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Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
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Actuación : 444

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Asunto : Solicitud de patente para: **PROCESO PARA LA
PREPARACIÓN DE COMPUESTOS HETEROCÍCLICOS N-
AMINO SUSTITUIDOS**
Solicitante : AVENTIS PHARMACEUTICALS INC.
Clase : A61K 031/404, A61K 031/4427, A61K 031/4439, C07D
209/000, C07D 209/008, C07D 209/086, C07D 401/000, C07D 401/004, C07D
401/012
Fecha solicitud: 31 de marzo de 2006

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. **7160** notificado por fijación en lista del 26 de junio de 2009 y atentamente presento junto con este escrito los siguientes documentos:

- 1.1 ANDERSEN ET AL.: J. MED. CHEM.,
Vol. 35, No. 26, 1992, pages 4823-4831
XP002314810
- 1.2 KLEIN ET AL.: J. MED. CHEM.,
Vol. 39, No. 2, 1996, pages 570-581
XP 002314811
- 1.3 DATABASE CAPLUS 'Online!
CHEMICAL ABSTRACTS SERVICE, COLUMBUS,
OHIO, US; 1976
Database accession No. 1976:164705
XP002314891
Abstract
&SOMEI ET AL.: "Preparation of N-aminoheterocycles and their
reactions"
1975, PHARM. INST., TOHOKU UNIV., SENDAI
JAPAN 8

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1.4 DATABASE BEILSTEIN 'Online!

Beilstein Institut zur Foederung der Chemischen
Wissenschaften;

XP002314814

see BRN: 136660 (RN = 91565-76-3),

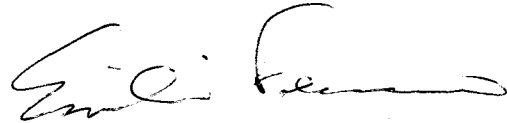
abstract

& ARBUSOW; KITAEW: ZH. OBSHCH. KHIM.,

Vol. 27, 1957, pages 2401-2407.

2. Puesto que se han atendido a cabalidad las peticiones hechas por su
Despacho sobre la presente solicitud de patente, atentamente solicito
que se continúe su tramitación.

Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

COLO-15896-841-001-5

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No. M-2009-158546\JMS

Selective, Centrally Acting Serotonin 5-HT₂ Antagonists. 2. Substituted 3-(4-Fluorophenyl)-1H-indoles

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A series of 3-(4-fluorophenyl)-1H-indoles substituted in the 1-position with 4-piperidinyl, 1,2,3,6-tetrahydro-4-pyridinyl, and 4-piperazinyl was synthesized. By variation of the substituents in the benzene part of the indole nucleus in 1-[2-[4-[3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinones, the highest 5-HT₂ receptor affinity and selectivity with respect to dopamine D₂ receptors and α_1 adrenoceptors were obtained by 5-methyl substitution. Different substituents were introduced in the 1-position of the piperidine ring in the 5-methyl-substituted derivative. Thus replacement of the 2-(2-imidazolidinon-1-yl)ethyl side chain with a 2-(1,3-dimethyl-1-ureido)ethyl or methyl substituent resulted in unchanged affinity and selectivity for 5-HT₂ receptors. Replacement with a 2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl side chain reduced binding to α_1 adrenoceptors with a factor of four, while affinities for 5-HT₂ and D₂ receptors were retained, compared to the 3-unsubstituted imidazolidinone. Indoles substituted in the 1-position with 4-piperazinyl had generally weaker affinity for both 5-HT₂ and D₂ receptors compared to corresponding 4-piperidinyl- and 1,2,3,6-tetrahydro-4-pyridinyl-substituted indoles. Introduction of a methyl group in the 2-position of the 5-methyl-substituted indole resulted in further increase of selectivity for the 5-HT₂ receptor. Compounds with potent receptor binding also potently inhibited the quipazine-induced head twitch syndrome in rats. The compounds were equally active after oral and subcutaneous administration and showed a long duration of action (>24 h). In general, the derivatives were found to be considerably more potent at 24 h than at 2 h after the administration. The compounds within this series were prepared as analogues of the previously described 1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indoles by interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus. The pharmacological results indicate that this isosteric replacement results in higher selectivity for 5-HT₂ receptors compared to the former series. The 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone has high affinity for 5-HT₂ receptors (IC₅₀ = 3.4 nM) and extremely low affinity for both dopamine D₂ receptors (IC₅₀ = 6900 nM) and α_1 adrenoceptors (IC₅₀ = 2300 nM).

Introduction

The preceding paper¹ within this series discussed the structure-activity relationship in a series of 6-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles, which led to the selective and highly potent serotonin 5-HT₂ antagonist Lu 26-042 (1, Figure 1). These compounds were the result of further development of a series of 5-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles, which in addition to binding affinity for serotonin 5-HT₂ receptors, have strong binding affinity for both dopamine D₂ receptors and α_1 adrenoceptors.² The atypical neuroleptic sertindole (2, Figure 1), which selectively blocks dopaminergic activity in limbic brain areas in rats after chronic treatment, is a member of this series of compounds.³⁻⁵

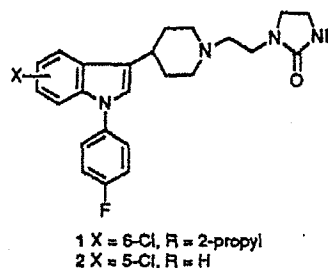


Figure 1. Structure of 1-(4-fluorophenyl)-3-(4-piperidinyl)-indoles.

The involvement of serotonin receptors in psychiatric disorders, such as anxiety and depression, is discussed in part 1¹ within this series. Selective 5-HT₂ antagonists⁶ and compounds, which have 5-HT₂ antagonistic activity as a main component (e.g. sertindole and related 5-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles),⁷ are active

[†] H. Lundbeck A/S.

[†] Royal School of Pharmacy.

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in animal models predictive of anxiolytic activity. In addition, several clinical studies with the 5-HT₂ antagonist ritanserin have suggested improvements in dysthymic disorders,⁸ negative symptoms in schizophrenia,⁹ and quality of sleep.¹⁰ These pharmacological and clinical results prompted us to investigate the possibilities of further increasing the selectivity for central 5-HT₂ receptors within indole derivatives with 5-HT₂ antagonistic activity.

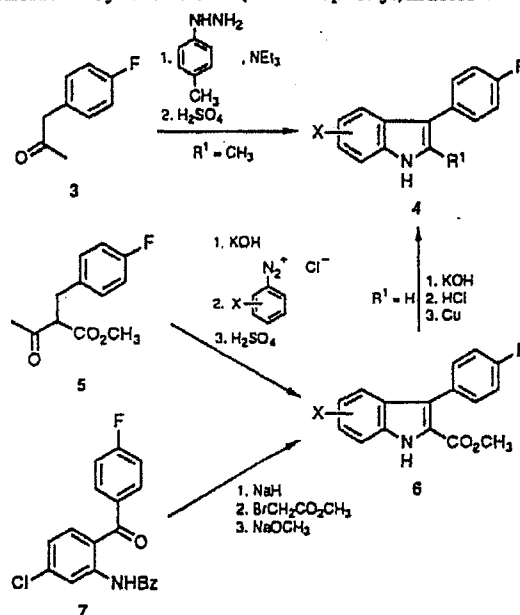
The increase in 5-HT receptor affinity, obtained by interchange of the C-3 atom and the nitrogen atom in the indole nucleus of the hallucinogenic agent dimethyltryptamine,¹¹ led us to investigation of the pharmacological effects of this isosteric replacement in the series of 1-phenyl-3-(4-piperidinyl)indoles, although the two structurally different series of molecules probably bind to two different subtypes of 5-HT receptors. Consequently, in this paper, we discuss the chemical development and structure-activity relationship within a new series of 3-(4-fluorophenyl)-1H-indoles substituted in the 1-position with 4-piperidinyl, 1,2,3,6-tetrahydro-4-pyridinyl, or 4-piperazinyl.

Chemistry

The preparation of 1-(1-methyl-4-piperidinyl)-3-phenyl-1H-indole as intermediate in the synthesis of substituted 2-benzoylaniline is described by Adachi et al.¹² This method, however, is not suitable for preparation of compounds with variation of substituents in the indole nucleus. Thus, we decided to develop new and more versatile methods, which in addition to 1-(4-piperidinyl)indoles (10) afforded 1-(1,2,3,6-tetrahydro-4-pyridinyl)indoles (12) and 1-(4-piperazinyl)indole (14). 1-Unsubstituted indoles (4) are key intermediates in these methods.

The key intermediates 4 were prepared as outlined in Scheme I. The 2-methylindole (4, R¹ = CH₃) was prepared by the Fischer indole synthesis¹³ from 4-tolylhydrazine and (4-fluorophenyl)acetone (3). The esters 6 used as intermediates in the preparation of 2-unsubstituted indoles (4, R¹ = H) were prepared by two routes. Japp-Klingemann reaction of unsubstituted and 2- and 4-substituted anilines with methyl 2-(4-fluorobenzyl)-3-oxobutanoate (5) followed by Fischer indole synthesis¹⁴ afforded the unsubstituted and 7- and 5-substituted esters

Scheme I Synthesis of 3-(4-Fluorophenyl)indoles 4



6, respectively. The 6-chloro-substituted ester (6, X = 6-Cl) was prepared from the 2-benzoylaniline 7 by a modification of the method described by Jones.¹⁵ Esters 6 were converted to the corresponding 2-unsubstituted indoles (4, R¹ = H) by hydrolysis followed by decarboxylation.¹⁶ The 4-methylindole (4, X = 4-CH₃) was prepared by removal of the bromine atom in 7-bromo-4-methylindole (4, X = 7-Br, 4-CH₃) which was prepared from 2-bromo-5-methylaniline by Fischer indole synthesis followed by hydrolysis and decarboxylation as described above. The bromo substituent was introduced to avoid formation of a mixture of 4- and 6-methylindole in the ring closure reaction.

Conversion of the indoles 4 to the corresponding 1-(4-piperidinyl)indoles 10 is described in Scheme II. Copper-catalyzed Ullmann arylation of indoles 4 with 4-chloro- or 4-bromopyridine in *N*-methyl-2-pyrrolidinone (NMP) afforded the corresponding 1-(4-pyridinyl)indoles 8. 4-Bromopyridine was used in the arylation of 2-methyl- and 7-methylindoles, which did not react with 4-chloropyridine, probably due to steric hindrance. It was possible to perform the decarboxylation described above and the arylation with 4-chloropyridine in a one-pot procedure. Catalytic hydrogenation of the 1-(4-pyridinyl)indoles 8 afforded the unsubstituted piperidinylindoles 9. 2-(2-Imidazolidinon-1-yl)ethyl side chains (formulas A and B, Chart I) in compounds 10 were introduced by alkylation of the unsubstituted piperidinylindoles 9 with appropriate alkylating agents. Urea side chains (formulas C and D, Chart I) were introduced by building up the side chain in a straightforward procedure as described previously.¹ Quaternization of 1-(4-pyridinyl)indoles 8 with 1-(2-iodoethyl)-2-imidazolidinone or methyl iodide, followed by reduction with NaBH₄ afforded the corresponding 1-(1,2,3,6-tetrahydro-4-pyridinyl)indoles 12. These compounds were reduced to piperidinylindoles 10 with am-

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Scheme II. Synthesis of 1-(4-Piperidiny)indoles 10 and 1-(1,2,3,6-Tetrahydro-4-pyridinyl)indoles 12 from the Corresponding 1-Unsubstituted Indoles 4

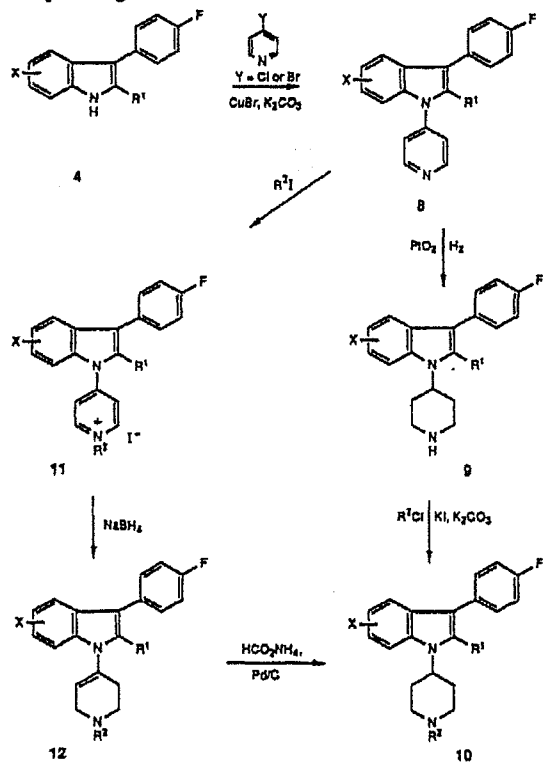
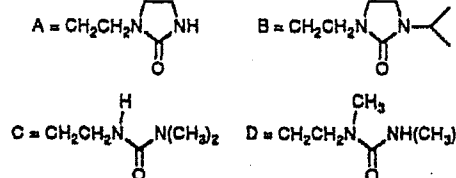


Chart I. Structures of Substituent R²



monium formate using palladium as catalyst. This alternative procedure was used for the preparation of 2- and 7-substituted 1-(4-piperidiny)indoles 10, since the corresponding 1-(4-pyridinyl)indoles 8 were inert to the catalytic hydrogenation conditions described above.

The 1-(4-piperazinyl)indole 14 was prepared from the corresponding indole 4c as outlined in Scheme III. Reaction of 4c with potassium hydroxylamine O-sulfate in dimethylformamide¹⁷ afforded a mixture of the desired 1-aminoindole 13 and starting material, due to the deaminating properties of potassium hydroxylamine O-sulfate.¹⁸ The aminoindole was easily isolated by chromatography. Reaction with *N,N*-bis(2-chloroethyl)-methylamine and sodium amide in toluene afforded the piperazinylindole 14.

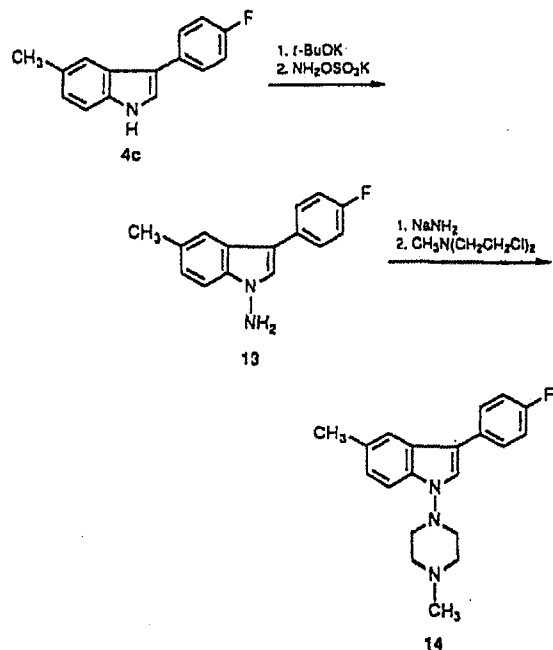
Results and Discussion

The pharmacological test models are described in details in the Experimental Section. Receptor binding affinities

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Scheme III. Synthesis of 1-(4-Piperazinyl)indole 14 from the Corresponding 1-Unsubstituted Indole 4c



(dopamine D₂, adrenergic α₁, serotonin 5-HT₂) are reported in Table I. The affinities are compared to the reference compound ritanserin, to the atypical neuroleptic sertindole (2, Figure 1), and to the 5-HT₂ antagonist Lu 26-042 (1, Figure 1). Ritanserin was the first centrally acting 5-HT₂ antagonist identified with considerable selectivity in respect of non-5-HT receptors,¹⁹ and the two latter compounds are members of the previously described series of 1-(4-fluorophenyl)-3-(4-piperidiny)indoles.^{1,2}

Compound 10a is isosterically related to sertindole (2, Figure 1) by interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus. By comparing the binding affinities of these two compounds it appears that this isosteric replacement results in a slightly weaker affinity for both 5-HT₂, D₂, and α₁ receptors. The unsubstituted derivative 10b has retained affinity for 5-HT₂ and α₁ receptors, whereas the affinity for D₂ receptors are slightly weakened compared to 10a. Introduction of substituents in the 5-position (10c-f) results in retained 5-HT₂ receptor affinity, while affinities for both D₂ and α₁ receptors are decreased. The highest affinity and selectivity for the 5-HT₂ receptor are obtained by methyl substitution (10e). Methyl substitution in the 4- and 7-positions afforded compounds 10g and 10h with affinity for the three receptors studied similar to that of the 5-fluoro-substituted compound 10c.

Exchange of the 3-unsubstituted imidazolidinone side chain in 10e with the 3-(2-propyl)-substituted imidazolidinone side chain (formula B, Chart I) reduces the affinity for α₁ adrenoceptors by a factor of 4 while the affinity for 5-HT₂ and D₂ receptors is retained (10j). The urea side chains (formulas C and D, Chart I) were designed as open-chain analogues of the imidazolidinone side chains. The 3,3-dimethyl-substituted derivative 10m has a lower selectivity for the 5-HT₂ receptor in respect to D₂ receptors,

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Table I. Substituents and Binding Affinities of 1-(4-Piperidinyl)indoles 10, 1-(1,2,3,6-Tetrahydro-4-pyridinyl)indoles 12, and 1-(4-Piperazinyl)indole 14

compd	substituents ^b			receptor binding ^a		
	X	R ¹	R ² ^c	serotonin 5-HT ₂ [³ H]ketanserin	dopamine D ₂ [³ H]apiperone	adrenergic α ₁ [³ H]prazosin
10a	6-Cl	H	A	1.9	37	11
10b	H	H	A	3.1	120	8.3
10c	5-F	H	A	3.2	250	19
10d	5-Cl	H	A	5.7	410	67
10e	5-CH ₃	H	A	1.6	920	71
10f	5-CF ₃	H	A	9.3	2500	190
10g	4-CH ₃	H	A	7.9	200	34
10h	7-CH ₃	H	A	3.6	370	23
10i	5-CH ₃	CH ₃	A	3.4	6900	2300
10j	5-CH ₃	H	B	2.7	1100	280
10k	5-CH ₃	H	CH ₃	4.5	540	190
10l	5-CH ₃	CH ₃	CH ₃	5.3	2600	2700
10m	5-CH ₃	H	C	2.3	260	89
10n	5-CH ₃	H	D	2.2	1200	54
12a	5-CH ₃	H	A	1.5	280	24
12b	7-CH ₃	H	A	5.8	530	27
12c	5-CH ₃	CH ₃	A	2.8	6300	1000
14	-	-	-	15	3900	500
Lu 26-042 (1)				1.5	130	70
sertindole (2)				0.39	4.1	3.4
ritanserin				0.40	12	47

^a Results are expressed as IC₅₀ values in nM and are the logarithmic mean of at least two determinations. Two full concentration curves were measured using five concentrations of test drug in triplicate (covering three decades). SD ratios were obtained by calculating the variance of repeated measures of ratios between the first and second IC₅₀ determination for a series of 100 drugs. In cases of ratios greater than 3 × SD (99% confidence interval) extra determinations were performed and outliers were discarded. The following 95% confidence ratios (2 × SD ratio) were calculated: D₂ 2.25; α₁ 2.20; 5-HT₂ 2.05. ^b Refer to substituents of structures 10 and 12 in Scheme 1. ^c See Chart I for definitions of R².

whereas the 1,3-dimethyl-substituted derivative 10n has similar affinity and selectivity for the 5-HT₂ receptor as 10e. Replacement of the side chains with a methyl group (10k) results in an affinity and selectivity for 5-HT₂ receptors comparable to that of the corresponding imidazolidinone-substituted derivative (10e).

By comparing the 5-chloro- and 5-methyl-substituted compounds 10d, 10e, and 10j with the corresponding 6-chloro- and 6-methyl-substituted compounds within the preceding series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles,¹ it appears that the former compounds have a slightly lower affinity for 5-HT₂ receptors, whereas the affinity for D₂ and α₁ receptors is decreased by a factor of 3–10, indicating that the interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus within 6-substituted 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles results in a higher selectivity for 5-HT₂ receptors.

It has previously been shown² that affinity for 5-HT₂ and D₂ receptors in 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles is independent of replacement of the piperidinyl group with a 1,2,3,6-tetrahydropyridin-4-yl or a 4-piperazinyl group. The 1,2,3,6-tetrahydropyridin-4-yl compounds 12a and 12b have similar affinities for the three studied receptor types compared to the corresponding 4-piperidinyl compounds 10f and 10h, respectively. In contrast, the 4-piperazinyl compound 14 has slightly weaker affinity than the corresponding 4-piperidinyl compound 10k for both 5-HT₂, α₁, and D₂ receptors. This might be due to electronic or basicity differences between the aniline-like nitrogen atom in the previously reported piperazinyl compounds and the 1-aminoindole nitrogen atom in compound 14.

In the preceding series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles methyl substitution in the 2-position of the indole nucleus reduces the affinity for both D₂ and α₁ receptors by a factor of 20–30, whereas the affinity for 5-HT₂ receptors is retained. Similarly, introduction of a

methyl group in the 2-position in the 5-methyl-substituted indole 10f results in retained affinity for 5-HT₂ receptors, whereas the affinity for D₂ and α₁ receptors is reduced by a factor of 8 and 30, respectively (10i, Table I). Replacement of the piperidine group in 10i with a 1,2,3,6-tetrahydro-4-pyridinyl group and replacement of the imidazolidinonyl side chain in 10i with a methyl group result in compounds 12c and 10l, respectively, with similar affinity and selectivity for 5-HT₂ receptors as the former compound. These 2,5-dimethyl-substituted derivatives have accordingly been developed from the previous series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles by combination of interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus with subsequent optimization of the substituent pattern in the indole nucleus. The thus obtained selectivity for the 5-HT₂ receptors is quite outstanding compared to the former compounds (e.g. sertindole and Lu 26-042).

