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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-091892- -00006-0000

Fecha: 2008-10-27 16:33:32 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COME

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REF:

Expediente 07-091-892

**TÍTULO SOLICITADO: PROCESO PARA LA PREPARACIÓN DE
DERIVADOS DE 1-AMINOPIPERIDINA.**

PUBLICACIÓN:

Gaceta 591 de 30/03/2008, N° de publicación 275

PRIORIDAD:

DE 102005011050.9 de 14/09/2006

SOLICITANTE:

SANOFI-AVENTIS.

APODERADO:

LUIS PATIÑO LEYVA.

TRÁMITE:

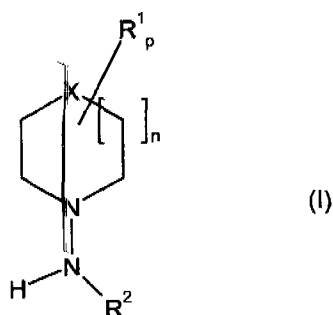
SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

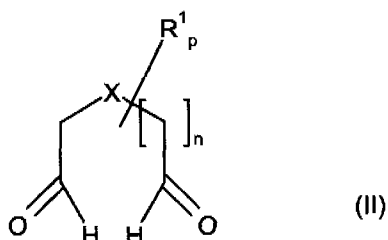
I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito exponer los argumentos que permitirán demostrar que la solicitud de la referencia, que reivindica un proceso para la preparación de compuesto de la formula general I

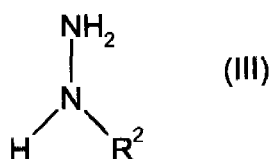
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bajo condiciones acidas o básicas, en el cual se parte de un compuesto dicarbonílico de la formula general II



que reacciona con un derivado de hidrazina de la fórmula general III



en donde R2 es un grupo N-protector el cual puede ser retirado bajo condiciones ácidas o básicas; y cuyo compuesto resultante se hidrogena en presencia de un metal de transición y se le retira opcionalmente el grupo R2 bajo condiciones acidas o básicas, incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentarlo.

Primero que todo, es relevante aclarar que el proceso sintético a través del cual se obtienen los derivados de 1-aminopiperidina sustituidos que se exponen en el capítulo reivindicatorio de la solicitud colombiana en trámite, resulta ser el resultado de la reacción de cierto tipo de compuestos –reacciones conocidas en química orgánica- que pueden de cierta manera desvirtuar el nivel inventivo de la misma.

Dichas reacciones consisten, como cualquier persona medianamente versada en la materia puede reconocer, en una adición nucleofílica del nitrógeno no sustituido del derivado de hidrazina (compuesto III), inicialmente, sobre uno de los carbonos

que sustentan el grupo carbonilo del compuesto dicarbonílico (compuesto II), con una posterior adición nucleofílica por parte del mismo nitrógeno del compuesto derivado de hidrazina (compuesto III) sobre el otro carbono que soporta el grupo carbonilo en el compuesto II, dando como resultado un intermediario dihidroxilado, que por reducción catalítica con hidrógeno en Pd o Pt da como resultado el compuesto de 1-aminopiperidina sustituido de fórmula general I. Así mismo, dicho proceso requiere de la protección de uno de los nitrógenos del compuesto de hidrazina (compuesto III) para que la adición sobre ambos carbonilos se lleve a cabo solo por uno de los nitrógenos de dicho compuesto de hidrazina.

