylacetoacetate (2c), ethyl 2-(2-furoyl)acetoacetate (2d), ethyl 2-(2-thenoyl)acetoacetate (2e), or 3-(2-chloro-6-fluorobenzyl)pentane (2g) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). In the case of 3-phenylpentane-2,4-dione (2f) (1 mmol), a catalytic amount of sodium hydride (0.3 mmol) instead of potassium carbonate was added. The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then the 1-aminocarbonyl-1,2-diaza-1,3-butadiene 1a–e (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (~10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane–ethyl acetate mixtures), affording 1,4-dihydropyridazines 5a–v that were crystallized from ethyl acetate–petroleum ether (40–60 °C).

5a: mp 63–65 °C; IR (Nujol) ν_{max} 3281, 1705, 1688, 1597 cm^{-1} ; ¹H NMR (CDCl₃) δ 2.03 (s, 3H, Me), 2.14 (s, 3H, Me), 2.31 (s, 3H, Me), 3.72 (s, 3H, CO₂Me), 4.31 (s, 1H, CH), 7.55

(br s, 1H, NH, D₂O-exch); ¹³C NMR (CDCl₃) δ 17.9 (Me), 22.3 (Me), 27.6 (Me), 51.2 (C4), 51.5 (CO₂Me), 89.6 (C5), 145.7 and 147.2 (C3 and C6), 167.2 (COO), 204.9 (CO); MS m/z 210 (2) [M⁺], 179 (5), 167 (100). Anal. Calcd. for C₁₀H₁₄N₂O₃: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.06; H, 6.65; N, 13.36.

5b: mp 94–96 °C. IR (Nujol) ν_{max} 3283, 1724, 1688, 1608 cm^{-1} ; ¹H NMR (CDCl₃) δ 2.13 (s, 3H, Me), 2.32 (s, 3H, Me), 3.69 (s, 3H, CO₂Me), 3.71 (s, 3H, CO₂Me), 4.35 (s, 1H, CH), 7.77 (br s, 1H, NH, D₂O-exch); ¹³C NMR (CDCl₃) δ 17.6 (Me), 22.2 (Me), 43.2 (C4), 51.0 (CO₂Me), 52.3 (CO₂Me), 89.0 (C5), 143.7 and 147.2 (C3 and C6), 167.2 (COO), 170.5 (COO); MS m/z 226 (5) [M⁺], 195 (4), 167 (100). Anal. Calcd. for C₁₀H₁₄N₂O₄: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.17; H, 6.32; N, 12.46.

Preparation of Hydrazones 7a,b. To a stirred solution of diethyl acetylmalonate (6a) or triethyl methanetricarboxylate (6b) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then the 1-aminocarbonyl-1,2-diaza-1,3-butadiene 1a,b (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (~10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane–ethyl acetate mixtures), affording hydrazones 7a,b that were crystallized from ethyl acetate–petroleum ether (40–60 °C).

7a: mp 103–105 °C; IR (Nujol) ν_{max} 3499, 3387, 1757, 1747, 1731 cm^{-1} ; ¹H NMR (CDCl₃) δ 1.28 (t, 9H, J = 7.1 Hz, 3 × CO₂CH₂Me), 2.03 (s, 3H, Me), 3.74 (s, 3H, CO₂Me), 4.19–4.33 (m, 7H, 3 × CO₂CH₂Me and CH), 5.82 (br s, 2H, NH₂, D₂O-exch), 9.00 (br s, 1H, NH, D₂O-exch); ¹³C NMR (CDCl₃) δ 13.7 (3 × Me), 17.0 (Me), 52.4 (CO₂Me), 55.4 (CH), 62.5 (3 × CO₂CH₂Me), 67.0 (C(CO)₂), 143.9 (CONH₂), 158.2 (CN), 165.6 (3 × COO), 169.2 (COO); MS m/z 403 (2) [M⁺], 326 (9), 255 (11), 183 (100). Anal. Calcd. for C₁₆H₂₅N₃O₉: C, 47.64; H, 6.25; N, 10.42. Found: C, 47.81; H, 6.35; N, 10.37.

Preparation of Pyridazines 9a–v from Reaction of 1,4-Dihydropyridazines 5a–v with Tribromide on Amberlyst A-26. To a stirred solution of 1,4-dihydropyridazine 5a–v (1 mmol) in dichloromethane (10 mL) was added tribromide on Amberlyst A-26 (1 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 2 h and then was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane–ethyl acetate mixtures), affording pyridazines 9a–v that were crystallized from ethyl acetate–petroleum ether (40–60 °C).