Other structural classes of 5-HT₂ antagonists in addition to affinity for 5-HT₂ receptors have affinity for receptors other than the receptors studied in this paper. Ritanserin has rather high affinity for histamine H₁ receptors¹⁹ and the piperazine derivative LY165163 (PAPP) in addition to 5-HT₂ receptor affinity has affinity for serotonergic 5-HT_{1A} receptors.²⁰ Testing of compound 10i for H₁ and 5-HT_{1A} receptor binding affinity, using [³H]mepyramine and [³H]-8-OH-DPAT as ligands, respectively, resulted in IC₅₀ values greater than 10 000 nM (unpublished results).

In the preceding paper within this series¹ two minimum conformations for the 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles were suggested. The minimum conformations were determined by molecular mechanics calculation of po-

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Table II. Pharmacological Activity of Selected 1-(4-Piperidinyl)indoles 10

compd	inhibition of quipazine-induced head twitches ^a			inhibition of pergolide-induced rotations ^a at 2 h (sc)
	2 h (sc)	24 h (sc)	24 h (po)	
10a	0.30 (0.11–0.81)	0.68 (0.20–2.31)	NT ^b	9.3 (2.6–32)
10e	0.019 (0.0042–0.085)	0.0081 (0.0034–0.019)	0.0041 (0.00067–0.025)	>24
10i	0.096 (0.041–0.22)	0.0041 (0.00041–0.040)	0.038 (0.014–0.098)	>23
10j	0.062 (0.029–0.13)	0.014 (0.0041–0.047)	0.019 (0.0059–0.060)	>18
10l	0.25 (0.10–0.60)	0.028 (0.0093–0.084)	0.046 (0.017–0.11)	>30
10n	0.036 (0.013–0.093)	0.0021 (0.00043–0.010)	0.0040 (0.0013–0.012)	>22
sertindole	0.035 (0.022–0.056)	0.030 (0.014–0.066)	0.039 (0.020–0.078)	3.7 (1.5–8.9)
Lu 26-042	0.11 (0.064–0.18)	0.052 (0.017–0.16)	0.055 (0.028–0.12)	>17
ritanserin	0.10 (0.056–0.18)	0.98 (0.35–2.7)	NT	>21

^a Results are expressed as ED₅₀ values in $\mu\text{mol/kg}$. 95% Confidence limits in brackets. ^b NT: not tested.

tential curves for the rotation of the piperidine ring. The calculations were performed with *N*-methyl derivatives for simplicity. The calculated potential curves for rotation of the chair conformation of the piperidine ring in the unsubstituted 3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)indole are qualitatively very similar to that of the 1-(4-fluorophenyl)-3-(1-methyl-4-piperidinyl)indole. The energy of the conformations of 3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)indole corresponding to the two minimum-energy conformations suggested for the 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles are calculated to be less than 1 kcal/mol higher than the energy of the global minimum conformation of the former compound (Gundertofte, K., H. Lundbeck A/S, Denmark, personal communication, 1991). These calculations indicate that the higher selectivity for 5-HT₂ receptors obtained within the series of 3-(4-fluorophenyl)-1-(4-piperidinyl)indoles compared to 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles cannot be explained by steric reasons, but is more likely due to differences in the electrostatic potentials around the indole nucleus. A further conformational study of the substituted 4-piperidinyl- and 1,2,3,6-tetrahydro-4-pyridinylindoles, described in this and the preceding paper,¹ and comparison with other structurally unrelated selective and nonselective 5-HT₂ receptor antagonists are in progress.

In Table II are reported some important *in vivo* pharmacological effects of selected compounds. Quipazine is a 5-HT₂ agonist which induces the characteristic head twitch syndrome in rats.²¹ The 6-chloro derivative 10a inhibited these head twitches with a lower potency than did the corresponding 1-(4-fluorophenyl)indole sertindole. In contrast, the 5-methyl-substituted indoles 10e, 10j, and 10n and the 2,5-dimethyl-substituted indoles 10i and 10l inhibited the head twitches with high potency. Even 24 h after administration of the substances the syndrome was effectively prevented, both after subcutaneous and oral administration. The latter derivatives were in general 2–20 times more efficient 24 h after administration compared to 2 h after the administration. The urea derivative 10n was actually the most potent 5-HT₂ antagonist *in vivo* within the present series of indoles. Some of the compounds within this series are even more potent centrally acting 5-HT₂ antagonists than the key derivatives sertindole and Lu 26-042 from the previously described 1-(4-fluorophenyl)indole series.^{1,2} In order to confirm the absence of any acute antidopaminergic activity, selective compounds were tested for their ability

to inhibit pergolide-induced (D₂ agonist) contralateral circling in rats with unilateral 6-OHDA lesions.²² This test model is very sensitive to classical dopamine D₂ antagonists. Neuroleptics, such as haloperidol and fluphenazine, are active in the range of 0.01–0.05 $\mu\text{mol/kg}$.⁵ Except for the less selective 6-chloro derivative 10a, none of the tested compounds were able to block the pergolide-induced circling behavior.

In comparison to ritanserin the key derivative 10i is quite outstanding both with regard to 5-HT₂ receptor selectivity (relative to D₂ and α_1 receptors) in binding studies (Table I) and *in vivo* 5-HT₂ antagonistic potency (Table II). This compound is at present being further studied in extended pharmacological test models as prototype of an extremely selective 5-HT₂ antagonist.

Experimental Section

All reactions were carried out under a positive pressure of nitrogen. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ¹H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, dd = double doublet, m = multiplet. Content of water in crystalline compounds was determined by Karl Fischer titration. Microanalyses were performed by Lundbeck Analytical Department and results obtained were within $\pm 0.4\%$ of the theoretical values.

Syntheses of 1-(2-Halogenoethyl)-2-imidazolidinones. 1-(2-Chloroethyl)-2-imidazolidinone was prepared according to literature.^{1,23} 1-(2-Chloroethyl)-2-imidazolidinone was easily converted to 1-(2-iodoethyl)-2-imidazolidinone by using the Finkelstein reaction.²⁴ The preparation of 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone followed the method reported by Costelli and Züst.²⁵

General Procedures for the Synthesis of Methyl 3-(4-Fluorophenyl)-1*H*-indole-2-carboxylates (6). Methyl 5-Methyl-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (6a). To a solution of *p*-toluidine (119.4 g, 1.1 mol) in concentrated aqueous HCl (0.58 L) was added a solution of NaNO₂ (84.6 g, 1.2 mol) in water (0.5 L) at 0–5 °C during 1.5 h. The reaction mixture was added in one portion to a mixture of methyl 2-(4-fluorobenzyl)-3-oxobutanoate (5) (250 g, 1.1 mol), KOH (220 g, 3.9 mol), water (0.5 L), ethanol (1.25 L), and ice (2 kg) under stirring. After

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reaction for 2 h at room temperature, the reaction mixture was extracted with diethyl ether (2 × 2 L). The combined organic phases were washed with water (3 L) and dried (Na₂SO₄). Evaporation of the solvents afforded the crude 4-tolylhydrazone of methyl 2-oxo-3-(4-fluorophenyl)propanoate (330 g), which was used without further purification.

A mixture of the crude hydrazone, methanol (2.25 L), and concentrated H₂SO₄ (0.1 L) was refluxed for 18 h. The reaction mixture was cooled to room temperature, and a part of the solvents were evaporated in vacuo. The thus obtained solution was cooled to 0 °C, and the precipitated compound was filtered off and dried overnight in vacuo: yield 180 g (58%); mp 151–155 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 3.80 (s, 3 H), 7.1–7.2 (m, 3 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.50 (dd, 2 H), 9.10 (broad s, 1 H). Anal. (C₁₇H₁₄FNO₂) C, H, N.

The following compounds were prepared accordingly: Methyl 3-(4-fluorophenyl)-1H-indole-2-carboxylate (5b) was isolated as an oil: ¹H NMR (CDCl₃) δ 3.80 (s, 3 H), 7.10–7.20 (m, 3 H), 7.30–7.50 (m, 2 H), 7.55 (dd, 2 H), 7.60 (d, 1 H), 9.05 (broad s, 1 H).

Methyl 5-Fluoro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6c): mp 169–170 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.10–7.30 (m, 4 H), 7.40 (dd, 2 H), 7.50 (dd, 1 H), 9.05 (broad s, 1 H). Anal. (C₁₈H₁₁F₂NO₂) C, H, N.

Methyl 5-Chloro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6d): mp 184–186 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 3.80 (s, 3 H), 7.15 (t, 2 H), 7.25–7.40 (m, 2 H), 7.50 (dd, 2 H), 7.55 (s, 1 H), 9.10 (broad s, 1 H). Anal. (C₁₈H₁₁ClFNO₂) C, H, N.

Methyl 3-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-indole-2-carboxylate (6e): mp 164–166 °C (methanol); ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.20 (t, 2 H), 7.50 (dd, 2 H), 7.55–7.65 (m, 2 H), 7.85 (s, 1 H), 9.30 (broad s, 1 H). Anal. (C₁₇H₁₁F₄NO₂) C, H, N.

Methyl 3-(4-Fluorophenyl)-7-methyl-1H-indole-2-carboxylate (6f): mp 159–161 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.50 (s, 3 H), 3.80 (s, 3 H), 7.00–7.20 (m, 4 H), 7.40 (d, 1 H), 7.50 (dd, 2 H), 8.90 (broad s, 1 H). Anal. (C₁₇H₁₄FNO₂) C, H, N.

Methyl 7-Bromo-3-(4-fluorophenyl)-4-methyl-1H-indole-2-carboxylate (6g): mp 112–116 °C (dichloromethane/*n*-heptane, 1:1); ¹H NMR (CDCl₃) δ 2.00 (s, 3 H), 3.75 (s, 3 H), 6.75 (d, 1 H), 7.10 (t, 2 H), 7.40 (d, 1 H), 7.55 (dd, 2 H), 9.00 (broad s, 1 H). Anal. (C₁₇H₁₃BrFNO₂) C, H, N.

Methyl 6-Chloro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6h). To a suspension of sodium hydride (52.5 g, 1.1 mol) (50% suspension in mineral oil, from which the mineral oil was removed by extraction with dry *n*-heptane) in dry tetrahydrofuran (250 mL) was added a solution of *N*-benzoyl-5-chloro-2-(4-fluorobenzoyl)aniline²⁶ (7) (129 g, 0.36 mol) in dry tetrahydrofuran (500 mL) during 0.5 h at 20 °C (ice cooling). This mixture was stirred for 1 h at room temperature. Then methyl 2-bromoacetate (101 mL, 1.1 mol) was added during 0.5 h at 20 °C (ice cooling), and the mixture was stirred for another 1 h. The solvents were evaporated in vacuo. The remaining oil was diluted with methanol (250 mL), and 5.4 M sodium methoxide in methanol (670 mL) was added carefully. After 1 h at room temperature, the solvents were evaporated in vacuo, and water (500 mL) was added. The thus obtained mixture was extracted with ethyl acetate (2 × 750 mL), and the combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation of the solvents in vacuo afforded the crude title compound, which was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:3). Pure title compound was obtained by crystallization from heptane (33 g, 30%); mp 194–196 °C; ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.05–7.25 (m, 3 H), 7.40–7.60 (m, 4 H), 9.10 (broad s, 1 H). Anal. (C₁₈H₁₁ClFNO₂) C, H, N.

(26) *N*-Benzoyl-5-chloro-2-(4-fluorobenzoyl)aniline was prepared by benzoylation of 5-chloro-2-(4-fluorobenzoyl)aniline prepared as described for 2-(3-chloro-4-methylbenzoyl)aniline. 2,3-Dichloroindone as a Dienophilic Compound. *J. Am. Chem. Soc.* 1959, 81, 5641–5646.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1H-indoles (4). 2,5-Dimethyl-3-(4-fluorophenyl)-1H-indole (4a). A solution of (4-fluorophenyl)acetone²⁷ (3) (60 g, 0.39 mol), 4-tolylhydrazine, HCl (68.8 g, 0.43 mol), and triethylamine (165 mL, 1.2 mol) in ethanol (600 mL) was refluxed for 18 h. The reaction mixture was cooled to room temperature, the solvents were evaporated in vacuo, and water (500 mL) was added to the remaining oil. The thus obtained mixture was extracted with ethyl acetate (2 × 250 mL). The combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation of the solvents afforded the crude (4-fluorophenyl)acetone tolylhydrazones (100 g) as an oil, which was used without further purification. The crude hydrazone (100 g, 0.39 mol), ethanol (700 mL), and concentrated H₂SO₄ (40 mL) were refluxed for 18 h. After cooling to room temperature, water (500 mL) was added. The thus obtained mixture was extracted with ethyl acetate (2 × 700 mL), the combined organic phases were washed with brine and dried (Na₂SO₄) and the solvents were evaporated in vacuo. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane, 1:4) which afforded 75.5 g (80%) of pure 4a as an oil. An analytical sample was crystallized from *n*-heptane: mp 124–128 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 6.95 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.35 (s, 1 H), 7.40 (dd, 2 H), 7.70 (broad s, 1 H). Anal. (C₁₈H₁₄FN) C, H, N.

3-(4-Fluorophenyl)-7-methyl-1H-indole (4b). A mixture of methyl 3-(4-fluorophenyl)-7-methyl-1H-indole-2-carboxylate (6f) (35.0 g, 0.12 mol), methanol (350 mL), and 1.8 M aqueous NaOH (50 mL) was refluxed for 1 h. Then the solution was cooled to room temperature and acidified with concentrated aqueous HCl to pH = 1. The precipitated product was filtered off and dissolved in ethyl acetate (1000 mL). The resulting solution was dried (Na₂SO₄), and the solvent was evaporated in vacuo. The crude acid was decarboxylated without further purification. A mixture of the crude acid (33.0 g, 0.12 mol), copper (2.5 g), and NMP (500 mL) was refluxed for 5 days. The reaction mixture was cooled to room temperature, and filtered, and water (250 mL) was added. The resulting mixture was extracted with diethyl ether (2 × 400 mL). The combined organic phases were washed with brine (3 × 500 mL) and dried (Na₂SO₄). Evaporation of the solvent and crystallization from diethyl ether afforded 20.9 g (77%) of the title compound: mp 151–153 °C; ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 7.00–7.20 (m, 2 H), 7.1 (t, 2 H), 7.30 (broad s, 1 H), 7.60 (dd, 2 H), 7.70 (d, 1 H), 8.10 (broad s, 1 H). Anal. (C₁₈H₁₃FN) C, H, N.

The following compound was prepared accordingly: 3-(4-Fluorophenyl)-5-methyl-1H-indole (4c): mp 123–128 °C (ethyl acetate/*n*-heptane, 1:3); ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H), 8.10 (broad s, 1 H). Anal. (C₁₈H₁₃FN) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1H-indole (4d). Methyl 7-bromo-3-(4-fluorophenyl)-4-methyl-1H-indole-2-carboxylate (6g) (17.5 g, 0.048 mol) was hydrolyzed and decarboxylated as described above, except that the reaction mixture was worked up before the arylation procedure. This afforded a mixture of two compounds, which were separated by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:5). The purification gave 3-(4-fluorophenyl)-4-methyl-1H-indole (6e) (3.4 g, 21%) (NMR as described below) and 7-bromo-3-(4-fluorophenyl)-4-methyl-1H-indole (6d) (5.1 g) as an oil. A mixture of the crude 6d (5.1 g, 0.017 mol), ammonium formate (5 g, 0.090 mol), 5% palladium on activated carbon (2.0 g), and methanol (50 mL) was refluxed for 1 h. After cooling to room temperature, the catalyst was filtered off. The solvents were evaporated and water (100 mL) was added. The thus formed mixture was made alkaline by addition of concentrated aqueous NaOH and extracted with diethyl ether (100 mL). The combined organic phases were dried (Na₂SO₄) and the solvent was evaporated. The remaining oil crystallized from diethyl ether and afforded further 3.5 g (29%) of the title compound 6e. An analytical sample was recrystallized from *n*-heptane: mp 80–82 °C; ¹H NMR (CDCl₃) δ 2.26 (s, 3 H),

(27) (4-Fluorophenyl)acetone was prepared from 4-fluorobenzyl cyanide by the method described for phenylacetone. Julian, P. L.; Olivier, J. J. In *Organic Syntheses*; Blatt, A. H., Ed.; Wiley & Sons: London, 1948; Collect. Vol. 2, pp 391–392.

6.90 (d, 1 H), 7.05 (s, 1 H), 7.05 (t, 2 H), 7.15 (t, 1 H), 7.25 (d, 1 H), 7.40 (dd, 2 H), 8.15 (broad s, 1 H). Anal. (C₁₅H₁₂FN) C, H, N.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1-(4-pyridinyl)-1H-indoles (8). 2,5-Dimethyl-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8a). 2,5-Dimethyl-3-(4-fluorophenyl)-1H-indole (6a) (50 g, 0.21 mol), 4-bromopyridine hydrochloride (80 g, 0.41 mol), K₂CO₃ (90 g, 0.65 mol), CuBr (10 g), and NMP (750 mL) were refluxed under stirring for 18 h. The reaction mixture was cooled, poured into water (1000 mL), and extracted with diethyl ether (2 × 750 mL). The combined organic phases were washed with brine (3 × 1000 mL), dried (Na₂SO₄), and treated with activated carbon. Evaporation of the diethyl ether afforded the title compound (29.8 g) which was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 3:1). The title compound 20.5 g (31%) crystallized from diethyl ether: mp 172–174 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 6.95 (broad d, 1 H), 7.10–7.25 (m, 3 H), 7.35 (m, 3 H), 7.45 (dd, 2 H), 7.70 (broad s, 2 H). Anal. (C₂₁H₁₇FN₂) C, H, N.

The following compound was prepared accordingly: 3-(4-Fluorophenyl)-7-methyl-1-(4-pyridinyl)-1H-indole (8b): mp 98–100 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.20 (s, 3 H), 7.05–7.30 (m, 5 H), 7.30 (d, 2 H), 7.60 (dd, 2 H), 7.75 (d, 1 H), 8.70 (d, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

3-(4-Fluorophenyl)-5-methyl-1-(4-pyridinyl)-1H-indole (8c). A mixture of methyl 3-(4-fluorophenyl)-5-methyl-1H-indole-2-carboxylate (6a) (180 g, 0.64 mol), methanol (2.5 L), and 1.8 M aqueous NaOH was refluxed for 1.5 h. Then the solution was cooled to room temperature and acidified with concentrated aqueous HCl to pH = 1. The precipitated product was filtered off and dissolved in ethyl acetate (1.0 L). The thus formed solution was dried (Na₂SO₄), and the solvents were evaporated in vacuo. The crude acid (140 g) was decarboxylated without further purification. A mixture of the crude acid (140 g, 0.52 mol), copper (12 g), and NMP (2.5 L) was refluxed for 5 days. The mixture was cooled to room temperature and 4-chloropyridine hydrochloride (140 g, 0.94 mol), K₂CO₃ (287 g, 2.1 mol), and CuBr (35 g) were added. The thus formed mixture was refluxed for 18 h. After cooling to room temperature, water (2.0 L) was added and the mixture was extracted with diethyl ether (2 × 2.5 L). The combined organic phases were washed with brine (2 × 2.5 L) and dried (Na₂SO₄). Evaporation of the solvents afforded 116.9 g (60%) of the title compound: mp 125–127 °C; ¹H NMR (CDCl₃) δ 2.50 (s, 3 H), 7.15 (d, 1 H), 7.20 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 2 H), 7.55–7.70 (m, 4 H), 8.70 (d, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

The following compounds were prepared accordingly: 6-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8d) was isolated as an oil: ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.25 (d, 1 H), 7.45 (s, 1 H), 7.60 (broad s, 2 H), 7.60 (dd, 2 H), 7.75 (s, 1 H), 7.80 (d, 1 H), 8.70 (broad s, 2 H).

3-(4-Fluorophenyl)-1-(4-pyridinyl)-1H-indole (8e): mp 115–118 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.25–7.40 (m, 2 H), 7.45–7.55 (m, 3 H), 7.60 (dd, 2 H), 7.75 (d, 1 H), 7.90 (d, 1 H), 8.70 (d, 2 H). Anal. (C₁₅H₁₁FN₂) C, H, N.

5-Fluoro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8f): mp 142–145 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.05 (dd, 1 H), 7.20 (t, 2 H), 7.40–7.55 (m, 4 H), 7.60 (dd, 2 H), 7.70 (dd, 1 H), 8.75 (d, 2 H). Anal. (C₁₅H₁₀F₂N₂) C, H, N.

5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8g): mp 162–164 °C (diethyl ether); ¹H NMR (DMSO-*d*₆) δ 7.30 (m, 3 H), 7.75–7.95 (m, 6 H), 8.25 (s, 1 H), 8.75 (d, 2 H). Anal. (C₁₅H₁₀ClFN₂) C, H, N.