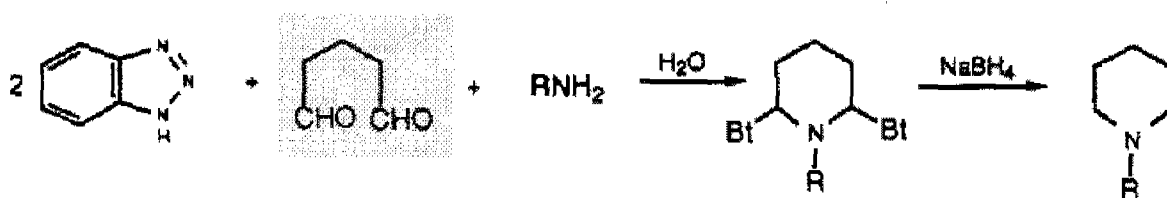
En el mismo sentido, existen documentos que describen con anterioridad de manera general el proceso de obtención, así como compuestos del mismo tipo que los expuestos por la solicitud colombiana en trámite, veamos:

- ❖ La publicación científica "A Novel And Versatile Synthesis Of 1-Alkyl-, 1-Aryl-, 1-(Alkylamino)-, Or 1-Amido-Substituted And Of 1,2,6-Trisubstituted Piperidines From Glutaraldehyde And Primary Amines Or Monosubstituted Hydrazines¹" revela:

Various primary amines and 1-mono- and 1,1-disubstituted hydrazines were converted into the corresponding N-substituted piperidines in good to excellent yields via the products of double condensations with benzotriazole and glutaraldehyde. Reduction of the 2,6-bis(benzotriazolyl) N-substituted piperidines 4 and 7 with sodium borohydride in tetrahydrofuran afforded N-substituted piperidines. The benzotriazole moieties were also replaced by alkyl groups by reaction with Grignard reagents to produce 1,2,6-trisubstituted piperidines.

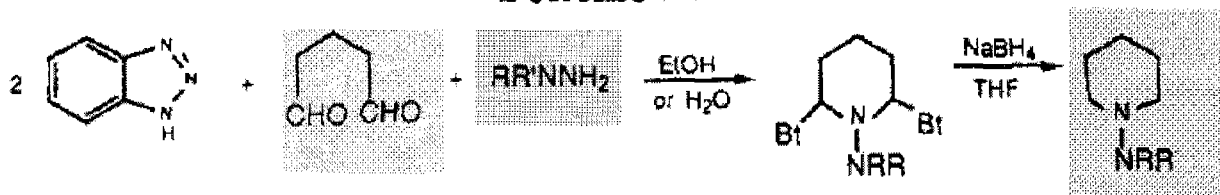
(...)

Scheme I



(...)

Scheme II



¹ Alan R. Katritzky* and Wei-Qiang Fan. J. Org. Chem., Vol. 55, No. 10, 1990.

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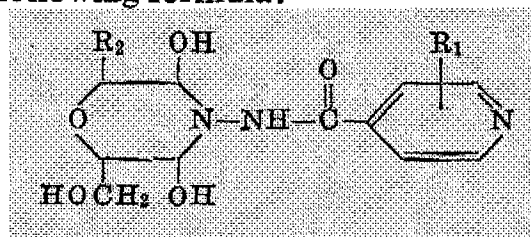
❖ La patente Americana US 3,542,776 publicada el 24 de Noviembre de 1970 y titulada "MORPHOLINOISONICOTINAMIDES" revela:

ABSTRACT OF THE DISCLOSURE

This invention relates to new isonicotinic acid hydrazides and more particularly to isonicotinic acid hydrazide derivatives of periodate oxidized pyrimidine and 6-amino-purine ribosides. The compounds are useful for blocking the auto-immune processes in warm-blooded animals.

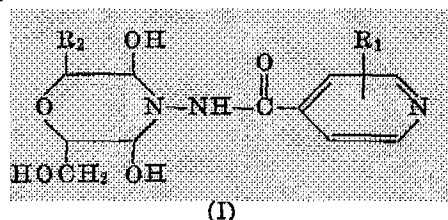
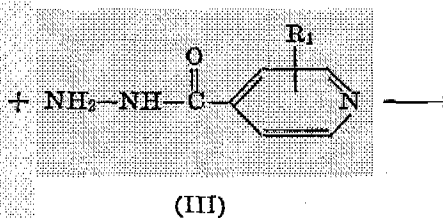
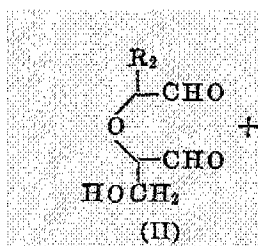
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ly active amount of a compound selected from the group having the following formula:



(I)

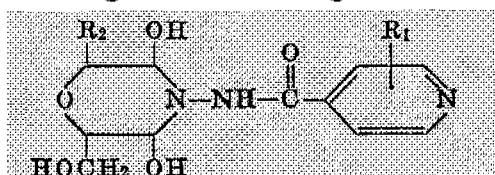
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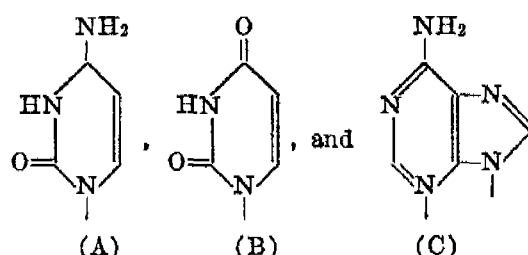
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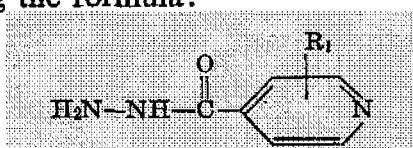
6. A process for preparing a compound selected from the group consisting of those having the formula:



wherein R_1 is selected from the group consisting of hydrogen and methyl and R_2 is selected from the group consisting of

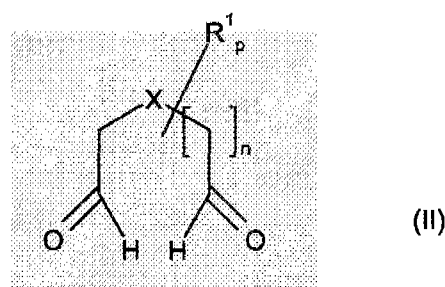


which comprises reacting the product of periodate oxidation of a compound selected from the group consisting of 6 - amino-9- β -D-ribofuranosyl-9H-purine, 4-amino-1- β -D-ribofuranosyl-2(1H)-pyrimidinone, and 1- β -D - ribofuranosyl-2,4-pyrimidinediol, with an isonicotinic acid hydrazide having the formula:

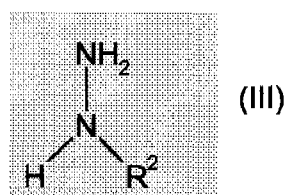


wherein R_1 is defined as above.

Como se puede apreciar en estas dos anterioridades se evidencia el uso de compuestos dicarbonílicos (ver recuadros de color verde) del mismo tipo que el compuesto de fórmula general II de la solicitud colombiana en trámite

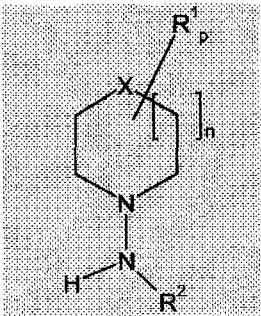


que reaccionan con derivados de hidrazina (ver recuadros de color rosado) del mismo tipo que los de la de la fórmula general III



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para producir finalmente compuestos de 1-aminopiperidina sustituidos (ver recuadros de color azul) del mismo tipo que los compuestos de fórmula general I



(I)

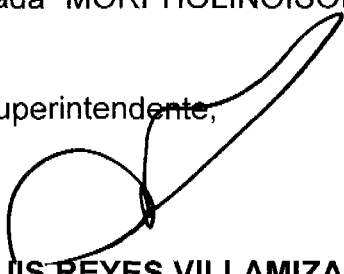
En conclusión y si bien es cierto que en estos documentos anteriores no se usan exactamente los mismos reactivos o bien no se expone claramente la existencia de la etapa de hidrogenación, la solicitud colombiana en trámite carece irrefutablemente de nivel inventivo puesto que reivindica intermediarios y un proceso de síntesis reconocible de manera general en el estado del arte y con reacciones de común empleo en química orgánica y obvias para una persona medianamente versada en la materia.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

II. ANEXOS.

- ❖ La publicación científica "A Novel And Versatile Synthesis Of 1-Alkyl-, 1-Aryl-, 1-(Alkylamino)-, Or 1-Amido-Substituted And Of 1,2,6-Trisubstituted Piperidines From Glutaraldehyde And Primary Amines Or Monosubstituted Hydrazines".
- ❖ La patente Americana US 3542776 publicada el 24 de Noviembre de 1970 y titulada "MORPHOLINOISONICOTINAMIDES".