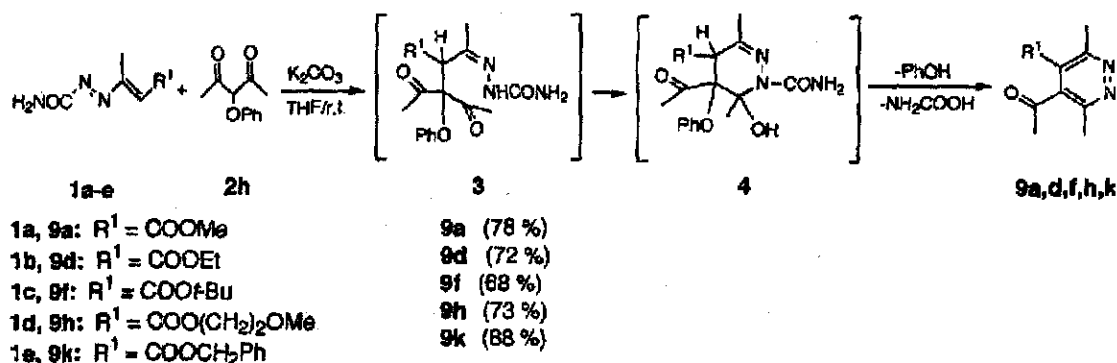
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Table 2. Yields of Pyridazines 9a-v

Entry 5 and 9	R ¹	R ²	R ³	Yield (%) ^a
a	COOMe	COMe	Me	89
b	COOMe	COOMe	Me	93
c	COOMe	COOEt	Me	93
d	COOEt	COMe	Me	86
e	COOEt	COOMe	Me	89
f	COO <i>i</i> -Bu	COMe	Me	91
g	COO <i>i</i> -Bu	COOMe	Me	91
h	COO(CH ₂) ₂ OMe	COMe	Me	84
i	COO(CH ₂) ₂ OMe	COOMe	Me	92
j	COO(CH ₂) ₂ OMe	COOEt	Me	93
k	COOCH ₂ Ph	COMe	Me	83
l	COOCH ₂ Ph	COOMe	Me	94
m	COOCH ₂ Ph	COOEt	Me	93
n	COOMe	COOEt		89
o	COOMe	COOEt		94
p	COO(CH ₂) ₂ OMe	COOEt		85
q	COO(CH ₂) ₂ OMe	COOEt		87
r	COOCH ₂ Ph	COOEt		96
s	COOMe	Ph	Me	87
t	COOEt		Me	84
u	COO(CH ₂) ₂ OMe		Me	86
v	COOCH ₂ Ph		Me	92

^aYield of pure isolated products.

Scheme 7



9a: mp 61–63 °C; IR (Nujol) ν_{max} 1723, 1701 cm⁻¹; ¹H NMR (CDCl₃) δ 2.52 (s, 3H, Me), 2.67 (s, 3H, Me), 2.84 (s, 3H, Me), 3.92 (s, 3H, CO₂Me), ¹³C NMR (CDCl₃) δ 19.7 (Me), 21.5 (Me), 30.8 (Me), 53.1 (CO₂Me), 124.7 and 138.3 (C4 and C5), 152.9 and 155.7 (C3 and C6), 165.5 (COO), 201.1 (CO); MS m/z 208 (100) [M⁺]. Anal. Calcd for C₁₀H₁₂N₂O₄: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.63; H, 5.85; N, 13.36.

9b: mp 66–68 °C; IR (Nujol) ν_{max} 1726, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 2.81 (s, 6H, 2 × Me), 3.96 (s, 6H, 2 × CO₂Me); ¹³C

NMR (CDCl₃) δ 20.7 (2 × Me), 53.1 (2 × CO₂Me), 128.0 (C4 and C5), 155.1 (C3 and C6), 165.6 (2 × COO); MS m/z 224 (100) [M⁺]. Anal. Calcd for C₁₀H₁₂N₂O₄: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.61; H, 5.46; N, 12.47.