3-(4-Fluorophenyl)-1-(4-pyridinyl)-5-(trifluoromethyl)-1H-indole (8h): mp 163–165 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.45–7.70 (m, 6 H), 7.80 (d, 1 H), 8.15 (s, 1 H), 8.80 (d, 2 H). Anal. (C₂₀H₁₂F₄N₂) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1-(4-pyridinyl)-1H-indole (8i): mp 100–102 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.25 (s, 3 H), 7.00 (d, 1 H), 7.10 (t, 2 H), 7.25 (t, 1 H), 7.30 (s, 1 H), 7.45 (dd, 2 H), 7.55 (broad d, 2 H), 7.65 (d, 1 H), 8.75 (broad s, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

General Procedure for the Synthesis of 1-[2-[4-[3-(4-Fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinones (12a–c). 1-[2-[4-[2,5-Dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12c). A mixture of 2,5-dimethyl-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8a) (5.0 g, 0.016 mol), 1-(2-iodoethyl)-2-imidazolidinone (7.6 g, 0.032 mol), and methylisobutylketone (50 mL) was refluxed for 6 h. After cooling to room temperature, the precipitated product was filtered off and dried in vacuo at 70 °C overnight. This afforded 6.3 g of 4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-[2-(2-imidazolidinon-1-yl)ethyl]pyridinium iodide. The crude pyridinium iodide (6.3 g, 0.011 mol) was suspended in ethanol (100 mL), and sodium borohydride (2.1 g, 0.055) was added in three portions during 3.5 h. Then the solvent was evaporated in vacuo and water (100 mL) was added. The thus obtained mixture was extracted with dichloromethane (2 × 50 mL). The combined organic phases were washed with brine (100 mL) and dried (MgSO₄). Evaporation of the solvents and purification by column chromatography on silica gel (eluted with ethyl acetate/ethanol 8:1 containing 4% triethylamine) afforded the title compound (2.8 g, 41%). An analytical sample was recrystallized from ethanol: mp 151–153 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.40–2.50 (m, 2 H), 2.45 (s, 3 H), 2.75 (t, 2 H), 2.90 (t, 2 H), 3.35–3.40 (m, 2 H), 3.50–3.55 (m, 4 H), 3.55–3.65 (m, 1 H), 4.30 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.40 (s, 1 H), 7.45 (dd, 2 H). Anal. (C₂₈H₂₇FN₃O) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12a): mp 129–131 °C (diethyl ether); ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 2.60–2.75 (m, 2 H), 2.75 (t, 2 H), 2.90 (t, 2 H), 3.40–3.50 (m, 2 H), 3.40–3.60 (m, 6 H), 4.65 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00–7.20 (m, 3 H), 7.25 (s, 1 H), 7.45 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H). Anal. (C₂₈H₂₇FN₃O) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-7-methyl-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12b): mp 126–128 °C (diethyl ether); ¹H NMR (CDCl₃) δ 2.45–2.60 (m, 2 H), 2.55 (s, 3 H), 2.80 (t, 2 H), 2.85 (t, 2 H), 3.20–3.30 (m, 2 H), 3.30–3.60 (m, 6 H), 5.25 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00 (d, 1 H), 7.05–7.20 (m, 4 H), 7.55 (dd, 2 H), 7.70 (d, 1 H). Anal. (C₂₈H₂₇FN₃O·0.5H₂O) C, H, N.

General Procedure for the Syntheses of Substituted 3-(4-Fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles (12d,e). The methyl-substituted compounds were prepared as described above for the 2-(2-imidazolidinon-1-yl)-ethyl-substituted compounds, except that the quaternization was performed with iodomethane in acetone at 40 °C overnight. The following compounds were prepared in this manner: 3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (12d) was isolated as an oil: ¹H NMR (CDCl₃) δ 2.25 (s, 6 H), 2.60–2.75 (m, 2 H), 2.80 (t, 2 H), 3.15–3.25 (m, 2 H), 5.85–5.95 (m, 1 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.20 (s, 1 H), 7.45 (d, 1 H), 7.45 (dd, 2 H), 7.60 (s, 1 H).

2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (12e): mp 98–100 °C (di-2-propyl ether/*n*-heptane, 1:1); ¹H NMR (CDCl₃) δ 2.35 (s, 3 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.40–2.50 (m, 2 H), 2.80 (t, 2 H), 3.20–3.30 (m, 2 H), 5.85–5.95 (m, 1 H), 7.00 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.40 (d, 1 H), 7.45 (dd, 2 H). Anal. (C₂₂H₂₀FN₂) C, H, N.

General Procedures for the Synthesis of Substituted 3-(4-Fluorophenyl)-1-(4-piperidinyl)-1H-indoles (10). 1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10d). 5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8g) (3.0 g, 0.0098 mol) was dissolved in acetic acid (100 mL), and PtO₂ (0.3 g) was added. After hydrogenation for 3 days at 3 atm the catalyst was filtered off, the acetic acid was evaporated in vacuo, and water (50 mL) was added. The acidic solution was made alkaline (pH > 9) with concentrated sodium hydroxide and extracted with ethyl acetate (2 × 50 mL). The combined organic phases were successively washed with diluted sodium hydroxide (50 mL), washed with brine, and finally dried (Na₂SO₄). Evaporation of the solvent gave 2.5 g of crude 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1H-indole as an oil, which was used without further purification.

A mixture of 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1H-indole (2.5 g, 0.0076 mol), 1-(2-chloroethyl)-2-imidazolidinone (2.1 g, 0.014 mol), K_2CO_3 (1.7 g, 0.012 mol), KI (0.1 g), and methyl isobutyl ketone (250 mL) was refluxed for 18 h. The reaction mixture was cooled, poured into water (100 mL), and extracted with ethyl acetate (2×100 mL). The combined organic phases were dried (Na_2SO_4), and the solvents were evaporated in vacuo. The remaining oil was precipitated from ethyl acetate: 1.8 g (43%); mp 171–174 °C; ^1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.35 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.45 (m, 1 H), 4.60 (broad s, 1 H), 7.10 (t, 2 H), 7.20 (d, 1 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.50 (dd, 2 H), 7.8 (s, 1 H). Anal. ($C_{24}H_{28}ClFN_4O$) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[6-Chloro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10a): mp 192–194 °C (2-propanol); ^1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.35 (m, 2 H), 2.65 (t, 2 H), 3.10–3.25 (m, 2 H), 3.45 (t, 2 H), 3.40–3.60 (m, 4 H), 4.10–4.30 (m, 1 H), 4.50 (broad s, 1 H), 7.10 (t, 2 H), 7.15 (d, 1 H), 7.30 (s, 1 H), 7.40 (s, 1 H), 7.55 (dd, 2 H), 7.75 (d, 1 H). Anal. ($C_{24}H_{28}ClFN_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10b): mp 172–173 °C (diethyl ether/*n*-heptane, 1:1); ^1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.6 (t, 2 H), 3.05–3.30 (m, 2 H), 3.35 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.45 (m, 1 H), 4.70 (broad s, 1 H), 7.05–7.30 (m, 4 H), 7.35 (s, 1 H), 7.40 (d, 1 H), 7.60 (dd, 2 H), 7.85 (d, 1 H). Anal. ($C_{24}H_{28}FN_4O$) C, H, N.

1-[2-[4-[5-Fluoro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10c): mp 153–156 °C (ethyl acetate/*n*-heptane, 1:1); ^1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.15–4.40 (m, 1 H), 4.70 (broad s, 1 H), 7.00 (dt, 1 H), 7.15 (t, 2 H), 7.35 (dd, 1 H), 7.40 (s, 1 H), 7.50 (dd, 1 H), 7.55 (dd, 2 H). Anal. ($C_{24}H_{28}F_2N_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10e): mp 186–188 °C (ethanol); ^1H NMR ($CDCl_3$) δ 1.95–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.50 (s, 3 H), 2.60 (t, 2 H), 3.10–3.20 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.15–4.40 (m, 1 H), 4.70 (broad s, 1 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.30 (s, 1 H), 7.35 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{25}H_{30}FN_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10f): mp 182–184 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ 2.05–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.20–4.40 (m, 1 H), 4.60 (broad s, 1 H), 7.15 (t, 2 H), 7.40 (s, 1 H), 7.50 (broad s, 2 H), 7.55 (dd, 2 H), 8.10 (s, 1 H). Anal. ($C_{26}H_{28}F_4N_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-4-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10g): mp 163–165 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ 1.95–2.20 (m, 4 H), 2.20–2.45 (m, 2 H), 2.25 (s, 3 H), 2.60 (t, 2 H), 3.05–3.20 (m, 2 H), 3.35 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.35 (m, 1 H), 4.60 (broad s, 1 H), 6.60 (d, 1 H), 7.05 (t, 2 H), 7.05–7.20 (m, 2 H), 7.25 (s, 1 H), 7.35 (dd, 2 H). Anal. ($C_{25}H_{30}FN_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (10j): mp 175–177 °C (acetone); ^1H NMR ($DMSO-d_6$) δ 1.05 (d, 6 H), 2.05–2.40 (m, 4 H), 2.40 (s, 3 H), 2.95–3.50 (m, 10 H), 3.50–3.65 (m, 2 H), 3.75–3.95 (m, 1 H), 4.50–4.70 (m, 1 H), 5.00–6.00 (broad s, 2 H), 7.05 (d, 1 H), 7.30 (t, 2 H), 7.55 (d, 1 H), 7.65 (s, 1 H), 7.70 (dd, 2 H), 7.75 (s, 1 H). Anal. ($C_{28}H_{38}FN_4O_4$) C, H, N.

1-[2-[4-[2,5-Dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10i). To a refluxing mixture of 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12c) (12 g, 0.028 mol), 5% palladium on activated carbon (5.0), and ethanol (160 mL) was added ammonium formate (17 g, 0.27 mol) during 25 h. The reaction mixture was cooled to room temperature and the catalyst filtered off. The solvents were evaporated and water (100 mL) was added. The thus formed mixture was made alkaline by concentrated NaOH and extracted with ethyl acetate (2×200 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated. The crude 10i (7.0 g)

was recrystallized from ethanol which gave 4.6 g (38%): mp 188–90 °C; ^1H NMR δ 1.80–1.95 (m, 2 H), 2.15–2.35 (m, 2 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 2.50–2.75 (m, 4 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.65 (m, 4 H), 4.10–4.30 (m, 1 H), 4.40 (broad s, 1 H), 6.95 (d, 1 H), 7.15 (t, 2 H), 7.30 (s, 1 H), 7.40 (dd, 2 H), 7.50 (d, 1 H). Anal. ($C_{28}H_{34}FN_4O$) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[3-(4-Fluorophenyl)-7-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10h): mp 141–144 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ 2.00–2.35 (m, 6 H), 2.60 (t, 2 H), 2.75 (s, 3 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.40–3.60 (m, 4 H), 4.45 (broad s, 1 H), 4.70–4.85 (m, 1 H), 6.95–7.05 (m, 2 H), 7.10 (t, 2 H), 7.35 (s, 1 H), 7.55 (dd, 2 H), 7.70 (d, 1 H). Anal. ($C_{28}H_{32}FN_4O$) C, H, N.

3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-4-piperidinyl)-1H-indole fumarate (10k): mp 170–172 °C (ethanol); ^1H NMR ($DMSO-d_6$) δ 1.90–2.30 (m, 4 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.45–2.55 (m, 4 H), 3.10–3.25 (m, 2 H), 4.35–4.60 (m, 1 H), 6.60 (s, 2 H), 7.05 (d, 1 H), 7.25 (t, 2 H), 7.50 (d, 1 H), 7.60 (s, 1 H), 7.70 (dd, 2 H), 7.75 (s, 1 H). Anal. ($C_{21}H_{22}FN_2 \cdot C_4H_4O_4$) C, H, N.

2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)-1H-indole (10l): mp 110–112 °C (*n*-heptane); ^1H NMR ($CDCl_3$) δ 1.75–2.00 (m, 2 H), 2.05–2.30 (m, 2 H), 2.35 (s, 6 H), 2.40 (s, 3 H), 2.60–2.80 (m, 2 H), 3.00–3.20 (m, 2 H), 4.10–4.30 (m, 1 H), 6.95 (d, 1 H), 7.10 (t, 2 H), 7.30 (s, 1 H), 7.40 (dd, 2 H). Anal. ($C_{27}H_{32}FN_2$) C, H, N.

The following urea derivatives were prepared as described previously¹ from the corresponding unsubstituted piperidinylindoles 9 prepared as described above: 1-[1-[2-(3,3-Dimethyl-1-ureido)ethyl]-4-piperidinyl]-3-(4-fluorophenyl)-5-methyl-1H-indole (10m): mp 126–128 °C (diethyl ether); ^1H NMR ($CDCl_3$) δ 1.90–2.40 (m, 6 H), 2.50 (s, 3 H), 2.60 (t, 2 H), 2.95 (s, 6 H), 3.05–3.15 (m, 2 H), 3.30–3.45 (m, 2 H), 4.15–4.35 (m, 1 H), 4.95 (broad s, 1 H), 7.05–7.15 (m, 3 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.55 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{28}H_{34}FN_4O$) C, H, N.

1-[1-[2-(1,3-Dimethyl-1-ureido)ethyl]-4-piperidinyl]-3-(4-fluorophenyl)-5-methyl-1H-indole hydrochloride (10n): mp 204–205 °C (acetone); ^1H NMR ($CDCl_3$) δ 2.20–2.35 (m, 2 H), 2.45 (s, 3 H), 2.75–3.35 (m, 6 H), 2.80 (s, 3 H), 3.00 (s, 3 H), 3.75–3.95 (m, 4 H), 4.25–4.45 (broad s, 1 H), 4.45–4.60 (m, 1 H), 7.05–7.15 (m, 3 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.55 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{28}H_{34}FN_4O \cdot HCl \cdot 0.65H_2O$) C, H, N.

Synthesis of 8-(4-Fluorophenyl)-5-methyl-1-(1-methyl-4-piperazinyl)-1H-indole (14). 1-Amino-3-(4-fluorophenyl)-5-methyl-1H-indole (13). Potassium *tert*-butoxide (7.5 g, 0.067 mol) was added to a solution of 3-(4-fluorophenyl)-5-methyl-1H-indole (4c) (15 g, 0.067 mol) in DMF during 15 min at 0–5 °C. Then a suspension of potassium hydroxylamine-*O*-sulfonate in DMF (prepared by addition of potassium *tert*-butoxide (7.5 g, 0.067 mol) to a suspension of hydroxylamine-*O*-sulfonic acid (7.6 g, 0.067 mol) in DMF (100 mL) during 0.5 h at 0–5 °C) was added slowly at 0–5 °C. After reaction at 0 °C for 1 h the mixture was poured onto ice and extracted with diethyl ether (2×250 mL). The combined organic phases were washed with brine (3×250 mL) and dried (Na_2SO_4). Evaporation of the solvents afforded a mixture of the title compound and the starting material, which were separated by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:3). This afforded starting material (9.0 g, 60%) and the title compound which crystallized from diethyl ether (4.3 g, 27%): mp 116–120 °C; ^1H NMR ($CDCl_3$) δ 2.50 (s, 3 H), 4.70 (s, 2 H), 7.05–7.20 (m, 3 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.55 (dd, 2 H), 7.60 (s, 1 H). Anal. ($C_{17}H_{18}FN_2$) C, H, N.

8-(4-Fluorophenyl)-5-methyl-1-(1-methyl-4-piperazinyl)-1H-indole (14). To a mixture of 1-amino-3-(4-fluorophenyl)-5-methyl-1H-indole (13) (1 g, 0.0042 mol) and toluene (20 mL) was added a 50% suspension of sodium amide in xylene (1.0 mL, 0.012 mol). After reaction for 15 min at room temperature a solution of *N,N*-bis(2-chloroethyl)methylamine (0.8 g, 0.0051 mol) in toluene (5 mL) was added slowly and the mixture was refluxed for 8 h. After cooling to room temperature, the solvents were evaporated in vacuo and water (100 mL) was added. The mixture was extracted with ethyl acetate (2×50 mL), and the combined organic phases were dried (Na_2SO_4). Evaporation of the solvents in vacuo and purification by column chromatography on silica

gel (eluted with ethyl acetate/ethanol 4:1 containing 4% triethylamine) afforded pure 14 (1.0 g, 74%) as an oil. An analytical sample crystallized from *n*-heptane: mp 105–107 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 2.70 (broad s, 4 H), 3.25 (t, 4 H), 7.10 (broad d, 1 H), 7.15 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 1 H), 7.55 (dd, 2 H), 7.50 (broad s, 1 H). Anal. (C₂₀H₂₂FN₃O) C, H, N.

Pharmacological Test Methods. Animals. Male Wistar rats (Møl:Wist, SPF, 170–270 g) were used. We have recently described the handling procedures in details.⁵

Calculations. ED₅₀ values were calculated by log-probit analyses. IC₅₀ values were estimated from concentration–effect curves using a log-concentration scale. Details are available from the references cited in the description of specific test methods below.

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.²¹ Test compounds were injected sc or po to rats 2 or 24 h before quipazine (15 μmol/kg, sc). Head twitches were counted 30–40 min after the quipazine treatment. The number of head twitches in the drug treated group (at least four animals per dose) was expressed in percent of the number of head twitches in a quipazine-treated control group.

Antagonism of Pergolide-Induced Circling Behavior in Rats with Unilateral 6-OHDA Lesions. This test method is described in detail by Arnt and Hyttel.²² Contralateral circling is induced in 6-OHDA-lesioned rats in response to administration of pergolide (0.05 μmol/kg, sc). Test compounds were injected

sc 2 h before pergolide. The effect of individual doses of test drugs is calculated as percent of the mean effect of control sessions 1 week before and 1 week after the test session for each rat (at least four rats per dose).

Receptor Binding. DA D₂ Receptors. Affinity of test compounds to dopamine D₂ receptors was estimated by their ability to displace [³H]spiperone from rat striatal membranes as described by Hyttel.²³

5-HT₂ Receptors. Affinity of test compounds to serotonin 5-HT₂ receptors was estimated by their ability to displace [³H]-ketanserin from rat cortical membranes as described by Hyttel.²³

α₁ Adrenoceptors. Affinity of test compounds to α₁ adrenoceptors was estimated by their ability to displace [³H]prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.²⁴

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Synthesis and Structure–Activity Relationships of *N*-Propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine (Besipirdine) and Related Analogs as Potential Therapeutic Agents for Alzheimer's Disease¹

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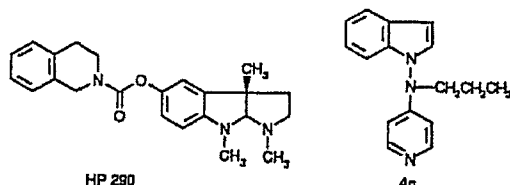
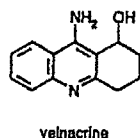
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A series of novel *N*-(4-pyridinyl)-1*H*-indol-1-amines and other heteroaryl analogs was synthesized and evaluated in tests to determine potential utility for the treatment of Alzheimer's disease. From these compounds, *N*-propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine (besipirdine, **4c**) was selected for clinical development based on in-depth biological evaluation. In addition to cholinomimetic properties based initially on *in vitro* inhibition of [³H]quinuclidinyl benzilate binding, *in vivo* reversal of scopolamine-induced behavioral deficits, and subsequently on other results, **4c** also displayed enhancement of adrenergic mechanisms as evidenced *in vitro* by inhibition of [³H]clonidine binding and synaptosomal biogenic amine uptake, and *in vivo* by reversal of tetrabenazine-induced ptosis. The synthesis, structure–activity relationships for this series, and the biological profile of **4c** are reported.

Introduction

Alzheimer's disease (AD) is an age-related, chronic neurodegenerative disorder occurring in middle or late life. The disease is characterized by a progressive dementia, which is associated with both severe disability in performing the activities of everyday life and a reduced life expectancy after onset of the disease. The disease is estimated to currently affect three to four million persons in the United States, and its prevalence is increasing as a greater proportion of the population reaches a longer life expectancy.² The well-known cholinergic hypothesis^{3–5} of AD was based on accumulated evidence suggesting that enzymes involved in the synthesis and/or hydrolysis of acetylcholine were deficient in brains of AD patients versus age-matched controls. This breakdown of central cholinergic transmission resulted in efforts to treat AD with cholinomimetic agents which either augment the synthesis or inhibit the hydrolysis of acetylcholine,⁴ or act directly at cholinergic receptors (first generation agents). On the basis of this approach, the potent acetylcholinesterase inhibitors velnacrine⁶ (HP 029) and HP 290,⁷ discovered in our laboratories, were advanced for clinical evaluation.



Neuropathological studies of brains from Alzheimer's patients also demonstrated that other neurotransmitter

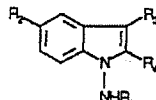
systems are affected in the disease process, including somatostatinergic,^{8,9} glutamatergic,^{10–12} and noradrenergic systems.^{13–15} In addition to enhancement of central cholinergic mechanisms, a program was initiated to discover compounds which would mitigate multiple biochemical deficits associated with AD. As a class, the aminopyridines were known to enhance release of both acetylcholine and norepinephrine.¹⁶ Since more lipophilic aminopyridine analogs had not been extensively investigated, synthesis of a series of (arylamino)-pyridines was initiated. The novel *N*-(4-pyridinyl)-1*H*-indol-1-amine **4c** emerged from this program, and the biological profile of **4c** shows a unique combination of adrenergic and cholinomimetic properties.¹ The synthesis, structure–activity relationships, and biological profile of **4c** constitute the subject of this paper. Various heteroaryl and pyrrole analogs of **4c** were reported in preliminary form,^{17,18} and results for the heteroaryl compounds are included in this paper. Pyrrole analogs of **4c** constitute the subject of a companion paper.¹⁹

Chemistry

Treatment of appropriately substituted indoles **1a–g**, pyrazole (**5a**), carbazole (**5b**), and indazole (**5c**) with hydroxylamine *O*-sulfonic acid and potassium or sodium hydroxide, utilizing the conditions reported by Somei and Natsume,²⁰ afforded substituted 1*H*-indol-1-amines **2a–g** and heteroaryl analogs **6a**,²¹ **6b**,²² **6c**,²³ and **6d**²³ (Tables 1 and 2, Schemes 1 and 2). Condensation of **2a–g** with 4-chloropyridine hydrochloride in 2-propanol or *N*-methyl-2-pyrrolidinone (NMP) provided the secondary pyridinylaminoindoles **3a–g**, which were alkylated to give tertiary (pyridinylamino)indoles **4a–n** (Table 3, Scheme 1). Deaza compounds **3h** and **4s** were prepared by alkylation of **1a** with 4-(chloromethyl)-pyridinium chloride and subsequent alkylation of the active methylene group with *n*-butyllithium and bromopropane.

Compounds **4p–r** were prepared from aldehyde **4o**, which was synthesized from **4c** under Vilsmeier condi-

⁹ Abstract published in *Advance ACS Abstracts*, December 15, 1995.

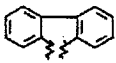
Table 1. Substituted 1*H*-Indol-1-amines


compd	R ₁	R ₂	R ₃	R ₄	starting mat.	mp, °C	yield, %
2a	H	H	H	H	1a	46–47 ^a	32
2b	H	H	CH ₃	H	1b	53–55 ^b	40
2c	H	H	H	CH ₃	1c	108–109 ^c	17
2d	H	Br	H	H	1d	oil	48
2e	H	Cl	H	H	1e	oil	55
2f	H	NO ₂	H	H	1f	166–167	18
2g	H	OCH ₃	H	H	1g	115–117	18
2h ^d	<i>n</i> -C ₃ H ₇	H	H	H	2a	oil	68

^a Literature²⁰ mp 41–41.5 °C. ^b Literature²⁰ mp 59.5–60.5 °C. ^c Literature²⁰ mp 114–115 °C. ^d C: calcd, 75.82; found, 75.41.

Table 2. Heteroaryl amines



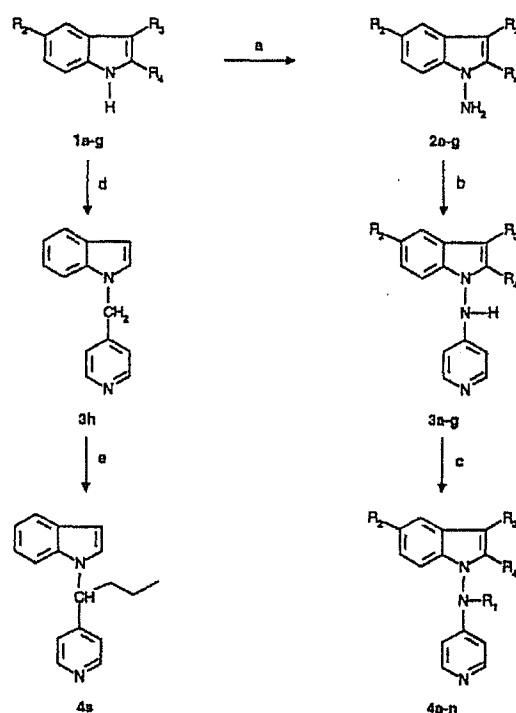
Compd.	R ₁ R ₂	Starting material
6a ^a		5a
6b ^b		5b
6c ^c		5c
6d ^c		5c

^a The amination product was a 1:1 mixture of 5a and 6a, which was used directly for the preparation of 7a without further purification. ^b The amination product was a 1:1 mixture of 5b and 6b, which was used directly for the preparation of 7b without further purification. ^c The amination afforded a 2:1 mixture of 6c and 6d which was separated by HPLC (silica, 10% ethyl acetate in DCM). The identity of each compound was determined by comparison of UV spectra to the literature.²³

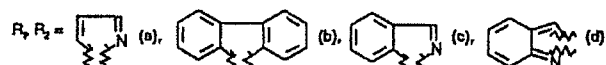
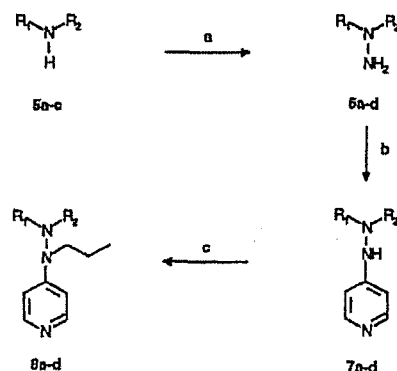
tions (Scheme 3, Table 3). Conversion of 4o to the oxime and subsequent dehydration with benzenesulfonyl chloride afforded nitrile 4p. Treatment of 4o with methylmagnesium bromide under Grignard conditions and oxidation of the intermediate carbinol with pyridinium dichromate provided ketone 4q. Wittig olefination of 4o with methyltriphenylphosphonium bromide and subsequent hydrogenation afforded the 3-ethyl analog 4r. Using similar synthetic methodology as previously described, various heteroaryl analogs related to 4c were also prepared (7a–d, 8a–d, 9a–d; Schemes 2 and 4; Table 4).

Discussion

Investigation of the pyrroloaminopyridines afforded a vinyl-substituted pyrrole analog as an initial lead compound with combined adrenergic and cholinomimetic-like properties.¹⁹ Extension of this lead provided a series of (pyridinylamino)indoles with enhanced adrenergic properties, and 4c emerged as the most promising compound. With respect to evaluation of preliminary mechanistic information and structure–activity relationships, all compounds were screened in a battery

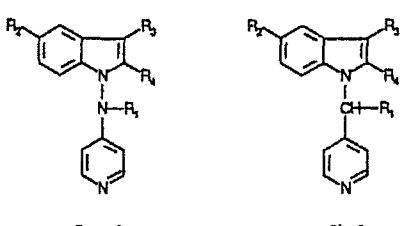
Scheme 1^a

^a (a) H₂NOSO₃H, KOH, DMF; (b) 4-chloropyridine hydrochloride, NMP; (c) R₁X or (R₁O)₂SO₂, NaH, DMF; (d) 4-(chloromethyl)pyridinium chloride; (e) *n*-BuLi, *n*-C₃H₇Br.

Scheme 2^a

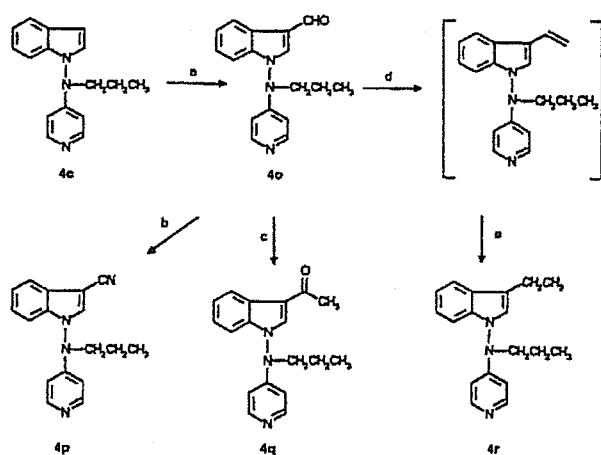
^a (a) H₂NOSO₃H, KOH, DMF; (b) 4-chloropyridine hydrochloride, NMP; (c) NaH, DMF; *n*-C₃H₇Br.

of assays, including assessment of potential cholinergic properties based on *in vitro* inhibition of acetylcholinesterase (CHEI), affinity for central muscarinic cholinergic receptors by *in vitro* inhibition of [³H]quinuclidinyl benzilate binding (QNB, a potent muscarinic antagonist), and *in vivo* reversal of the amnestic-like effects of the muscarinic receptor antagonist scopolamine in the scopolamine dementia dark avoidance (SDDA, mice) paradigm. Potential enhancement of adrenergic mechanisms was also assessed by *in vitro* inhibition of synaptosomal biogenic amine (norepinephrine) uptake and by *in vivo* prevention of tetrabenazine-

Table 3. *N*-(4-Pyridinyl)-1*H*-indol-1-amines and Analogs


compd	R ₁	R ₂	R ₃	R ₄	starting mat.	mp, °C	yield, % ^a	recrystn solvent ^b	formula ^c
3a	H	H	H	H	2a	145–146	50	A	C ₁₃ H ₁₁ N ₃ ·C ₄ H ₄ O ₄
3b	H	H	CH ₃	H	2b	137	72	B	C ₁₄ H ₁₃ N ₃ ·C ₂ H ₂ O ₄ ^d
3c	H	H	H	CH ₃	2c	75–78	31		C ₁₄ H ₁₃ N ₃
3d	H	Br	H	H	2d	161–162	49	A	C ₁₃ H ₁₀ BrN ₃ ·C ₄ H ₄ O ₄
3e	H	Cl	H	H	2e	150–152	33	A	C ₁₃ H ₁₀ ClN ₃ ·C ₄ H ₄ O ₄
3f	H	NO ₂	H	H	2f	300–302	47	A	C ₁₃ H ₁₀ N ₄ O ₂ ·HCl
3g	H	OCH ₃	H	H	2g	oil	27		C ₁₄ H ₁₃ N ₃ O
3h	H	H	H	H	1a	65–68	83		C ₁₄ H ₁₂ N ₂
4a	CH ₃	H	H	H	3a	103–104	18	A	C ₁₄ H ₁₃ N ₃ ·C ₄ H ₄ O ₄
4b	CH ₂ CH ₃	H	H	H	3a	119–120	60	A	C ₁₅ H ₁₅ N ₃ ·C ₄ H ₄ O ₄
4c	CH ₂ CH ₂ CH ₃	H	H	H	3a	115–116	65	A	C ₁₆ H ₁₇ N ₃ ·C ₄ H ₄ O ₄
4d	CH ₂ CH ₂ CH ₂ CH ₃	H	H	H	3a	108–110	22	B	C ₁₇ H ₁₉ N ₃ ·C ₄ H ₄ O ₄
4e	CH(CH ₃) ₂	H	H	H	3a	121–123	39	A	C ₁₆ H ₁₇ N ₃ ·C ₄ H ₄ O ₄
4f	CH ₂ CH=CH ₂	H	H	H	3a	111–112	24	A	C ₁₅ H ₁₅ N ₃ ·C ₄ H ₄ O ₄
4g	CH ₂ C≡CH	H	H	H	3a	107–109	16	B	C ₁₆ H ₁₃ N ₃ ·C ₄ H ₄ O ₄
4h	CH ₂ CH ₂ CH ₃	H	H	CH ₃	3c	155–156	34	B	C ₁₇ H ₁₉ N ₃ ·C ₄ H ₄ O ₄
4i	CH ₃	Br	H	H	3d	110–111	31	B	C ₁₄ H ₁₂ BrN ₃ ·C ₄ H ₄ O ₄
4j	CH ₂ CH ₂ CH ₃	Br	H	H	3d	157–158	63	A	C ₁₆ H ₁₆ BrN ₃ ·C ₄ H ₄ O ₄
4k	CH ₂ CH ₂ CH ₃	Cl	H	H	3e	130	63	A	C ₁₆ H ₁₆ ClN ₃ ·C ₄ H ₄ O ₄
4l	CH ₃	NO ₂	H	H	3f	174–175	30	A	C ₁₄ H ₁₂ N ₄ O ₂ ·C ₄ H ₄ O ₄
4m	CH ₂ CH ₂ CH ₃	OCH ₃	H	H	3g	138–139	52	B	C ₁₇ H ₁₉ N ₃ O·C ₄ H ₄ O ₄
4n	CH ₂ CH ₂ CH ₃	H	CH ₃	H	3b	148–149	51	A	C ₁₇ H ₁₉ N ₃ ·C ₄ H ₄ O ₄
4o	CH ₂ CH ₂ CH ₃	H	CHO	H	4c	169–171	66	A	C ₁₇ H ₁₇ N ₃ O·C ₄ H ₄ O ₄
4p	CH ₂ CH ₂ CH ₃	H	CN	H	4o	163–164	58	A	C ₁₇ H ₁₆ N ₄ ·C ₄ H ₄ O ₄
4q	CH ₂ CH ₂ CH ₃	H	COCH ₃	H	4o	103–105	32	C	C ₁₈ H ₁₉ N ₃ O
4r	CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₃	H	4o	133–134	40	A	C ₁₈ H ₂₁ N ₃ ·C ₄ H ₄ O ₄
4s	CH ₂ CH ₂ CH ₃	H	H	H	3h	91–94	56		C ₁₇ H ₁₈ N ₂

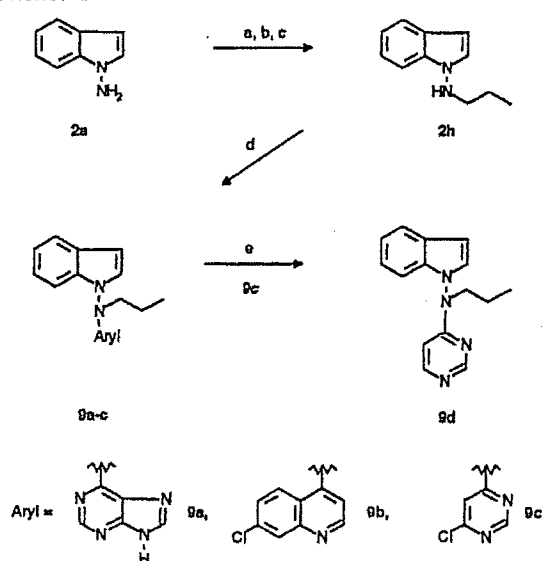
^a Yield from immediate precursor. ^b A = methanol-ether; B = ethanol-ether; C = methanol. ^c Elemental analysis agrees within $\pm 0.4\%$ of the theoretical values for C, H, N, except for 3g, which was not analyzed and used directly for the preparation of 4m. C₄H₄O₄ represents maleate salt unless otherwise noted. ^d Oxalate salt.

Scheme 3^a

^a (a) POCl₃-DMF, DCE; (b) H₂NOH·HCl, pyridine; C₆H₅SO₂Cl, pyridine; (c) CH₃MgBr, ether; pyridinium dichromate, DMF; (d) CH₃P(C₆H₅)₃Br, ether; (e) H₂/Pd-C.

induced ptosis (TBZ, mice). The data are summarized in Tables 5 and 6, including reference standard data in Table 6.

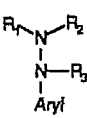
In contrast to our previous experience with aminoacridine and carbamate type acetylcholinesterase inhibitors, most of these compounds (3a–f; 4a–o,q,r;

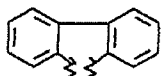
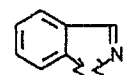
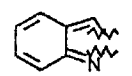
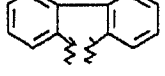
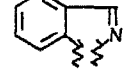
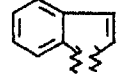
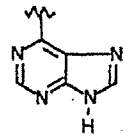
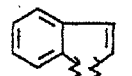
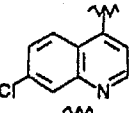
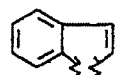
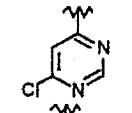
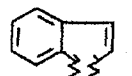
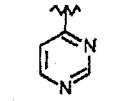
Scheme 4^a

^a (a) ClCO₂C₂H₅, pyridine, toluene; (b) KOtBu, THF; *n*-C₃H₇Br; (c) CH₂(OH)CH₂OH, NaOH, H₂O; (d) Cl-aryl, HCl, NMP; (e) H₂, 10% Pd/C, MgO, C₂H₅OH.

7a–d; 8a–d; 9c,d) were, at best, weak *in vitro* acetylcholinesterase inhibitors with the exception of 4p which

Table 4. Heteroaryl Analogs of 4c



Cmpd.	R ₁ , R ₂	Aryl	R ₃	Starting material	mp	yield % ^a	Recryst. solvent ^b	Formula ^c
7a		4-pyridyl	H	6a	147-148	47	B	C ₈ H ₈ N ₄ ·C ₄ H ₄ O ₄
7b		4-pyridyl	H	6b	165-167	60	A	C ₁₇ H ₁₃ N ₃ ·C ₄ H ₄ O ₄
7c		4-pyridyl	H	6c	148-150	13	A	C ₁₂ H ₁₀ N ₄ ·C ₄ H ₄ O ₄
7d		4-pyridyl	H	6d	174-175	28	B	C ₁₂ H ₁₀ N ₄ ·C ₄ H ₄ O ₄
8a		4-pyridyl	n-C ₃ H ₇	7a	145-146	65	A	C ₁₁ H ₁₄ N ₄ ·C ₄ H ₄ O ₄
8b		4-pyridyl	n-C ₃ H ₇	7b	174-175 (dec)	62	A	C ₂₀ H ₁₉ N ₃ ·C ₄ H ₄ O ₄
8c		4-pyridyl	n-C ₃ H ₇	7c	119-120	46	A	C ₁₅ H ₁₆ N ₄ ·C ₄ H ₄ O ₄
9a			n-C ₃ H ₇	2h	90-95	25	-	C ₁₆ H ₁₆ N ₆ ^d
9b			n-C ₃ H ₇	2h	137-138	20	B	C ₂₀ H ₁₈ ClN ₃ ·C ₄ H ₄ O ₄
9c			n-C ₃ H ₇	2h	oil	46	-	C ₁₅ H ₁₅ ClN ₄
9d			n-C ₃ H ₇	9c	oil	66	-	C ₁₅ H ₁₆ N ₄

^a Yield from immediate precursor. ^b A = methanol-ether; B = ethanol-ether. ^c Elemental analysis agrees within $\pm 0.4\%$ of the theoretical values for C, H, N, and C₄H₄O₄ represents maleate salt unless otherwise noted. ^d N: calcd, 28.75; found, 28.20.

exhibited moderate inhibitory activity. With respect to *in vitro* affinity for muscarinic binding sites, secondary (pyridinylamino)indoles 3a-f only weakly inhibited [³H]-QNB binding²⁴ in comparison with the muscarinic agonist reference standard oxotremorine (-Zn column in Tables 5 and 6). N-Alkylation of 3a provided tertiaryamines 4a-g which displayed significantly enhanced affinity for [³H]QNB-labeled muscarinic binding sites, with the N-propyl (4c) and N-butyl (4d) analogs being approximately equipotent to oxotremorine. Introduction of indole C-2, C-3, and C-5 aromatic substituents did not provide any further enhancement in binding affinity (4h-r vs 4c). However, the indole N-amino nitrogen is apparently required for more optimal binding affinity (3a vs 3h; 4c vs 4s). With the exception of 8b,c, various heteroaryl analogs (7a-d, 8a,d, 9a-d) of 3a and 4c also only weakly inhibited [³H]QNB binding.

Inhibition of [³H]QNB binding cannot, however, distinguish between muscarinic agonists (e.g. oxotremorine) and antagonists (e.g. scopolamine). Aronstam *et al.*²⁵ demonstrated that zinc and other heavy metals or sulfhydryl reagents increase the affinity of QNB binding sites for cholinergic agonists in rat forebrain membranes, and this selective agonist-enhancing effect of zinc was purported to provide a useful *in vitro* procedure to identify agonist activity. In our laboratory,²⁶ a muscarinic agonist-like profile for a compound is associated with a ratio of [³H]QNB IC₅₀ values equal to or greater than 3 obtained in the absence (-Zn) and presence (+Zn) of zinc. As shown in Tables 5 and 6, many of these compounds (3d-f; 4b,c,e-h,i,n,q-s; 7a,c,d; 8a-d; 9a,d) are characterized by -Zn/+Zn ratios greater than 3.0, suggesting that these compounds may be muscarinic receptor agonists.