Preparation of Pyridazines 9a,d,f,h,k from Reaction of 1-Aminocarbonyl-1,2-diaza-1,3-butadienes 1a–e with 3-Phenoxy-2,4-pentanedione (2h). To a stirred solution of 3-phenoxy-2,4-pentanedione (2h) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). The

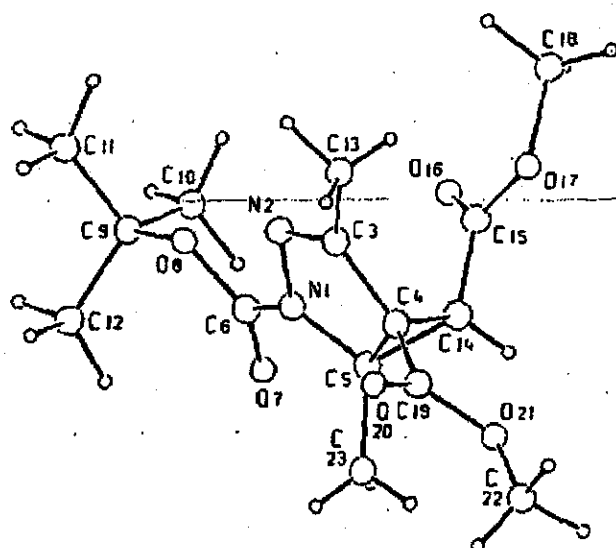


Figure 1. X-ray molecular structure of 1-*tert*-butoxycarbonyl-3,5-dimethyl-4-methoxycarbonyl-4,5(4*H*,5*H*)-(methoxycarbonylcyclopropyl)-1*H*-pyrazole (13c) with the atom numbering system used in the crystallographic analysis.

reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then 1-aminocarbonyl-1,2-diaza-1,3-butadiene 1a-e (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (~20 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane-ethyl acetate mixtures), affording pyridazines 9a (78%), 9d (72%), 9f (68%), 9h (73%), and 9k (88%) that were crystallized from ethyl acetate-petroleum ether (40–60 °C).

Preparation of 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a-c. To a stirred solution of methyl 2-acetylacetoacetate (2b) (1 mmol) in tetrahydrofuran (5 mL) was added potassium carbonate (4 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then 1-alkoxycarbonyl-1,2-diaza-1,3-butadiene 1f-h (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (~10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane-ethyl acetate mixtures), affording 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a-c that were crystallized from ethyl acetate-petroleum ether (40–60 °C). To isolate the intermediates 11a-c, the reaction mixture was filtered, concentrated under reduced pressure, and rapidly chromatographed as soon as the red color of 1-alkoxycarbonyl-1,2-diaza-1,3-butadiene 1f-h disappeared.

11a: ¹H NMR (CDCl₃) δ 1.92 (s, 3H, Me), 2.08 (s, 3H, Me), 2.45 (s, 3H, Me), 3.71 (s, 6H, 2 × CO₂Me), 3.76 (s, 3H, CO₂Me), 6.79 (br s, 1H, OH, D₂O, exch), 12.84 (br s, 1H, NH, D₂O, exch); MS *m/z* 344 (2) [M⁺], 302 (5), 284 (18), 252 (50), 227 (56), 213 (48), 181 (100).

13a: mp 57–59 °C; IR (Nujol) ν_{max} 1745, 1724, 1606 cm⁻¹; ¹H NMR (CDCl₃) δ 1.83 (s, 3H, Me), 2.25 (s, 3H, Me), 2.82 (s, 1H, CH), 3.64 (s, 3H, CO₂Me), 3.84 (s, 3H, CO₂Me), 3.87 (s, 3H, CO₂Me); ¹³C NMR (CDCl₃) δ 15.0 (Me), 15.4 (Me), 26.5 (CH), 50.1 (C4), 51.6 (CO₂Me), 52.5 (CO₂Me), 52.9 (CO₂Me), 59.2 (C5), 149.4 and 152.5 (C3 and NCO), 164.5 (COO), 165.0 (COO); MS *m/z* 284 (35) [M⁺], 252 (100). Anal. Calcd for C₁₂H₁₆N₂O₆: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.67; H, 5.65; N, 9.89.

Preparation of 1-Alkoxycarbonyl-1,4-Dihydropyridazines 14a-c. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazole 13a-c (1 mmol) was dissolved in acetic

acid (5 mL), and the reaction mixture was allowed to stand at room temperature under magnetic stirring for 10 min. Acetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) and washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on a silica gel column (elution with cyclohexane-ethyl acetate mixtures), affording 1-alkoxycarbonyl-1,4-dihydropyridazines 14a-c that were crystallized from ethyl acetate-petroleum ether (40–60 °C).