Table 5. Biological Data for 3a–h, 4a–s^a

compd	AChEI ^b IC ₅₀ , μM	QNB ^c		uptake inhibition ^d rat, IC ₅₀ (μM) [³ H]NE	TBZ ^e ED ₅₀ (mg/kg, ip)	SDDA ^f A, NA, or NT, mg/kg, sc (% response)
		IC ₅₀ (μM) –Zn	+Zn			
3a	>100	40 (33–49)	16 (12–22)	2.5 (1.9–3.4)	3.0 (2.6–3.3)	A (3/9) 0.02 (27), 0.08 (20), 0.16 (23)
3b	>100	82 (48–140)	35 (22–55)	12.8 (5.8–28.1)	1.0 (0.9–1.1)	A (1/6) 0.31 (33)
3c	>100	60 (32–114)	29 (15–56)	3.6 (2.0–6.5)	<10	NA (0/3)
3d	>100	44 (25–75)	7.5 (5.5–10)	>20	>20	NT
3e	>100	42 (34–52)	5.9 (3.0–11)	>20	>20	NA (0/3)
3f	>100	146 (76–278)	12 (9.6–16)	9.9 (3.6–27)	>20	NT
3g	NT	NT	NT	NT	NT	NT
3h	NT	223 (134–372)	84 (63–111)	>20	NT	A (2/3) 0.3 (33), 1.0 (20)
4a	>100	9.0 (7.3–11)	5.1 (3.9–6.8)	1.0 (0.56–1.7)	3.5 (3.3–3.6)	A (3/9) 0.02 (33), 0.04 (53), 0.08 (33)
4b	>100	10 (3.5–21)	2.4 (1.3–4.7)	0.25 (0.15–0.44)	3.3 (3.0–3.6)	A (1/6) 0.63 (33)
4c	>100	3.0 (1.9–4.6)	0.94 (0.56–1.6)	0.43 (0.29–1.7)	3.1 (2.9–3.4)	A (5/6) 0.02 (24), 0.04 (30), 0.08 (33), 0.16 (27), 0.63 (40)
4d	62 (45–84)	4.0 (2.4–6.6)	1.5 (1.1–1.9)	0.43 (0.32–0.50)	5.4 (5.0–5.9)	A (1/6) 0.04 (23)
4e	>100	6.0 (4.5–8.0)	0.63 (0.25–1.6)	2.3 (1.1–4.9)	2.9 (2.7–3.1)	A (5/6) 0.16 (33), 0.31 (60), 1.25 (36), 2.5 (20), 5.0 (20)
4f	>100	7.3 (5.6–9.4)	1.0 (0.57–1.9)	6.2 (1.4–28)	4.2 (4.1–4.5)	NA (0/6)
4g	>100	11 (9.1–14)	2.5 (1.4–4.4)	0.68 (0.18–2.6)	3.9 (3.6–4.2)	A (3/11) 2.5 (21), 10 (21), 20 (27)
4h	>100	7.2 (3.9–13)	1.4 (1.1–1.7)	1.1 (0.9–1.4)	3.2 (2.9–3.5)	A (3/9) 0.02 (20), 2.5 (20), 5.0 (23)
4i	>100	4.6 (2.6–7.9)	2.5 (1.3–4.8)	13 (9.8–17)	>20	A (1/3) 1.0 (44)
4j	>100	4.4 (3.4–5.6)	1.6 (1.2–2.1)	2.6 (2.0–3.5)	>20	A (2/6) 0.63 (33), 5.0 (33)
4k	>100	5.8 (4.5–7.6)	2.4 (1.9–3.2)	1.9 (1.5–2.5)	>20	A (1/6) 1.25 (20)
4l	>100	29 (18–47)	7.6 (4.4–13)	>30	>20	A (4/6) 0.16 (20), 0.63 (20), 1.25 (20), 5.0 (20)
4m	>100	14 (7.3–26)	4.8 (2.8–8.4)	0.57 (0.31–1.0)	>20	A (4/6) 0.16 (20), 0.31 (20), 0.63 (26), 5.0 (36)
4n	29 (22–37)	19 (12–33)	4.5 (1.7–12)	1.3 (0.63–2.6)	1.8 (1.6–2.1)	A (2/10) 0.04 (22), 0.31 (20)
4o	20 (15–26)	3.3 (2.2–4.8)	1.8 (0.90–3.3)	2.2 (0.55–8.6)	18 (15–21)	NA (0/6)
4p	6.8 (5.1–9.1)	8.6 (5.1–15)	3.5 (2.8–4.4)	0.75 (0.53–1.1)	9.2 (8.5–10)	A (5/6) 0.16 (40), 0.31 (53), 0.63 (36), 1.25 (29), 5.0 (27)
4q	58 (44–77)	29 (19–44)	2.7 (1.7–4.3)	3.3 (1.6–6.8)	5.0 (4.7–5.3)	A (1/10) 0.16 (20)
4r	20 (16–25)	2.7 (2.1–3.4)	0.71 (0.55–0.92)	2.1 (1.2–3.5)	0.44 (0.41–0.47)	NA (0/9)
4s	NT	142 (93–215)	29 (17–51)	0.67 (0.34–1.3)	NT	A (1/3) 0.30 (20)

^a IC₅₀ and ED₅₀ values are corrected for the percentage of base compound in the case of salts. Numbers in parentheses are 95% confidence limits unless otherwise noted. ^b Inhibition of acetylcholinesterase (AChEI) in a rat striatal preparation using acetylthiocholine (5 mM) as substrate. ^c Inhibition of [³H]quinuclidinyl benzilate (QNB) binding from rat forebrain membranes in the absence (–Zn) and presence (+Zn) of zinc. ^d Inhibition of [³H]norepinephrine (NE) uptake in rat whole brain synaptosome preparations. ^e Prevention of tetrabenazine-induced (TBZ) ptosis by intraperitoneal compound administration in mice. ^f Antagonism of scopolamine-induced behavioral deficits in mice in the scopolamine dementia dark avoidance (SDDA) paradigm. A cutoff was defined for the scopolamine–vehicle group as the value for the animal with the second longest latency time. Results are reported as active (A), not active (NA), or not tested (NT) with the number of active (≥20% response) dosages versus the total number of dosages evaluated in parentheses. For active compounds, the second line of data represents the active doses (mg/kg, sc) with the percent response (i.e. the percent of animals in the scopolamine–drug group with latencies greater than the cutoff time) in parentheses.

With respect to adrenergic properties, most secondary and tertiary amines were assessed *in vitro* for inhibition of synaptosomal norepinephrine uptake and *in vivo* for prevention of TBZ-induced ptosis (Table 5). Compounds

3a,c inhibited *in vitro* norepinephrine uptake at micromolar concentrations, while compounds 3b,d–f were much weaker. Secondary amine 3a and the 2-methyl analog 3b significantly antagonized TBZ-induced ptosis,

Table 6. Biological Data for 7a-d, 8a-d, and 9a-d^a

compd	AChEI ^b IC ₅₀ , μM	QNB ^c		ratio -Zn/+Zn	uptake inhibition ^d rat, IC ₅₀ (μM) [³ H]NE	TBZ ^e ED ₅₀ (mg/kg, ip)	SDDA ^f A, NA, or NT, mg/kg, sc (% response)
		-Zn	+Zn				
7a	>100	>1000	247 (137-444)	>4	>20	>20	NT
7b	>100	20 (11-36)	8.2 (6.7-10)	2.4	1.4 (0.57-3.4)	2.3 (2.0-2.6)	NA (0/6)
7c	>100	128 (66-248)	29 (15-54)	4.4	17 (7.5-37)	3.8 (3.5-4.2)	NA (0/6)
7d	>100	409 (238-702)	128 (77-211)	3.2	>20	>20	NT
8a	>100	127 (66-247)	31 (23-41)	4.1	>20	>20	NT
8b	>100	5.5 (3.0-10)	0.5 (0.12-1.9)	11	2.4 (1.3-4.4)	1.5 (1.2-1.9)	A (2/8) 1.25 (20), 10 (24)
8c	>100	13 (10-17)	4 (3.7-5.2)	3.3	1.4 (0.8-2.3)	11 (9.5-13)	NA (0/6)
8d	>100	91 (53-154)	15 (11-19)	6.1	4.7 (2.4-9.2)	>20	NT
9a	NT	>300	58 (32-105)	>5.2	12 (6.1-24)	>20	A (2/6) 0.16 (20), 0.63 (20)
9b	NT	>300	180 (94-344)	>1.7	6.9 (4.0-12)	>20	A (1/6) 2.5 (29)
9c	>100	>1000	>1000		2.6 (0.9-7.6)	>20	A (3/6) 0.63 (33), 2.5 (33), 5.0 (20)
9d	>100	391 (82-1860)	11 (8-14)	35	1.4 (0.6-3.4)	>20	A (1/6) 5.0 (23)
Oxotremorine	NT	2.7 (2.2-3.7)	0.66 (0.43-1.0)	4.2	NT	NT	NT
Scopolamine	NT	0.004 (0.0031-0.0051)	0.004 (0.0021-0.0075)	1	NT	NT	
Clonidine	NT	NT	NT		>20	0.36 (0.31-0.42)	NA (0/6)
Yohimbine	NT	NT	NT		>20	>8	NT
THA ^g	0.32 (0.25-0.42)	7.3 (5.9-9.0)	5.9 (3.5-9.8)	1.2	11 (6.3-19)	>10	A (3/6) 0.63 (33), 2.5 (31), 5.0 (33)
idazoxan	NT	NT	NT		>20	NT	A (5/6) 0.31 (60), 0.63 (43), 1.25 (47), 2.5 (53), 5.0 (33)

^{a-f}See corresponding footnotes to Table 5. ^gTetrahydroaminoacridine (tacrine, THA).

while other nuclear-substituted secondary amines 3c-f were much less potent in this *in vivo* assay. Tertiary amines 4a-g inhibited *in vitro* norepinephrine uptake at micromolar and submicromolar concentrations, and also significantly antagonized TBZ-induced ptosis *in vivo*. Interestingly, the nature of the nitrogen alkyl substituent appeared to have little influence on the level of anti-TBZ activity of 4a-g. Introduction of indole C-3 alkyl substituents (4n,r) resulted in a possible slight enhancement of *in vivo* antagonism of TBZ-induced ptosis versus 4c, while C-3 electron-withdrawing substituents diminished activity (4o-q). Substitution at C-5 led to a significant loss of anti-TBZ activity (4i-m) regardless of the nature of the aromatic substituent.

Although the SDDA paradigm is a passive avoidance model used by many laboratories to assess compound effects on learning and memory, it was noted some time ago that research in the Alzheimer's disease area presents formidable challenges due to the unavailability of proven efficacious drugs (with exception of the cholinesterase inhibitor tacrine which recently received FDA approval) and the lack of definitive biological models.²⁷ In this respect, the SDDA paradigm is not highly specific for cholinomimetics and gives positive results with other compounds including analgesics, motor stimulants, and nootropics.²⁸ Evidence has also

accumulated associating α_2 adrenergic mechanisms with the cognitive decline in aged nonhuman primates,²⁹ and the α_2 antagonist idazoxan was reported to facilitate memory retrieval in rats.³⁰ Idazoxan was also active in the SDDA paradigm (Table 6). Thus, it is highly desirable to have biochemical or other data to mechanistically support the observed activity of a compound in SDDA.

In the SDDA assay, an animal (mouse) is placed on the lighted side of a divided chamber. The normal behavior is to escape into the adjacent dark compartment, and when this occurs a foot shock is received through a floor grid. After 24 h an animal is assessed for its ability to remember the experience by determining the increased time interval (latency) before the animal reenters the dark compartment. Scopolamine is an anticholinergic agent known to cause memory impairment in humans. If scopolamine is administered before an animal's initial exposure to the test apparatus, the animal is observed to reenter the dark compartment just shortly after being placed in the test chamber 24 h later, as do naive animals. Experience with a number of reference standards in SDDA led to the development of an empirical level of positive activity at 20% of the animals with latencies greater than a cutoff value. Due to the numerous dosages (ranging from 0.01 to 20 mg/kg, sc) utilized to evaluate the compounds in this study,

Table 7. Adrenergic Biochemical Properties and SDDA Comparison^a

compd	inhibition of [³ H]NE uptake ^b IC ₅₀ (μM)	inhibition of binding, IC ₅₀ (μM)		SDDA, ^c mg/kg, sc (% response)
		[³ H]clonidine ^c	[³ H]WB4101 ^d	
3a	2.5 (1.9–3.4)	0.008 (0.004–0.015)	0.51 (0.38–0.69)	A (3/9) 0.02 (27), 0.08 (20), 0.16 (23)
4a	1.0 (0.60–1.7)	0.024 (0.017–0.033)	1.2 (0.91–1.5)	A (3/9) 0.02 (33), 0.044 (53), 0.08 (33)
4b	0.25 (0.15–0.44)	0.11 (0.08–0.14)	3.3 (2.5–4.2)	A (1/6) 0.63 (33)
4c	0.43 (0.29–1.7)	0.33 (0.22–0.51)	10 (6.4–17)	A (5/6) 0.02 (24), 0.04 (30), 0.08 (33), 0.16 (27), 0.63 (40)
4d	0.43 (0.32–0.50)	0.63 (0.55–1.6)	NT	A (1/6) 0.04 (23)
4e	2.3 (1.1–4.9)	>10	NT	A (5/6) 0.16 (33), 0.31 (60), 1.25 (36), 2.5 (20), 5.0 (20)
4g	0.68 (0.18–2.6)	0.50 (0.28–0.91)	NT	A (3/11) 2.5 (21), 10 (21), 20 (27)
4h	1.1 (0.9–1.4)	2.3 (1.7–3.0)	NT	A (3/9) 0.02 (20), 2.5 (20), 5.0 (23)
4n	1.3 (0.63–2.6)	2.5 (0.98–6.4)	NT	A (2/10) 0.04 (22), 0.31 (20)
4r	2.1 (1.2–3.5)	3.6 (1.7–7.6)	NT	NA (0/9)
8b	2.4 (1.3–4.4)	0.54 (0.24–1.2)	3.2 (1.6–6.4)	A (2/8) 1.25 (20), 10 (24)

^a IC₅₀ values are corrected for the percentage of base compound in the case of salts. Numbers in parentheses are 95% confidence limits unless otherwise noted. ^b Inhibition of [³H]norepinephrine (NE) uptake in rat whole brain synaptosome preparations. ^c Rat cortical membranes. ^d Rat whole brain minus cerebella. ^e Scopolamine dementia dark avoidance (SDDA) paradigm in mice. See Footnote f of Table 5.

SDDA results are reported as active (A) or not active (NA) in Tables 5 and 6. To provide an index of activity, the number of active versus the total number of doses evaluated is given in parentheses, and the active doses with the percent response in parentheses are presented in the second line of SDDA data for each compound. On the basis of positive activity in SDDA, compounds of interest were arbitrarily selected as those with cholinomimetic mechanistic support as provided by a QNB IC₅₀ ≤ 10 μM and a –Zn/+Zn ratio greater than 3, in combination with potential enhancement of adrenergic mechanisms as supported by *in vitro* inhibition of norepinephrine uptake and *in vivo* low dose (<5 mg/kg, ip) antagonism of TBZ-induced ptosis (4b,c,e,g,h,n; 8b). Of these compounds, 4c and 4e produced the most robust reversal of scopolamine-induced behavioral deficits in SDDA, with activity at low doses (4c) and over a broad dosage range (4c,e).

Previous investigation of the (pyrroloamino)pyridines also revealed significant affinity for α adrenergic binding sites was associated with some compounds.¹⁸ As will be discussed below, *in vitro* evaluation of 4c indicated that α₂ antagonist properties are associated with the compound and raised the possibility of enhancing adrenergic neurotransmission by multiple mechanisms. Compounds 3a, 4a–e,g,h,n,r, and 8b were additionally assessed for α₂ adrenoceptor affinity by inhibition of [³H]-clonidine binding and compounds 3a, 4a–c, 8b for α₁ adrenoceptor affinity by inhibition of [³H]WB4101 binding (to assess potential α₁ mediated cardiovascular side effect liability). These data are presented in Table 7, and inhibition of NE uptake and SDDA are included for ease of comparison. Secondary amine 3a exhibited nanomolar affinity for α₂ adrenoceptors, with a 64-fold lower affinity for α₁ adrenoceptors. Introduction of linear *N*-alkyl substituents resulted in a significant enhancement of norepinephrine uptake inhibitory properties, but affinity for α₁ and α₂ binding sites progres-

sively decreased (3a vs 4a–c). Of the compounds mentioned above (4b,c,e,g,h,n; 8b), 4c again appeared to offer the most promising combination of biochemical properties including submicromolar inhibition of norepinephrine uptake, submicromolar affinity for α₂ adrenoceptors, and a 32-fold separation in IC₅₀ values for α₂ versus α₁ adrenoceptors. Although 4e,g,h,n appeared interesting based on activity in QNB and TBZ, 4e,h,n exhibited much weaker affinity for α₂ adrenoceptors than 4c, and 4g was not as robustly active in SDDA as 4c. Carbazole 8b displayed only a 6-fold separation in α₁/α₂ binding affinities and also was not robustly active in SDDA.

On the basis of this assessment, 4c was advanced for further study, and the overall profile of the compound is summarized in Table 8. With respect to *in vitro* α₂ adrenergic properties, 4c also inhibited α₂ antagonist binding ([³H]yohimbine, [³H]idazoxan) in the same concentration range as observed for the inhibition of α₂ agonist ([³H]clonidine) binding. Rodbell *et al.*³¹ reported that in the presence of the nonhydrolyzable guanine nucleotide 5'-guanylimidodiphosphate [GPP(NH)P] the apparent affinities of α₂ adrenoceptor agonists for [³H]-idazoxan-labeled receptors are reduced while the binding affinity of α₂ adrenoceptor antagonists are largely unaffected. The observation that the inhibition of [³H]-idazoxan binding by 4c in the presence of GPP(NH)P was not reduced suggested that the compound is not an α₂ agonist. Subsequent investigation demonstrated that 4c increases electrically-stimulated norepinephrine release from cortical tissue slices, which is consistent with α₂ antagonist activity.³² In addition, 4c significantly inhibits norepinephrine (in both whole brain and hypothalamic synaptosomes) and dopamine reuptake, and the compound antagonizes TBZ-induced ptosis *in vivo*. More recently, 4c at low concentrations was shown to enhance [³H]norepinephrine release due to a combination of α-adrenergic blockade and norepineph-

Table 8. Biological Profile of 4c

<i>in vitro</i> assay	IC ₅₀ (μM) ^a
Receptor Binding: Adrenergic	
[³ H]clonidine ^b (α ₂ , cortex)	0.33 (0.22–0.51)
[³ H]yohimbine ^b (α ₂ , cortex)	0.25 (0.18–0.33)
[³ H]idazoxan ^b (α ₂ , cortex)	0.47 (0.24–0.91)
+GPP(NH)P ^c	0.14 (0.07–0.29)
[³ H]WB4101 ^d (α ₁ , whole brain)	10 (6.4–17)
Biogenic Amine Uptake ^e	
[³ H]norepinephrine	
whole brain	0.43 (0.29–1.7)
hypothalamus	0.27 (0.11–0.67)
[³ H]dopamine (striatum)	0.41 (0.23–0.73)
[³ H]serotonin (whole brain)	2.6 (1.4–5.0)
Receptor Binding: Cholinergic	
[³ H]QNB ^f (muscarinic, forebrain)	3.0 (1.9–4.6)
+Zn ²⁺	0.94 (0.56–1.6)
[³ H]pirenzepine ^b (M ₁ , cortex)	1.3 (1.0–1.8)
[³ H]-N-methylscopolamine ^g	1.0 (0.81–1.2)
(M ₂ , cerebellum)	
oxotremorine	0.016 (0.011–0.024)
+GPP(NH)P ^c	0.65 (0.53–0.80)
oxotremorine	0.053 (0.035–0.082)
[³ H]oxotremorine-M ^h (muscarinic, forebrain)	0.46 (0.33–0.64)
oxotremorine	0.008 (0.0043–0.0148)
[³ H]NMCC ⁱ (nicotinic, cortex)	> 20
AChE Inhibition ^j	
acetylthiocholine (striatum)	> 100
<i>in vivo</i> assay	
SDDA ^k	active at 0.02, 0.04, 0.08, 0.16, 0.63 mg/kg, sc
TBZ ^l	ED ₅₀ 3.1 (2.9–3.4) mg/kg, ip; 5.1 (4.5–5.8) mg/kg, po

^a IC₅₀ and ED₅₀ values are corrected for the percentage of base compound in the case of salts. Numbers in parentheses are 95% confidence limits. ^b Rat cortical membranes. ^c 5'-Guanylimidodiphosphate. ^d Rat whole brain minus cerebella. ^e Rat brain synaptosomes. ^f Inhibition of [³H]quinuclidinyl benzilate binding, rat forebrain membranes. ^g Rat cerebellum. ^h Rat forebrain. ⁱ Inhibition of [³H]-N-methylcarbamylcholine (NMCC) binding, rat cortical membranes. ^j Acetylcholinesterase inhibition (rat striatum) using acetylthiocholine as substrate. ^k Scopolamine dementia dark avoidance paradigm (mice). ^l Prevention of tetrabenazine-induced ptosis (mice).

rine uptake inhibition,³³ and at higher concentrations 4c further enhances [³H]norepinephrine release via a calcium-independent mechanism (purportedly from a cytoplasmic origin).³⁴ These combined properties distinguish 4c from pure biogenic amine uptake inhibitors and α₂ antagonists and strongly suggest that 4c would significantly enhance adrenergic mechanisms in the clinic.

Confirmation of the cholinomimetic properties of 4c has been more challenging. As previously discussed, 4c significantly inhibited [³H]QNB binding with an increased affinity in the presence of zinc, suggesting that the compound may be a muscarinic agonist. With respect to muscarinic receptor selectivity and affinity, 4c displayed equal affinity for M₁- and M₂-muscarinic receptors as determined by inhibition of binding of the selective muscarinic antagonists [³H]pirenzepine and [³H]-N-methylscopolamine from cortical and cerebellar preparations, respectively (Table 8). Aronstam *et al.*³⁵ have shown that guanine nucleotides, including GPP-(NH)P, induce conversion of muscarinic binding sites from high- to low-affinity states. Thus the muscarinic agonist oxotremorine showed a 3-fold decrease in binding affinity for [³H]-N-methylscopolamine-labeled sites in the presence of GPP(NH)P, whereas the binding

Table 9. Additional Receptor Binding Assays for 4c

receptor	[³ H] ligand	tissue ^a	IC ₅₀ (μM)
dopamine-D ₁	SCH 23390	striatum	> 20
dopamine-D ₂	spiroperidol	striatum	> 20
5HT _{1A}	DPAT	hippocampus	≤ 20
5HT _{1B}	5HT	striatum	> 20
5HT ₂	spiroperidol	cortex	> 20
opiate-μ	DHM ^b	whole brain	> 1
opiate-K	bremazocine	cerebellum ^c	> 10
NMDA	CPP ^d	cortex	> 20
PCP	TCP ^e	cortex	> 20
Ca ²⁺ channel	nitrendipine	heart	> 100

^a Rat, unless otherwise specified. ^b [³H]Dihydromorphine. ^c Guinea pig. ^d [³H]-(±)-[3-(2-Carboxypiperazin-4-yl)propyl]phosphonate. ^e [³H]-N-[1-(2-Thienyl)cyclohexyl]piperidine.

affinity of 4c was not reduced in the presence of GPP-(NH)P. The compound also inhibited binding of the full muscarinic agonist oxotremorine-M, but was less potent than the partial agonist oxotremorine in this assay. In contrast to the -Zn/+Zn [³H]QNB data, the lack of a guanine nucleotide induced decrease in binding affinity and data from subsequent studies³² suggest that 4c is not a muscarinic agonist. The disparity between the QNB data and these studies is unclear, given the fact that various compounds from different therapeutic classes with anticholinergic properties (scopolamine, atropine, clozapine, thioridazine, amitriptyline, imipramine) failed to produce significant zinc shifts.²⁶ In addition, the weak inhibition of binding of the nicotinic agonist N-methylcarbamylcholine (NMCC) to frontal cortex preparations by 4c suggests the compound has little affinity for nicotinic binding sites, nor is the compound an acetylcholinesterase inhibitor (AChE inhibition, Table 8). It can also be seen from Table 9 that 4c shows little affinity for dopaminergic, serotonergic, opiate, NMDA, and PCP binding sites, nor for nitrendipine-labeled calcium channels.

Subsequent studies demonstrated *in vivo* cholinomimetic-like effects of 4c with respect to modulation of brainstem auditory-evoked potentials (BAEP) in rats. Wave VI of the BAEP is modulated by cholinergic neuronal pathways.³⁶ Cholinomimetics (e.g. oxotremorine, physostigmine) increase the amplitude of wave VI, and 4c was observed to produce the same effect over a broad dosage range (0.01–0.08 mg/kg, sc). Hemicholinium blocks high-affinity choline uptake, which results in depletion of acetylcholine and reduction of cholinergic neurotransmission. Compound 4c was shown to reverse the reduction in wave VI induced by pretreatment with hemicholinium.³⁷ The α₂ antagonist yohimbine was not active in BAEP, an observation which provides support for the association of cholinomimetic properties with 4c.

In addition to the above studies, 4c was independently evaluated in a combined cholinergic–noradrenergic lesion model designed to assess whether or not noncholinergic deficits in Alzheimer's brain may contribute to the cognitive impairments associated with the disease.³⁸ The results indicated that a nucleus basalis of Meynert (nbM, cholinergic) lesion combined with a lesion of the ascending noradrenergic bundle (ANB) did not exacerbate 72-h passive avoidance retention deficits beyond the degree of impairment produced by nbM lesions alone. However, the addition of an ANB lesion did block the efficacy of the cholinomimetics physostigmine and oxotremorine to reverse the lesion-induced memory impairment. Memory in combined lesioned rats was

restored when cholinomimetic therapy was administered in combination with the α_2 agonist clonidine, suggesting that pharmacological enhancement of both neurotransmitter systems was necessary for improving retention of the passive avoidance response. Compound 4c produced memory-enhancing effects in these combined lesion animals without the need for clonidine.

In summary, 4c appears to be a unique compound which displays combined adrenergic and cholinomimetic properties. Although the cholinomimetic properties of 4c are supported by activity in a number of *in vivo* models, its mechanism of action via a cholinergic target is unclear. Further investigation of non-receptor-mediated cholinomimetic effects of 4c, possibly through interaction with ion channels, is the subject of another paper.³⁹ Given the fact that multiple biochemical deficits are associated with Alzheimer's disease, compounds which exhibit facilitatory modulation of neurotransmission by multiple biochemical mechanisms may find utility in a broader patient population than pure cholinesterase inhibitors. Compound 4c indeed may be the first example of a "second generation" agent to provide such therapeutic benefit to Alzheimer's disease patients, and the compound⁴⁰ is presently in advanced clinical trials.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are supported by their IR (Perkin-Elmer 1420 ratio recording infrared spectrophotometer or Nicolet 205 FT-IR), ¹H-NMR (Varian XL 200, chemical shifts are reported in δ units downfield relative to tetramethylsilane as internal standard), and mass (Finnigan 4023) spectra. Reactions were generally conducted under a dry nitrogen atmosphere with exclusion of moisture. Organic product solutions were dried over anhydrous magnesium sulfate. Preparative HPLC separations were performed on silica gel with a Waters Associates Prep LC/System 500 equipped with a Gow Mac Model 80-800 UV detector. Product yields were not maximized. Elemental analyses were performed by either Micro-Tech Laboratories, Inc., Skokie, IL, Midwest Microlab, Indianapolis, IN, or Oneida Research Services, Inc., Whitesboro, NY.

General Procedure for Preparing Compounds 2 and 6. Aminoindoles 2a-g (Table 1) and heteroaryl analogs 6a-d (Table 2) were prepared by modification of the procedure previously described by Somel and Natsume.²⁰ A typical procedure is reported for the synthesis of 2a. A cooled solution of indole (1a, 0.1 mol) in DMF (100 mL) was treated with powdered potassium hydroxide (1 mol) and then slowly with hydroxylamine O-sulfonic acid (0.2 mol) such that the internal temperature remained below 20 °C. After stirring an additional hour at room temperature, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with water and brine, then dried, and concentrated *in vacuo*. Separation from unreacted 1a was achieved by preparative HPLC using dichloromethane (DCM)-hexanes (1:1) as eluent. Product *N*-amino compounds 2a-g and 6a-d were used directly in condensations with 4-chloropyridine hydrochloride or other chloroheterocyclics. Starting materials 1a-g, pyrazole (5a), carbazole (5b), and indazole (5c) were purchased from Aldrich Chemical Co.

***N*-Propyl-1*H*-indol-1-amine (2h).** A stirred solution of 2a (80.7 g, 0.61 mol), pyridine (54 mL, 0.67 mol), and toluene (620 mL) was treated over 1.25 h with a solution of ethyl chloroformate (59 mL, 0.61 mol) and toluene (59 mL). After the reaction was complete, 3 *N* hydrochloric acid solution (500 mL) was added and the resultant mixture was filtered through Celite, the Celite pad being washed with toluene (100 mL). Separation of the filtrate layers and concentration of the

toluene layer under reduced pressure afforded a residue which was purified by chromatography (silica gel, eluted with toluene followed by 3% 2-propanol in toluene). Concentration of the appropriate fractions provided a solid (49 g) which was recrystallized from 3% 2-propanol in hexanes to give 34 g (27%) of *N*-(ethoxycarbonyl)-1*H*-indol-1-amine as a pale yellow solid, mp 89-90 °C. To a cold (5 °C) stirred solution of the ethoxy carbamate (15 g, 0.074 mol) and tetrahydrofuran (THF, 100 mL) was added potassium *tert*-butoxide (9 g, 0.08 mol). After stirring for 1 h, the cold solution was treated with 1-bromopropane (7.3 mL, 0.08 mol) which was followed by stirring for 5 h at room temperature. The mixture was poured into ice-water (300 mL) and extracted with ethyl acetate. The organic phase was washed with water, dried, filtered, and concentrated to afford *N*-(1*H*-indol-1-yl)-*N*-propylcarbamate ester as a brown oil (16 g). A solution of the oil, sodium hydroxide (10 g, 0.25 mol), water (20 mL), and ethylene glycol (35 mL) was stirred at 120 °C for 4 h. The mixture was poured into ice-water (300 mL), stirred for 5 min, and extracted with ethyl acetate. The organic phase was washed with water, dried, filtered, and concentrated to give a brown oil (9 g). Purification of the oil by Kugelrohr distillation provided 2h (8 g, 68%) as a light yellow oil: bp 145 °C (1 mmHg). IR (CHCl₃) 3060, 3018, 2970, 2940, 2880, 1512, 1470, 1458, 1330, 1135, 1090, 1040, 1010 cm⁻¹; ¹H NMR (CDCl₃) δ 0.96 (t, 3H, *J* = 8 Hz), 1.48 (sextet, 2H, *J* = 8 Hz), 3.15 (t, 2H, *J* = 8 Hz), 4.58 (br s, 1H), 6.40 (d, 1H, *J* = 4 Hz), 7.10 (q, 1H, *J* = 8 Hz), 7.17 (m, 2H), 7.46 (d, 1H, *J* = 8 Hz), 7.58 (d, 1H, *J* = 7 Hz); MS *m/e* 174. Properties of 2h are included in Table 1.

***N*-(4-Pyridinyl)-1*H*-indol-1-amine Maleate (3a).** A solution of 2a (0.22 mol) and 4-chloropyridine hydrochloride (0.22 mol) in 150 mL of 2-propanol was stirred at 80 °C for 2 h. After cooling, the mixture was poured into 500 mL of ice-water and made basic by slow addition of sodium carbonate. The product, which separated, was extracted into DCM (3 $\times$ 200 mL). The organic layer was washed with water and brine, dried, and filtered, and the solvent was removed *in vacuo*. Elution of the residue with ethyl acetate via preparative HPLC afforded 24 g of 3a free base as a yellow oil which solidified, mp 140 °C. An analytical sample of 3a was obtained by converting 3.5 g of the free base to the maleate salt: mp 145-146 °C; IR (KBr) 3440, 3260, 3100, 1645, 1460 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 6.13 (s, 2H), 6.55-6.75 (m, 3H), 7.10-7.33 (m, 3H), 7.56 (d, 1H, *J* = 4 Hz), 7.70 (d, 1H, *J* = 10 Hz), 8.42 (d, 2H, *J* = 10 Hz), 12-15 (br s, 3H, exchangeable with deuterium oxide); MS *m/e* 209. Properties of 3a, and of 3b-g and 7a-d prepared in a similar manner, are included in Tables 3 and 4.

***N*-Propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine Maleate (4c).** A solution of 3a (0.03 mol) in 25 mL of DMF was added dropwise to an ice-cooled suspension of sodium hydride (60% oil dispersion, 0.03 mole, washed with hexanes) in 5 mL of DMF. After 1 h a solution of 1-bromopropane (0.03 mol) in 5 mL of DMF was added. After stirring 1 h at ambient temperature, the reaction mixture was poured into 500 mL of ice-water and extracted with DCM. The organic layer was washed with water and brine, dried, and filtered. After concentration *in vacuo*, the residue was purified eluting with ethyl acetate via preparative HPLC, followed by elution with ether through alumina via column chromatography, to afford 6.4 g of a yellow oil. Conversion to the maleate salt provided 6.8 g of 4c as pale yellow crystals: mp 115-116 °C; IR (CHCl₃) 3010, 1710, 1643, 1515, 1470, 1450, 1350, 880, 820, 645 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (t, 3H, *J* = 8 Hz), 1.82 (sextet, 2H, *J* = 8 Hz), 3.95 (m, 2H), 6.32 (s, 2H), 6.50-6.70 (br s, 2H), 6.72 (d, 1H, *J* = 4 Hz), 7.05-7.16 (m, 2H), 7.20-7.33 (m, 2H), 7.75 (d, 1H, *J* = 8 Hz), 8.35 (d, 2H, *J* = 8 Hz), 15.3-16.5 (br s, 2H, exchangeable with deuterium oxide); MS *m/e* 251. Properties of 4c, and of 4a,b,d-n and 8a-d prepared in a similar manner, are included in Tables 3 and 4.

***N*-Propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine-3-carboxaldehyde Maleate (4o).** A Vilsmeier formylating complex was prepared by slow addition of phosphorous oxychloride (0.1 mol) to ice-cooled DMF (0.1 mol). A solution of 4c (0.05 mol) in 200 mL of dichloroethane was added, and the resultant solution was stirred at 80-85 °C for 5 h. The solution was then cooled and hydrolyzed with sodium acetate trihydrate

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(0.15 mol) in 200 mL of water. After 1 h, the reaction mixture was made basic by slow addition of sodium carbonate, the phases were separated, and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organics were washed with water and brine and dried. After filtering, the solvent was removed *in vacuo* and elution of the residual oil through silica with ethyl acetate via flash column chromatography gave 14 g of an oil. Repeated elution of a 3 g aliquot provided 2.2 g of **4o** free base as an oil. Conversion to the maleate salt afforded 2.8 g of **4o** as white crystals: mp 169–171 °C; IR (KBr) 3110, 2960, 2575, 1675, 1640, 1520, 1470, 1375, 1350, 1210, 1125, 870, 820, 740, 640 cm⁻¹; ¹H NMR (CDCl₃/DMSO-*d*₆ (10:1)) δ 1.06 (t, 3H, *J* = 8 Hz), 1.80 (sextet, 2H, *J* = 8 Hz), 4.03 (m, 2H), 6.30 (s, 2H), 6.75 (d, 2H, *J* = 10 Hz), 7.20 (m, 1H), 7.33–7.48 (m, 2H), 8.12 (s, 1H), 8.35–8.50 (m, 3H), 10.12 (s, 1H), 10.5–12.0 (br s, 2H, exchangeable with deuterium oxide); MS *m/e* 279. Properties of **4o** are included in Table 3.

3-Cyano-*N*-propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine Maleate (4p). Hydroxylamine hydrochloride (0.07 mol) was added to a solution of **4o** (0.04 mol) in 100 mL of pyridine. After stirring for 1 h at ambient temperature, the mixture was concentrated *in vacuo*. The residue was stirred with water, made basic by slow addition of sodium carbonate, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and filtered. The solvent was removed *in vacuo* and the residue eluted through silica with ethyl acetate via flash column chromatography to give 10 g (98%) of the intermediate oxime as an oil.

Benzenesulfonyl chloride (0.03 mol) was added to a solution of the oxime (0.03 mol) in 125 mL of ether and pyridine (0.06 mol). The mixture was warmed gently on a steam bath to near dryness, and was then cooled, poured into water, and made basic by slow addition of sodium carbonate. The product was extracted into ethyl acetate, washed with water and brine, dried, and filtered. The solvent was removed *in vacuo* and the residue eluted through silica with ethyl acetate–DCM (1:1) via flash column chromatography to give 5.5 g of **4p** free base as an oil. An analytical sample was obtained by converting 2.5 g of the free base to the maleate salt, which was recrystallized to afford 2.8 g of **4p** as pale yellow crystals: mp 163–164 °C; IR (CHCl₃) 3030, 2250, 1720, 1650, 1525, 1465, 1360, 1240, 880, 825, 655 cm⁻¹; ¹H NMR (CDCl₃/DMSO-*d*₆ (10:1)) δ 1.05 (t, 3H, *J* = 8 Hz), 1.77 (sextet, 2H, *J* = 8 Hz), 3.98 (m, 2H), 6.33 (s, 2H), 6.65 (d, 2H, *J* = 10 Hz), 7.20 (m, 1H), 7.45 (m, 2H), 7.90 (m, 2H), 8.45 (d, 2H, *J* = 10 Hz), 10.6–12.8 (br s, 2H, exchangeable with deuterium oxide); MS *m/e* 276. Properties of **4p** are included in Table 3.

3-Acetyl-*N*-propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine (4q). Methylmagnesium bromide (3.2 M in ether, 0.048 mol) was added slowly to a solution of **4o** (0.014 mol) in 300 mL of anhydrous ether. After stirring for 1 h at ambient temperature, the mixture was hydrolyzed by slow addition of ammonium chloride (20 g) in 400 mL of water. The mixture was then made basic by slow addition of sodium carbonate and extracted with ether. The organic layer was washed with water and brine, dried, filtered, and concentrated *in vacuo* to an oil. Elution through silica with ethyl acetate via flash column chromatography afforded 3.8 g (90%) of the intermediate carbinol as a white solid, mp 114–116 °C.

Pyridinium dichromate (0.035 mol) was added to a solution of the carbinol (0.027 mol) in 80 mL of DMF. After stirring for 1 h at ambient temperature, the mixture was poured into water, made basic by slow addition of sodium carbonate, and extracted with ether. After filtering, the organic layer was washed with water and brine, dried, filtered, and concentrated *in vacuo* to an oil. Elution through silica with ethyl acetate via flash column chromatography afforded 6.5 g of an oil, which was crystallized from methanol to provide 5.5 g of **4q** as a white solid. Recrystallization afforded 2.5 g of white crystals: mp 103–105 °C; IR (CHCl₃) 3020, 2980, 1660, 1595, 1535, 1510, 1380, 1200, 990, 940, 810 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (t, 3H, *J* = 8 Hz), 1.70 (sextet, 2H, *J* = 8 Hz), 2.55 (s, 3H), 3.80 (m, 2H), 6.30 (d, 2H, *J* = 6 Hz), 7.12 (d, 1H, *J* = 10 Hz),

7.25–7.40 (m, 2H), 7.80 (s, 1H), 8.30 (d, 2H, *J* = 6 Hz), 8.48 (d, 1H, *J* = 10 Hz); MS *m/e* 293. Properties of **4q** are included in Table 3.

3-Ethyl-*N*-propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine Maleate (4r). Potassium *tert*-butoxide (0.031 mol) was added to a suspension of methyltriphenylphosphonium bromide (0.031 mol) in 200 mL of anhydrous ether. A solution of **4o** (0.021 mol) in 200 mL of anhydrous ether was then added to the freshly prepared phosphorane. After stirring for 2 h at ambient temperature, the mixture was poured into water and separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with water and brine, dried, and filtered. After concentration *in vacuo*, the residue was eluted through silica with ethyl acetate–DCM (1:1) via flash column chromatography to provide 13 g of the product contaminated with triphenylphosphine oxide. Separation was achieved by conversion of the product to the hydrochloride salt in ether, filtration, and basification of the filter cake to afford the intermediate olefin as an oil.

A solution of the olefin (0.014 mol) in 250 mL of 95% ethanol containing 0.25 g of PtO₂ was hydrogenated at 60 psi on a Parr hydrogenation apparatus for 6 h. The catalyst was removed by filtration through Celite, the filtrate was concentrated *in vacuo*, and the residue was eluted through silica with 30% ethyl acetate in DCM via flash column chromatography to yield an oil. Conversion to the maleate salt and recrystallization afforded 2.3 g of **4r** as white crystals: mp 133–134 °C; IR (CHCl₃) 3020, 1710, 1645, 1520, 1460, 1350, 1200, 870, 820, 640 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (t, 3H, *J* = 8 Hz), 1.38 (t, 3H, *J* = 8 Hz), 1.82 (sextet, 2H, *J* = 8 Hz), 2.85 (q, 2H, *J* = 8 Hz), 3.92 (m, 2H), 6.32 (s, 2H), 6.60 (br s, 2H), 6.88 (s, 1H), 7.08 (m, 1H), 7.27 (m, 2H), 7.70 (m, 1H), 8.33 (d, 2H, *J* = 10 Hz); MS *m/e* 279. Properties of **4r** are included in Table 3.

***N*-(1*H*-indol-1-yl)-*N*-propyl-6-purinamine (9a).** A stirred solution of 6-chloropurine (5.0 g, 0.032 mol) and 1-methyl-2-pyrrolidinone (50 mL) was acidified with ethereal hydrogen chloride solution, and then a solution of **2h** (5.2 g, 0.030 mol) and *N*-methyl-2-pyrrolidinone (50 mL) was added. After stirring at 120 °C for 6 h, the mixture was cooled and decanted into water (500 mL). After adjusting to pH 10 with Na₂CO₃, the mixture was extracted with ethyl acetate and the organic phase was dried, filtered, and concentrated to an oil. The crude oil was purified by HPLC eluting with ethyl acetate and the desired fractions were combined and concentrated to afford **9a** (2.2 g, 25%) as a tan solid: mp 90–95 °C; IR (CHCl₃) 3450, 3020, 1580, 1470, 1420, 1265, 1095 cm⁻¹; ¹H NMR (CDCl₃) δ 0.98 (t, 3H, *J* = 8 Hz), 1.73 (sextet, 2H, *J* = 8 Hz), 4.12 (m, 1H), 4.68 (m, 1H), 6.62 (d, 1H, *J* = 6 Hz), 7.15 (m, 3H), 7.25 (d, 1H, *J* = 6 Hz), 7.63 (m, 1H), 7.70 (s, 1H), 8.45 (s, 1H), 11.30 (br s, 1H); MS *m/e* 292. Properties of **9a**, and of **9b,c** prepared in a similar manner, are included in Table 4.

***N*-(1*H*-indol-1-yl)-*N*-propyl-4-pyrimidinamine (9d).** A mixture of **9c** (4.2 g, 0.014 mol), 10% Pd/C (1.2 g), MgO (1.0 g), and ethanol (100 mL) was stirred at atmospheric pressure under hydrogen for 3 h. The mixture was filtered, and the filtrate was concentrated to afford a yellow oil which was purified by HPLC eluting with 10% ethyl acetate in DCM. Concentration of the desired fractions provided **9d** (2.4 g, 64%) as a viscous yellow oil: IR (CHCl₃) 2980, 1590, 1490, 1400, 1340, 1225, 1130, 990, 830 cm⁻¹; ¹H NMR (CDCl₃) δ 1.0 (t, 3H, *J* = 8 Hz), 1.70 (sextet, 2H, *J* = 8 Hz), 3.96 (m, 1H), 4.28 (m, 1H), 5.64 (d, 1H, *J* = 8 Hz), 6.67 (d, 1H, *J* = 6 Hz), 7.12 (d, 1H, *J* = 6 Hz), 7.23 (m, 3H), 7.72 (d, 1H, *J* = 8 Hz), 8.12 (d, 1H, *J* = 10 Hz), 8.80 (s, 1H); MS *m/e* 252. Properties of **9d** are included in Table 4.