14a: mp 68–69 °C; IR (Nujol) ν_{max} 1739, 1716, 1704, 1656 cm⁻¹; ¹H NMR (CDCl₃) δ 2.32 (s, 3H, Me), 2.65 (s, 3H, Me), 3.68 (s, 3H, CO₂Me), 3.79 (s, 3H, CO₂Me), 3.92 (s, 3H, CO₂Me), 4.55 (s, 1H, CH); ¹³C NMR (CDCl₃) δ 17.7 (Me), 21.8 (Me), 44.3 (C4), 51.5 (CO₂Me), 52.4 (CO₂Me), 53.6 (CO₂Me), 104.4 (C5), 146.8 (NCO), 151.3 and 151.9 (C3 and C6), 165.5 (COO), 167.4 (COO); MS *m/z* 284 (5) [M⁺], 253 (8), 225 (100). Anal. Calcd for C₁₂H₁₆N₂O₆: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.73; H, 5.63; N, 9.86.

Preparation of 1-Unsubstituted 1,4-Dihydropyridazines 5b,e from 1-Alkoxycarbonyl-1,4-dihydropyridazines 14a-c. 1-Alkoxycarbonyl-1,4-dihydropyridazine 14a-c (1 mmol) was dissolved in a 1 M methanolic solution of sodium hydroxide (5 mL) and allowed to stand at room temperature under magnetic stirring for 15 min. Methanol was evaporated under reduced pressure, the residue was dissolved with ethyl acetate (40 mL) and then washed with water (3 × 25 mL) affording 1-unsubstituted 1,4-dihydropyridazines 5b,e in nearly quantitative yields that were crystallized from ethyl acetate-petroleum ether (40–60 °C).

Preparation of 1-Aminopyrroles 15a-c from 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a-c. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazole 13a-c (1 mmol) was dissolved in trifluoroacetic acid (5 mL), and the reaction mixture was heated under reflux for 2 h (13a,b), or allowed to stand at room temperature under magnetic stirring for 15 min (13c). Trifluoroacetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on silica gel column (elution with cyclohexane-ethyl acetate mixtures), affording 1-aminopyrroles 15a-c in good yields that were crystallized from ethyl acetate-pentane.

Preparation of 1-Aminopyrroles 15a-c from 1-Alkoxycarbonyl-1,4-dihydropyridazines 14a-c. 1-Alkoxycarbonyl-1,4-dihydropyridazine 14a-c (1 mmol) was dissolved in trifluoroacetic acid (5 mL), and the reaction mixture was heated under reflux for 2 h (14a,b), or allowed to stand at room temperature under magnetic stirring for 15 min (14c). Trifluoroacetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) and washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on silica gel column (elution with cyclohexane-ethyl acetate mixtures), affording 1-aminopyrroles 15a-c that were crystallized from ethyl acetate-pentane.

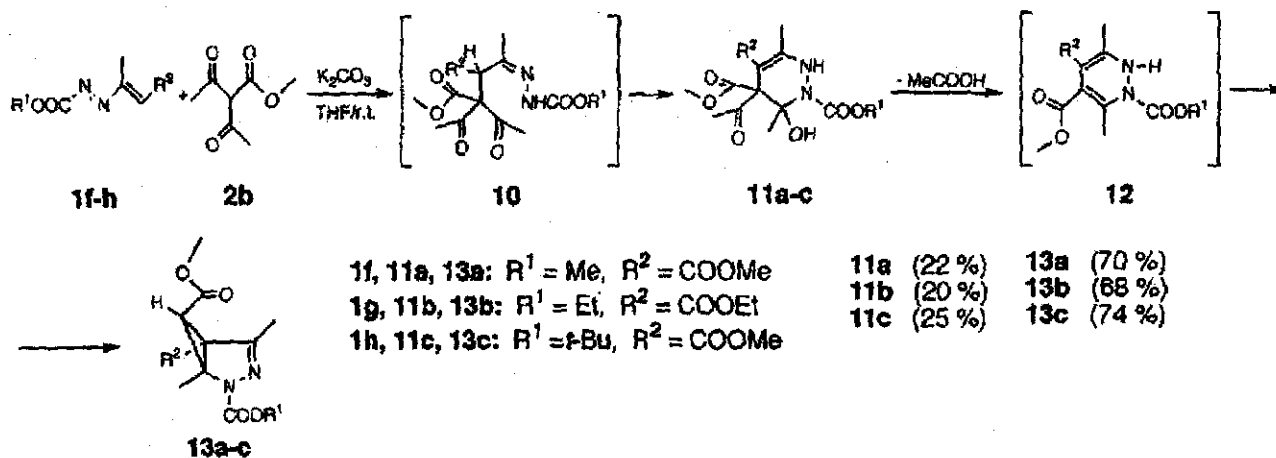
15a: 100%.