Biological Methods. Procedural details for the *in vivo* prevention of tetraabenazine-induced (TBZ) ptosis^{41,42} and reversal of scopolamine dementia dark avoidance (SDDA),^{6,43} and *in vitro* inhibition of synaptosomal biogenic amine (norepinephrine, serotonin, dopamine) uptake^{6,44} and inhibition of [³H]quinuclidinyl benzilate (QNB),^{24, 26,44} [³H]-*N*-methylscopolamine,³⁵ [³H]SCH23390,⁴⁴ [³H]spiroperidol,⁴⁴ [³H]WB4101,^{44,45} [³H]clonidine,⁴⁶ [³H]yohimbine,⁴⁷ [³H]idazoxan,^{31,48} [³H]-(±)-[3-(2-carboxypiperazin-4-yl)propyl]phosphonate (CPP),⁴⁹ [³H]-*N*-(1-(2-thienyl)cyclohexyl)piperidine (TCP),⁴⁹ [³H]nitrendipine,⁵⁰

[³H]-8-hydroxy-2-(di-*n*-propylamino)tetralin (DPAT),⁵¹ [³H]di-hydromorphine (DHM),⁵² [³H]bremazocine,⁵³ [³H]pirenzepine,⁵⁴ [³H]oxotremorine-M⁵⁵ and [³H]-*N*-methylcarbamylcholine⁵⁶ binding were previously reported. *In vitro* inhibition of acetylcholinesterase was determined by the method of Ellman.⁵⁷

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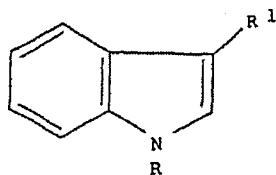
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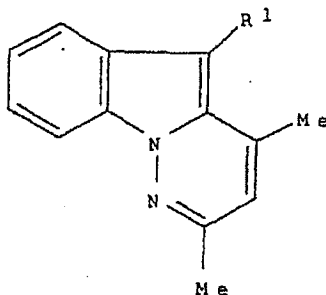
Franz Weiberth, et al

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I, R = H

II, R = NH₂



III

AB Indoles I (R₁ = H, Me, CH₂CN, COMe, CH₂CH:CM₂, etc.) were aminated with H₂NOSO₃H in anhyd. HCONMe₂ contg. KOH to give the corresponding 1-aminoindoles II, which were reacted with acid chlorides, carboxylic acids, isocyanates, pyrylium salts, aldehydes, diketones, epoxides, and ribose to give the expected 1-(substituted amino)indoles. E.g., II (R₁ = Me, SPh, H) reacted with (MeCO)₂CH₂ followed by cyclization to give the pyridazinoindoles III.

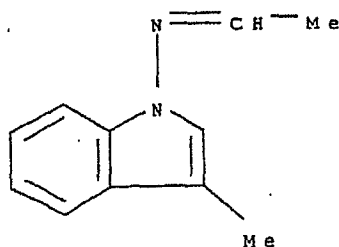
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IT - 54917-21-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(prepn. and cyclization of)

RN - 54917-21-4 CAPLUS

CN - 1H-Indol-1-amine, N-ethylidene-3-methyl- (9CI) (CA INDEX NAME)

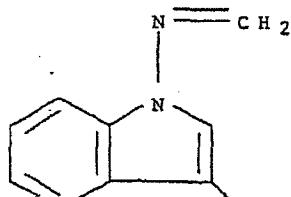


IT - 54917-24-7P

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN - 54917-24-7 CAPLUS

CN - 1H-Indol-1-amine, 3-methyl-N-methylene- (9CI) (CA INDEX NAME)



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SYNTHESES OF HETEROCYCLIC COMPOUNDS BASED ON THE FISCHER REACTION

II. THE ANOMALOUS COURSE OF THE FISCHER REACTION

A. E. Arbuzov and Yu. P. Kitaev

An anomalous Fischer reaction was discovered by one of us in 1913. It was first observed in catalytic decomposition of aldehyde phenylhydrazones in the presence of cuprous chloride [1], when the former underwent nitrile decomposition. A detailed investigation of this reaction showed that aldehyde phenylhydrazones with large radicals form, almost exclusively, nitriles and aniline while lower aldehydes also give indole. It was then also discovered that acetone phenylhydrazone underwent catalytic decomposition in the presence of cuprous chloride not to form 2-methylindole, but a new compound, ammonia and aniline. This observation and a series of other unpublished facts suggested the hypothesis that ketone phenylhydrazones, not containing a CH_2 group next to the carbonyl group, would also decompose anomalously under these conditions.

In 1950 O. M. Shapshinskaya [2] attempted to study the anomalous reaction of the catalytic decomposition of acetone phenylhydrazone in detail. She isolated two fractions from the reaction mixture, one of which was found to be aniline. The second fraction boiled at $267-269^\circ$ (d 1.054). The substance in this fraction did not dissolve in water, but dissolved in dilute (1:1) hydrochloric acid; hydrolysis of it gave acetone. According to analytical data, the compound obtained had the composition $\text{C}_6\text{H}_7\text{N}$, but considering the high boiling point, the authors consider that this formula should be doubled. The anomalous decomposition of acetone phenylhydrazone may then be illustrated by the overall equation



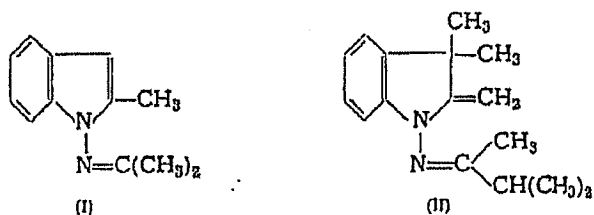
The authors were unable to elucidate the structure of the anomalous product.

We decided to check, first of all, if the phenylhydrazones of all ketones, which do not contain a methylene group next to the carbonyl group, would actually undergo an anomalous Fischer reaction in the presence of cuprous chloride. For this purpose we studied the decomposition of phenylhydrazones of acetone, methyl isopropyl ketone, pinacolin, pyruvic acid, ethyl pyruvate, acetophenone, p-chloroacetophenone and acetone methylphenylhydrazone. The anomalous reaction products were isolated only in the case of the phenylhydrazones of acetone and methyl isopropyl ketone. The amount of ammonia evolved in these cases corresponded to the above reaction scheme. Of the other phenylhydrazones that we investigated, their decomposition gave considerably less ammonia than that required by the equation of the normal reaction, but sometimes somewhat more than what should have been evolved in an anomalous reaction. From the tars formed from the phenylhydrazones of acetophenone, p-chloroacetophenone and ethyl pyruvate we were able to isolate the normal catalytic decomposition products — indoles — in the first two cases in insignificant amounts and in the last, in a yield of 19.1%. On heating acetone methylphenylhydrazone to 250° with cuprous chloride, very small amounts of ammonia were evolved and the reaction mixture became tarry. The tar contained the starting hydrazone and lower boiling decomposition products.

Several repetitions of the experiments, the use of solvents (kerosene, nitrobenzene, dimethylaniline, etc.) as well as fractionation under high vacuum, chromatography on silica gel and aluminum oxide and the use of selective solution in working over the tars obtained did not result in the separation of individual compounds. Apparently, due to the high temperatures during the reaction, the anomalous products were decomposed; we

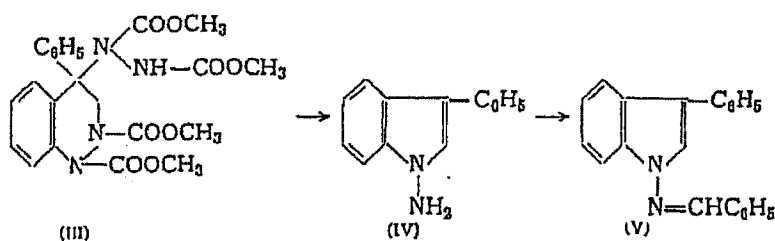
therefore stopped working in this direction and then set out to clarify the structure of the compounds obtained from the phenylhydrazones of acetone and methyl isopropyl ketone.

Hydrolysis of the anomalous products with dilute sulfuric acid gave acetone and methyl isopropyl ketone; the former was detected by reaction with salicylaldehyde and from the latter we obtained a dinitrophenylhydrazone. We established the presence of three labile hydrogen atoms, corresponding to the 2-methyl group of indole, in a molecule of the compound, prepared from acetone phenylhydrazone. As we could not obtain an anomalous product by the catalytic decomposition of acetone methylphenylhydrazone in the presence of cuprous chloride, we concluded that the product was an N-substituted indole. This was also supported by the fact that regardless of the high boiling point the substance did not crystallize even when cooled to -70° and it is known that all N-substituted indoles of the corresponding molecular weight are high boiling, noncrystallizing liquids [3]. Considering the above observations, we assigned the compounds obtained the structure of acetone 2-methylindol-1-aminide (I) and methyl isopropyl ketone 3,3-dimethyl-2-methylenindolin-1-aminide (II).



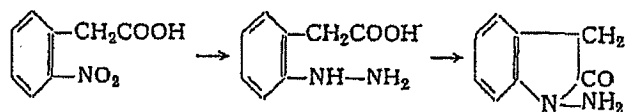
Both compounds were yellow liquids, reddening rapidly in air and readily soluble in dilute acids and organic solvents; they did not give a reaction for indole with a pine splinter. Nitrogen analysis in both cases gave results that agreed with the proposed reaction formulas. The yield was 21-41% of (I) and 12% of (II). It should be noted that in different experiments the yields of acetone 2-methylindol-1-aminide (I) varied greatly and it could not be isolated at times. Apparently, this was due to the varying purity of the catalyst.

Recently K. Alder and H. Niklas [4] obtained a derivative of N-aminoindole for the first time. The authors were studying the reaction of substituted styrene with azodicarboxylic esters. From α -phenylstyrene and two molecules of ester they obtained compound (III), which belongs to the tetrahydrocinnoline series.



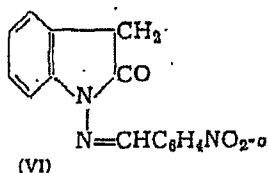
Treatment of this compound with hydrazine hydrate gave a good yield of 3-phenyl-N-aminoindole (IV) (m. p. 104°), which was a colorless crystalline material, readily oxidized and becoming yellow. The amino group in this compound had hydrazine properties; thus, K. Alder and H. Niklas treated it with benzaldehyde to obtain N-benzalimino-3-phenylindole (V), whose melting point (108°) hardly differed from the melting point of the starting amine. Compound (V) was similarly prepared by us as an anomalous Fischer reaction product.

Considerably earlier P. Neber et al. [5, 6] and A. Kliegel [7] prepared N-aminooxindole by the following reaction



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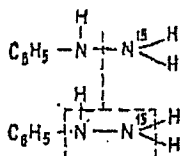
In the given case the amino group also had a hydrazine character; with o-nitrobenzaldehyde it gave compound (VI).



Consequently, in order to prove the structure of the products obtained by us conclusively, we may use one of these methods for their synthesis. Furthermore, it was necessary to try to isolate 1-aminoindoles by hydrolysis of the anomalous products since, on the one hand, this would also prove the structure of the latter and, on the other, would make it possible to study the properties of the former compounds, which up to now have been poorly accessible.

After establishing the structure of the anomalous products it was necessary to elucidate their formation mechanism. We started with the assumption that the formation of nitriles from aldehyde arylhydrazones and anomalous products from ketone arylhydrazones proceeded by the same mechanism.

One of us found [8] that heating to 150° with cuprous chloride caused the decomposition of phenylhydrazine with the evolution of nitrogen, ammonia and aniline. Even earlier, Struthers [9] observed the decomposition of phenylhydrazine in the presence of mercury or copper cyanide and, besides the products mentioned, he also isolated benzene. It seemed to us that this process might be connected with the anomalous course of the Fischer reaction. We shall not mention here all the information on other substances which cause this decomposition of arylhydrazones, but shall only examine the report by K. Clusius [10], who studied the catalytic decomposition of phenylhydrazine labeled with the isotope N^{15} , using cuprous chloride. The author synthesized $C_6H_5NH \cdot N^{15}H_2$ and, having decomposed it in a special apparatus, isolated nitrogen, ammonia, benzene and aniline in a pure state. All nitrogen-containing products were decomposed and the nitrogen obtained from them analyzed for isotope content. It must be noted that all the work was carried out with 0.6 g of the substance, but with great accuracy. The results of the isotopic analysis are given in Table 1 and show that the nitrogen atoms labeled with the isotope N^{15} passed quantitatively into ammonia, half into nitrogen, and were completely absent from aniline; this process K. Clusius illustrated by the scheme



According to Clusius, one phenylhydrazine molecule loses nitrogen and hydrogenates its own phenyl and a second molecule with the elimination of the amino group.

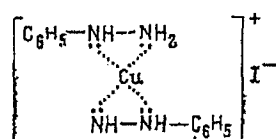
TABLE 1

Substances		Average N15 content (in at. %)	
		found	calculated
Starting	1) $N^{15}H_4Cl - NaN^{15}O_2$	4.86	
	2) phenylhydrazine	2.58	$2.62 = \frac{0.38 * + 4.86}{2}$
Reaction products	3) nitrogen	2.56	2.58
	4) ammonia	4.79	$4.78 = 2 \cdot 2.58 - 0.38 *$
	5) aniline	0.39	0.38 *

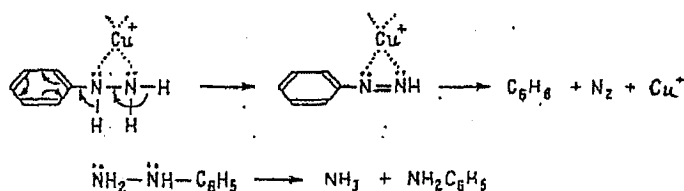
* N15 content in normal nitrogen.

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On the basis of the ideas of the general theory of conjugation, we proposed the following explanation for the mechanism of the catalytic decomposition of phenylhydrazine. The catalyst forms a complex with phenylhydrazine; for example, $C_6H_5NHNH_2 \cdot CuCN$ [9], $2C_6H_5NHNH_2 \cdot CuI$ [8], $2C_6H_5NHNH_2 \cdot ZnCl_2$ [11], etc. have been isolated. Consequently, some part of the phenylhydrazine is present in the reaction mass as a complex while the other part remains unchanged. In all probability both nitrogen atoms in the complex form a coordination bond with the metal, i. e., for example, the complex with CuI has the structure given below and is similar to the "chelate compounds."



In forming the coordination bond the metal attracts the unshared electron pairs from the nitrogen atoms and this causes a certain displacement of the electrons of the $N-H$ bond toward nitrogen, i. e., these bonds are weakened. Furthermore, the $N-H$ bonds are conjugated with the benzene ring bonds which makes the hydrogen atoms even more labile. In free phenylhydrazine the unshared electron pairs give to the nitrogen atoms a nucleophilic character, which includes the capacity of these atoms to form hydrogen bonds [12, 13]. The reaction of the complex compound and free phenylhydrazine, proceeding by the scheme



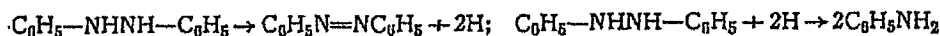
results in the formation of diazobenzene, ammonia and aniline. Due to the high temperature and the catalyst, the diazobenzene decomposes to nitrogen and benzene. The catalyst is thus freed and again forms a complex, and this causes further conversions.

This explanation agrees fully with Clusius' observations and shows the similarity between the decomposition of phenylhydrazine and the known reaction of hydrazobenzene disproportionation [14].

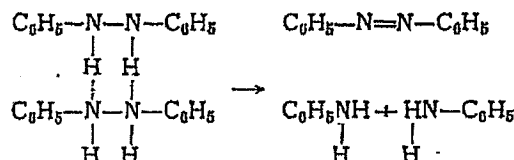


In this case the azo compound is stable and nitrogen is not evolved.

Disproportionation is caused by heating or irradiating an alcoholic solution of the hydrazo compound with ultraviolet light. Recently, P. F. Holt and B. P. Hughes [13] investigated the thermal decomposition of hydrazobenzene, containing nitrogen labeled with a heavy isotope. The azobenzene obtained did not differ in isotope content from the starting hydrazobenzene which showed that during the reaction the $N-N$ bond was not broken, but this contradicts the radical mechanism of disproportionation. In 1912 Wieland [16] proposed an intermolecular oxidation-reduction mechanism.



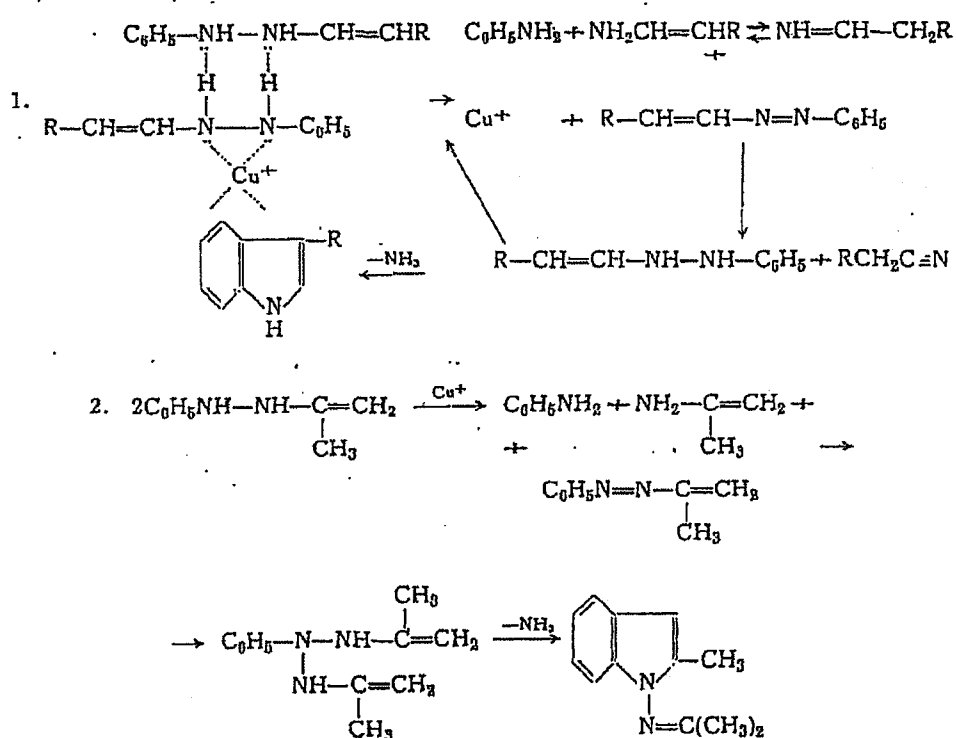
On the basis of their experimental results, P. F. Holt and B. P. Hughes consider that disproportionation did occur either in accordance with Wieland's mechanism or by the scheme



In order to prove the above scheme the authors made cryoscopic measurements and showed that association of hydrazobenzene molecules may actually occur.

One would expect that α, β -alkylphenylhydrazines are also capable of disproportionation to form amine, benzeneazobenzene and aniline. It is possible that the appearance of azo compounds and hydrazones observed by M. P. Grammaticakis [17] in alcoholic solutions of alkylphenylhydrazines is also due to this process and not to the oxidation of the hydrazine with aerobic oxygen.

It seems to us that the formation of nitriles and N-substituted indoles from arylhydrazones in the presence of cuprous chloride may be explained by using the same scheme which we had put forward above for the catalytic decomposition of phenylhydrazine and disproportionation of hydrazobenzene.



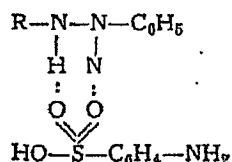
The details of these schemes should be studied and confirmed experimentally. However, we do not question the accuracy of such a mechanism.

We cannot yet prove why an anomalous Fischer reaction occurs in the presence of cuprous chloride and is not observed in the presence of zinc chloride, but maintain that it is due to the nature of the metal. Regrettably, the complexes of phenylhydrazine and phenylhydrazones have not yet been studied, but our assertions are based on the following. Firstly, zinc and copper chlorides behave differently in a Fischer reaction; secondly, the complexes of these salts with phenylhydrazine have a different reaction to heating: the zinc complex decomposes smoothly, while, as one of us noted earlier, the copper one decomposes with an explosion [8]. Apparently, both nitrogen atoms in the copper complex are under quite a strong influence from the complex-former, the zinc, however, either combines with only one nitrogen atom of the arylhydrazone, or else its effect on the nitrogen atom is less.

It is interesting to note that if cuprous chloride that had been stored for a long time was used for the reaction, no anomalous product could be isolated though neither was 2-methylindole formed if acetone phenylhydrazine was used.

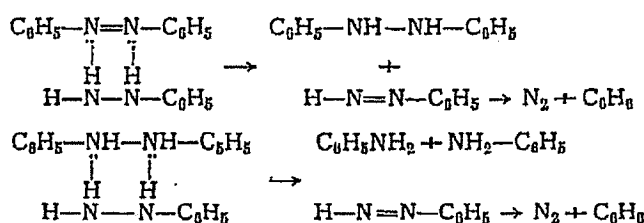
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We succeeded in finding another catalyst for the anomalous reaction in whose presence acetone phenylhydrazone gave the 2-methylindol-N-aminide of acetone (I) in a 70% yield and isovaleraldehyde phenylhydrazone gave the corresponding nitrile (42%). This catalyst is sulfanilic acid, which also catalyzes the decomposition of phenylhydrazine [18] to nitrogen, ammonia, aniline and benzene. In all probability, sulfanilic acid forms hydrogen bonds with the hydrazine or enehydrazine, i. e., in this case the free base would be the reducing agent.



Thus, the common catalysts of the two analogous processes seem to us to give further proof of their common mechanism.

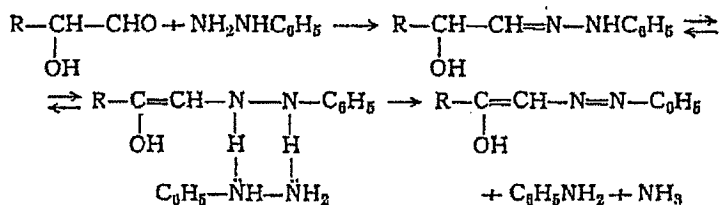
Interesting observations, confirming our mechanism, are contained in the paper by P. Walther [19]. In particular, the author found that heating azobenzene with phenylhydrazine gave hydrazobenzene, nitrogen and benzene, and that, in its turn, hydrazobenzene with phenylhydrazine gave aniline, nitrogen and benzene. The processes occurring in reactions investigated by P. Walther, may be illustrated thus



The reaction of a hydroxyazo compound with phenylhydrazine has the same mechanism [20].