15b: mp 70–72 °C; IR (Nujol) ν_{max} 3238, 1761, 1713, 1671 cm⁻¹; ¹H NMR (CDCl₃) δ 1.29 (t, 3H, J = 7.1 Hz, 2 × CO₂CH₂Me), 2.12 (s, 6H, 2 × Me), 3.76 (s, 3H, CO₂Me), 4.24 (q, 4H, J = 7.1 Hz, 2 × CO₂CH₂Me), 8.39 (br s, 1H, NH, D₂O, exch); ¹³C NMR (CDCl₃) δ 9.7 (2 × Me), 14.2 (Me), 14.4 (Me), 51.5 (CO₂Me), 60.4 (CO₂CH₂Me), 62.6 (CO₂CH₂Me), 109.8 and 110.1 (C3 and C6), 134.6 (C2 and C5), 154.8 (NHCO), 165.5 (COO), 166.0 (COO); MS *m/z* 312 (35) [M⁺], 280 (68), 266 (100). Anal. Calcd for C₁₄H₂₀N₂O₆: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.78; H, 6.50; N, 8.91.

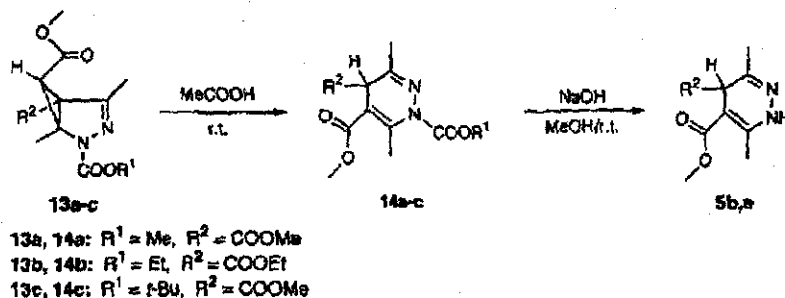
Crystal data: C₁₄H₂₀N₂O₆, M = 326.35, monoclinic, space group P2₁/n, a = 13.454(8) Å, b = 9.506(2) Å, c = 13.570(6) Å, β = 100.09(5)°, U = 1709(2) Å³, Z = 4, D_c = 1.27 Mg m⁻³, F(000)

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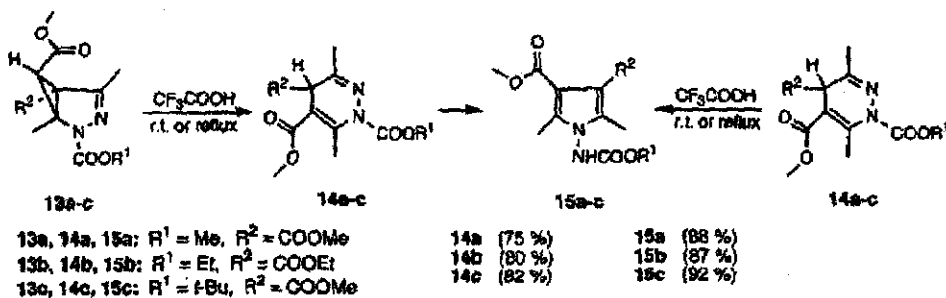
Scheme 8



Scheme 9



Scheme 10



$d = 696$, $\lambda = 0.71069$ Å, $T = 293$ K, (Mo K α) $\mu = 0.098$ mm $^{-1}$, crystal dimensions $0.50 \times 0.70 \times 0.30$ mm. A total of 3148 reflections were collected (3013 unique, $R_{\text{int}} = 0.0099$).

Data Collection and Processing. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo K α radiation, $\omega/2\theta$ scan mode, range $2.63^\circ < \theta < 25.02^\circ$. The unit cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections $7.9^\circ < \theta < 12.6^\circ$.

Structure Analysis and Refinement. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 , using the SHELX program packages.^{21,22} In the final refinement cycles 2338 reflections having $I > 2\sigma(I)$ were used, with 209 parameters varied. In refinements were used weights in accord with the scheme $w = 1/[\sigma^2(F_o^2) + (0.0782P)^2]$

$+ 0.5678P]$ where $P = (F_o^2 + 2F_c^2)/3$. The hydrogen atoms were located by geometrical calculation and refined using a "riding" model. The final agreement indices were $R_1 = 0.0439$ and $wR_2 = 0.1252$. Goodness of fit on $F^2 = 1.047$. Largest difference peak and hole was 0.312 and -0.236 e Å $^{-3}$. Full crystallographic results for this X-ray determination have been deposited with the Cambridge Crystallographic Data Centre.

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Supporting Information Available: Experimental procedures (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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