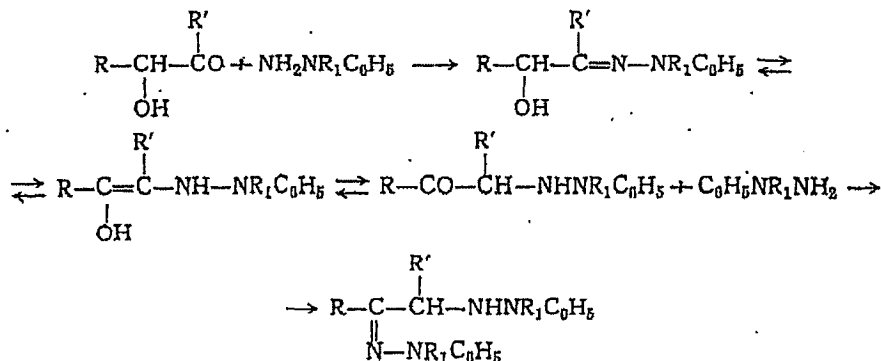
Oxidation-reduction reactions of hydrazines also occur in the formation of osazones.

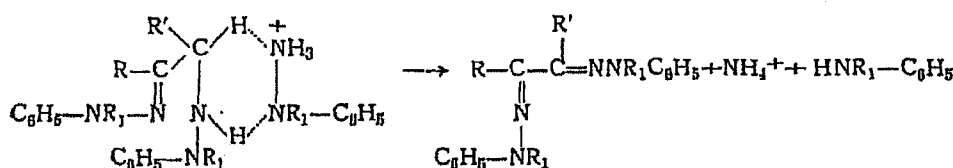
Many authors have discussed the formation mechanism of osazones and we shall not repeat here the various hypotheses put forward to explain it. We consider that at least in the case of an aldose the reaction proceeds in the following way



We have already mentioned the further conversion of intermediate azo compound in discussing the mechanism of the Fischer reaction [15].

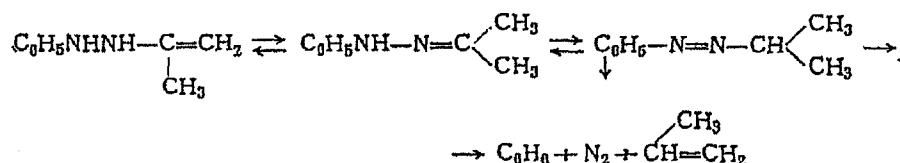
It is possible that ketoses react in the same way with phenylhydrazine, and according to G. Bloink and K. Pausacker's scheme [21], with methylphenylhydrazine.





Consequently, the statement by G. Reddelien [11] on the mechanism of the catalytic decomposition of phenylhydrazine is not without basis, but he was incorrect in assuming that the complex was the oxidant.

We also found that in the catalytic decomposition of acetone phenylhydrazone in the presence of ZnCl_2 and NiCl_2 a certain amount of aniline was always formed, i. e., apparently in these cases an anomalous reaction occurred as a side process. Furthermore, it was established that in all cases studied of the decomposition of acetone phenylhydrazone, a gas passed through the ammonia absorber which when ignited, burned with a smoky flame. The smell of the gas was reminiscent of benzene. It decolorized an acid solution of potassium permanganate and bromine water. It appears to us that besides the main reaction, in these cases decomposition of a mixed azo compound occurred, as its partial formation cannot be excluded.



i. e., the gas passing through the absorber in all probability was a mixture of nitrogen and propylene, possibly with traces of benzene vapor. Thus, in one experiment in decomposing 57 g of acetone phenylhydrazone, the losses, mainly of unabsorbed gas, were 2.5 g.

In conclusion we note that we could not solve the problem of why all arylhydrazones did not undergo the anomalous reaction in the presence of cuprous chloride. The effect of sulfanilic acid as a catalyst of the anomalous Fischer reaction is being studied and will be discussed in detail in a future report. The effect of a substituent in the phenylhydrazine nucleus on the course of the anomalous reaction is also being studied.

EXPERIMENTAL

The hydrazones used in the work were prepared by the usual methods recommended in the literature and had the constants given in Table 2.

Decomposition of acetone phenylhydrazone in the presence of cuprous chloride. 25.5 g of hydrazone and 1.0 g of cuprous chloride were heated in an Arbuzov flask on a metal bath. The reaction began at 180° in the bath and proceeded for 35 min with a bath temperature of $260-270^\circ$. We trapped 1.3 g of ammonia (by the anomalous reaction scheme there should be 1.46 g and by the normal Fischer reaction - 2.93 g). A gas came through the ammonia absorber, which smelled of benzene and burnt with a smoky flame, on ignition. At 71° , several drops of a colorless liquid (n_D^{20} 1.5010) fell into the receiver. During the reaction a yellow liquid (b. p. $182-185^\circ$) began to distill off. When ammonia was no longer evolved, the dark reaction mixture was distilled in vacuum to give a certain amount of a yellow liquid and a dark red tarry residue. The distillate was then separated into two fractions by distillation: 1st $68-75^\circ$ (10mm), 7.8 g; 2nd $138-139^\circ$ (10 mm), 3.3 g.

The first fraction was treated with acetic anhydride to give a solid substance with m. p. $112.5-113^\circ$ (from water), which melted at 112° , when mixed with acetanilide, i. e., we had isolated aniline.

The 2nd fraction (yield 20.6%) had the following constants:

d_4^{20} 1.0520, n_D^{20} 1.5801, M_{rD} 58.94, calculated 59.09. Found %: N 15.21, 15.12. $\text{C}_{12}\text{H}_{14}\text{N}_2$ (I). Calculated %: N 15.05.

231 754

TABLE 2

Expt. No.	Phenylhydrazones	Melting point	Boiling point	d_4^{20}	n_D^{20}	MR_D	Yield (%)
1	Acetone	—	128° (10 mm)	1.0123	1.5865	49.15	83.2
2	Methyl isopropyl ketone	—	108.5 (0.5 mm)	0.9751	1.5639	58.78	93.6
3	Pinacol	—	147.9 (12 mm)	—	1.5525	—	—
4	Acetophenone	104.5°	—	—	—	—	98
5	p-Chloroacetophenone	113—114	—	—	—	—	94
6	Pyruvic acid	179—181	—	—	—	—	87.5
7	Isovaleraldehyde	—	115—116 (1.5 mm)	0.9722	1.5611	58.74	92
8	Ethyl pyruvate	114—115	—	—	—	—	—
9	Acetone methylphenylhydrazone	—	116—117 (15 mm)	—	1.5578	—	—

The substance did not give an indole reaction with a pine splinter. It dissolved in dilute acids and also in acetone, ether, alcohol and benzene.

For hydrolysis of the substance with b. p. 138–139° (10 mm) (2nd fraction), 1.5 g of it was dissolved in 20 ml of 10% sulfuric acid and the solution boiled under reflux for 5 hrs. Then the reflux condenser was exchanged for a straight one and 12 ml of liquid distilled off. A dark mobile liquid remained in the flask. To 5 ml of the distillate were added 5 drops of salicylaldehyde and 2.5 ml of concentrated sulfuric acid. After heating, an orange red color appeared in the upper layer — a characteristic reaction for acetone. A blank experiment gave a yellow color; consequently, the substance contained the $-N=C(CH_3)_2$ group.

Determination of the active hydrogen by the Chugaev-Tserevitinov method showed that the substance contained three labile hydrogen atoms, corresponding to the $\alpha-CH_3$ group of indole.

Decomposition of methyl isopropyl ketone phenylhydrazone in the presence of cuprous chloride. 29.9 g of hydrazone and 0.8 g of catalyst were reacted. Decomposition began at a bath temperature of 210° and then proceeded at a bath temperature of 240–270°. We trapped 1.4 g of ammonia (for the anomalous reaction there should be 1.45 g). During the decomposition, a yellow liquid distilled off at 170–189°. A further small amount of yellow liquid came over during vacuum distillation of the dark reaction mixture, with b. p. 58–170° (13 mm) (decomp.).

Subsequent distillation of the liquid at 10 mm gave the following fractions: 1st 57–78°, a yellow liquid; 2nd 144–145°, 2.2 g, a bright yellow liquid; 3rd 148–155°, 1.3 g, a yellow liquid.

By treating it with acetic anhydride, we obtained acetanilide with m. p. 113° from the 1st fraction; the mixed melting point was 112–113°.

The substance of the 2nd fraction was insoluble in water, but dissolved in dilute sulfuric acid, acetone and alcohol. On standing in air, it became red.

For hydrolysis of the substance with b. p. 144–145° (10 mm) (2nd fraction), 0.95 g of it was dissolved in 15 ml of 10% H_2SO_4 and boiled under reflux for 4 hrs. Then 10 ml of liquid was distilled off and the distillate treated with an acid solution of dinitrophenylhydrazine. The precipitate was recrystallized from alcohol and melted at 117–118°. A mixture with methyl isopropyl ketone dinitrophenylhydrazone melted at 117°. Conse-

quently, methyl isopropyl ketone was liberated on hydrolysis, i. e., the substance contained the $-N=C\begin{matrix} CH_3 \\ CH(CH_3)_2 \end{matrix}$ group.

Found %: N 11.73. $C_{16}H_{22}N_2$ (II). Calculated %: N 11.56.

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Decomposition of acetone phenylhydrazone in the presence of sulfanilic acid. 33.0 g of hydrazone and 0.3 g of sulfanilic acid were heated in an Arbuzov flask on a Wood's metal bath. The evolution of ammonia began at a bath temperature of 200°; the reaction proceeded vigorously at 240° and was complete after 3.5 hrs. A gas passed through the ammonia absorber, which burnt with a smoky flame on ignition. We trapped 1.7 g of ammonia (for the anomalous reaction there should be 1.9 g). Vacuum distillation of the reaction mixture gave 24.2 g of a yellow liquid and 4.0 g of tar was left in the flask.

Distillation of the liquid gave the following fractions: 1st 72-78° (13 mm), 7.7 g; 2nd 130-135° (11 mm), 14.9 g; residue 1.4 g.

From the 1st fraction we isolated 7.2 g of aniline, which was identified as acetanilide. A second distillation of the 2nd fraction at 6 mm gave two fractions: 1st 120-130°, 0.8 g; 2nd 132-133°, 14.0 g; residue 0.1 g.

The 2nd fraction of the second distillation was the anomalous product and had the constants: n_D^{20} 1.5808, d_4^{20} 1.0532, close to those given above for substance (I). The yield was 70%; the same as the yield of aniline. The substance did not crystallize at -70° (cooling mixture: dry ice + ether).

Decomposition of isovaleraldehyde phenylhydrazone in the presence of sulfanilic acid. 25.7 g of hydrazone and 0.2 g of catalyst were reacted. Decomposition began when the bath temperature reached 200° and was complete after 1 hr at a bath temperature of 260°. The vapor temperature of the liquid distilling off was 170°. We trapped 0.1 g of ammonia. With slight decomposition, 16.0 g of a yellow liquid distilled off with b. p. 135-140° and 7.7 g of a dark red tar was left in the reaction flask. Subsequent distillation of the liquid obtained gave the following fractions: 1st 128-130°, 5.0 g; 2nd 176-186°, 7.1 g.

The substance of the 1st fraction was identified as isovaleronitrile by the boiling point and characteristic smell; the yield was 42%. The 2nd fraction was aniline (acetanilide was prepared), which was obtained in 53% yield.

Decomposition of acetophenone phenylhydrazone. 25.0 g of the phenylhydrazone and 0.8 g of cuprous chloride were heated in an Arbuzov flask on a Wood's metal bath in an atmosphere of CO₂. Evolution of ammonia began at 190° (in the bath) and was accompanied by the formation of a white deposit in the condenser - (NH₄)₂CO₃. The decomposition was complete after 1.5 hr at a bath temperature of 270°. We trapped 0.9 g of NH₃ (for the anomalous reaction 1.01 g should be liberated). The brown reaction mixture was distilled at 2 mm to give the following fractions: 1st 45-50°, 4.1 g, n_D^{20} 1.5764; 2nd 135-170°, 0.8 g, crystallized; residue 18.0 g (tar).

The 1st fraction was mainly aniline, identified by preparing acetanilide. The 2nd fraction was recrystallized from ligroin to give 0.3 g of yellow plates with m. p. 184-185°, which sublimed on heating. They dissolved in ether and benzene. A mixture with 2-phenylindole, prepared by E. Fischer's method, melted at 184-186°; consequently 2-phenylindole was isolated.

Another time 85.0 g of phenylhydrazone was decomposed in the presence of 0.9 g of cuprous chloride. Decomposition began at 215°, proceeded vigorously at a bath temperature of 250-260° and was accompanied by the evolution of ammonia and a gas, which passed through absorbers with water and sulfuric acid, burnt with a smoky flame and had the smell of benzene. We trapped 4.2 g of ammonia (for the anomalous reaction 3.4 g is required).

About 50 g of the mass obtained was placed in a flask, through which steam was passed. The mass became liquid. Approximately 1000 ml of distillate was collected, containing only traces of oil. Thus the reaction product did not contain substances, volatile in steam.

Decomposition of p-chloroacetophenone phenylhydrazone. 12.0 g of phenylhydrazone and 0.5 g of cuprous chloride were used. Decomposition began at 170° (bath temperature). At 240° we observed the vigorous evolution of ammonia and a combustible gas. 0.4 g of NH₃ was evolved (theoretical also 0.4 g) and 1.1 g of a turbid, colorless liquid distilled off in the range 68-115°. On distillation, we obtained 0.5 g of a substance with b. p. 170-185° (3 mm); a deposit of yellow crystals was formed on the walls of the apparatus; then decomposition began and distillation was stopped.

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After recrystallization from an alcohol-water mixture, the yellow crystals (0.2 g) were converted into a finely crystalline, white powder with m. p. 195-196°. Literature data for 2-(4-chlorophenyl)-indole: m. p. 201-202° [3].

The thick black tar left in the reaction flask was treated with alcohol and partially dissolved. White curds (~ 1 g) were precipitated from the alcohol solution with water and these could not be converted into a crystalline state. They did not have a definite melting point and on heating, darkened and melted gradually.

Decomposition of phenylhydrazone of ethyl pyruvate. 6.0 g of hydrazone and 5.5 g of cuprous chloride were used in the reaction. Decomposition lasted about 2 hrs at a bath temperature of 210-250°. After cooling, the dark melt obtained was washed twice with 20 ml portions of hydrochloric acid (1:10) to remove catalyst. Then the solid mass was treated with ether (50 ml). After evaporating off the solvent, the ether extract gave a shiny, red, crystalline mass, which was distilled. At 150° (4 mm), we collected 1.50 g of a yellowish liquid, which quickly crystallized as fine plates. After two recrystallizations from alcohol, we isolated 1.05 g (19.1%) of a slightly yellowish, finely crystalline mass with m. p. 120.5-121.5°. A mixture with the starting hydrazone melted at 93-97°.

Found %: N 7.50, 7.65. $C_{11}H_{11}O_2N$. Calculated %: N 7.40. Literature data for 2-carboethoxyindole m. p. 107° [3].

Decomposition of pinacolin phenylhydrazone. 16.5 g of hydrazone and 0.3 g of cuprous chloride were heated in an Arbuzov flask. Evolution of ammonia began when the temperature of the bath reached 210°; then a yellowish liquid distilled off (69-85°). Then the bath temperature was raised to 250° and then a yellow liquid distilled over in the range 185-190°. We trapped 0.4 g of ammonia. In an attempt to distill the remaining reaction mixture in vacuum, we collected a small amount of a yellow liquid, boiling at 135-150° (13 mm), after which, a thick red liquid began to distill with decomposition. Aniline, detected as acetanilide, was found in the distillate, which came over at atmospheric pressure. The other products were not identified.

Decomposition of acetone methylphenylhydrazone. 16.0 g of hydrazone and 0.2 g of cuprous chloride were used in the reaction. The decomposition proceeded with the gentle evolution of gas at a bath temperature of 220-260°. We trapped 0.3 g of ammonia (for the anomalous reaction 0.84 g should be liberated). 11.5 g of a yellow liquid was distilled off from the reaction mixture in vacuum and 3.7 g of tar remained in the distillation flask. Distillation of the liquid at 15 mm gave the following fractions: 1st 85-88°, 2.7 g, n_D^{21} 1.5512; 2nd 90-110°, 2.2 g, n_D^{21} 1.5614; 3rd 111-118°, 5.1 g, n_D^{21} 1.5568; residue 1.3 g.

The 3rd fraction was the starting hydrazone with n_D^{21} 1.5578 and b. p. 116-117° (at 15 mm). The first fractions were not investigated more closely.

Decomposition of acetone phenylhydrazone under different conditions. a) 29.3 g of phenylhydrazone and 0.5 g of zinc chloride were heated in Arbuzov flask on a metal bath. The reaction began when the bath temperature reached 230° and proceeded for 3 hrs at a temperature of 240°-250°. The reaction was accompanied by the evolution of ammonia, which was absorbed in water and sulfuric acid and a gas, which passed through the absorbers and burnt with a smoky flame. 2.4 g of ammonia was liberated (theoretical 3.36 g). Distillation of the reaction mixture in vacuum gave 18.6 g of a yellow liquid.

On distilling this liquid, we collected the following fractions: 1st 40-50° (3 mm), 2.6 g, n_D^{20} 1.5778; 2nd 98-102° (2 mm), 2.8 g; 3rd 103-105° (2 mm), 12.5 g, n_D^{20} 1.6016; the residue was a small amount of a mobile cherry red tar.

The 1st fraction gave a crystalline product with acetic anhydride, which melted at 112.5-114° after boiling with animal charcoal and recrystallization from water, i. e., it was acetanilide (mixed melting point). Consequently, the main part of the first fraction was aniline.

The 2nd and 3rd fractions crystallized on standing and were recrystallized from aqueous alcohol to give 14.5 g (60%) of 2-methylindole with m. p. 58.5-59.5°.

On heating 2-methylindole with acetone phenylhydrazone in the presence of cuprous chloride, tar formation occurred and ammonia was evolved at 190°. The anomalous product was not isolated from the thick reaction mixture.

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b) 57.1 g of phenylhydrazone and 1.0 g of cuprous chloride were heated under the same conditions as in the first experiment. The gas, passing through the ammonia trap, was passed through an acid solution of KMnO_4 and bromine water. We observed the decoloration of the bromine water without the evolution of HBr and the KMnO_4 solution (rapidly), if it was heated to 40° . The gas causing the decoloration, had a smell reminiscent of the smell of benzene and burnt quietly with a smoky flame on ignition. During the reaction, which lasted for 195 min, 2.5 g of a gas, which was not absorbed by acid, was liberated. We trapped 3.1 g of ammonia (theoretical 3.27 g). During the reaction, 14.5 g of a yellow liquid distilled off and then a further 25.1 g of reaction product was distilled off in vacuum (14 mm) to leave a residue of tar. Subsequent fractionation in vacuum gave the following fractions: 1st 42° (50 mm), a few drops of a colorless liquid; 2nd $79-83^\circ$ (16 mm), n_D^{20} 1.5630, 15.35 g; 3rd $140-146^\circ$ (16 mm), n_D^{20} 1.5818, 13.25 g; 4th $148-150^\circ$ (16 mm) (decomp.); 5th - tar.

A second distillation of the 3rd and 4th fractions gave 13.1 g (40.7%) of 2-methylindole-1-aminide of acetone with b. p. $139-141^\circ$ (12 mm), n_D^{20} 1.5805. From the 2nd fraction we obtained acetanilide (m. p. $112.5-113^\circ$), i. e., it was mainly aniline.

c) 16.2 g of phenylhydrazone and 20.7 g of cuprous chloride were heated in a distillation apparatus on a metal bath. At 160° (in the bath) the liquid reaction mixture began to boil and frothed vigorously. The process gradually speeded up and ended with the reaction mixture coming out of the flask, when even cooling the flask with water did not help. The brown reaction mixture became green in air. If the reaction vessel was not cooled, then an explosion occurred in which a voluminous, yellow smoke was formed.

d) From a catalytic decomposition using 16.4 g of phenylhydrazone and 0.2 g of nickelous chloride, we obtained 7.1 g of a crystalline substance with m. p. $58-59^\circ$, corresponding to 2-methylindole with the characteristic smell of indole, and 0.95 g of aniline. The decomposition was accompanied by the evolution of ammonia and a gas, which passed through traps with water and sulfuric acid and burnt on ignition.

The reaction of phenylhydrazine with cuprous chloride and zinc chloride. On mixing different weights of phenylhydrazine and cuprous chloride, we observed heating up from 19 to 65° . After heating the mixture to 80° , vigorous evolution of heat began, at first without the formation of ammonia. The reaction finished with an explosion, when the temperature of the mixture reached 260° .

The reaction of phenylhydrazine with zinc chloride was studied similarly; in this case the mixture heated up to 80° . On heating the mixture, which crystallized on cooling, above 100° , decomposition began with the evolution of ammonia and benzene vapor.

SUMMARY

1. We studied the catalytic decomposition of the phenylhydrazones of acetone, methyl isopropyl ketone, pinacoln, pyruvic acid, ethyl pyruvate, acetophenone and p-chloroacetophenone and the methylphenylhydrazone of acetone in the presence of cuprous chloride.

2. It was established that in catalytic decomposition in the presence of cuprous chloride, ketone phenylhydrazones, not containing CH_2 groups next to the carbonyl, do not, as a rule, form indoles, corresponding to the scheme of the Fischer reaction.

We isolated the anomalous reaction products of the phenylhydrazones of acetone and methyl isopropyl ketone and established their structure.

3. We found that sulfanilic acid is a catalyst of the anomalous Fischer reaction.

4. We showed the analogy between and gave the general scheme for the reaction mechanism of the catalytic decomposition of phenylhydrazine, the anomalous decomposition of some ketone phenylhydrazones and the formation of nitriles from aldehyde phenylhydrazones, first found by A. E. Arbuzov in 1911-1913.

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