Señor Superintendente,


JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

phosphate buffer ($\mu = 1.0$, KCl) was added 708 mg of Frey's salt. The mixture was stirred at room temperature for 1 h, during which time red *syn-2b* crystallized from solution. Filtration, washing the solids with a small volume of water, and then drying afforded *syn-2b* as a fibrous red solid: 61 mg (36%) yield. The filtrate was extracted with 2 $\times$ 50 mL of chloroform. Evaporation of the dried extracts (MgSO_4) to a residue and then trituration with acetone afforded yellow *anti-2b* (21 mg (12%) yield).

Physical properties of *syn-2b*: mp 312 °C dec; TLC (acetone) $R_f = 0.57$; IR (KBr pellet) 3340, 1745, 1625, 1601, 1380, 1238 cm^{-1} ; ^1H NMR (dimethyl sulfoxide- d_6) δ 9.34 and 6.68 (2 H, 2 br s, imine protons), 5.99 (1 H, m, C(3) proton), 4.24 (2 H, m, C(1) diastereomeric methylene), 3.04 and $\sim$ 2.5 (2 H, 2 m, C(2) diastereomeric methylene), 2.07 (3 H, s, 7-methyl), 1.74 and 1.54 (6 H, 2 s, acetate and acetamido methyls); ^{13}C NMR (dimethyl sulfoxide- d_6) 176.2, 169.6, 154.7, 154.1, 149.8, 138.7, 130, 110.6, 96.8, 65.5, 43.3, 34.1, 25.5, 20.6, 8.7 cps; mass spectrum (EI mode), m/z 316 (P^+). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_4 \cdot 0.25\text{H}_2\text{O}$: C, 56.15; H, 5.18; N, 17.45. Found: C, 55.94; H, 5.19; N, 17.18.

Physical properties of *anti-2b*: mp 304 °C dec; TLC (same as *syn-2b*); IR (KBr pellet) 3188, 1740, 1714, 1644, 1627, 1487, 1378, 1310, 1230 cm^{-1} ; ^1H NMR (dimethyl sulfoxide- d_6) δ 11.65 (1 H, s, amide proton), 9.64 (1 H, s, imine proton), 6.06 (1 H, dd, $J = 8$ Hz, $J = 3.8$ Hz, C(3) proton), 4.29 (2 H, m, C(1) diastereomeric methylene), 3.06 and $\sim$ 2.6 (2 H, 2 m, C(2) diastereomeric methylene), 2.08 (6 H, 2 s), and 1.8 (3 H, s), 7-methyl, acetamido, and acetate methyls, no assignments made; mass spectrum (same as *syn-2a*).

6-Acetamido-5-amino-8-hydroxy-7-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (19). A solution of 25 mg (0.09 mmol) of *syn-2a* in 5 mL of methanol was shaken under 50 psi of H_2 in the presence of 5 mg of 5% Pd on charcoal. The catalyst was then removed by filtering through Celite, and the filtrate immediately concentrated to a solid. Dissolution of the solid in 5 mL of chloroform/methanol (1:4) and adding hexane resulted in precipitation of 19: 20 mg (79%) yield; TLC (chloroform/methanol [6:4]) $R_f = 0.4$; IR (KBr pellet) 3322, 3210, 3140, 1660, 1640, 1505 cm^{-1} ; ^1H NMR (dimethyl sulfoxide- d_6) δ 9.19 (1 H, s,

amide proton), 8.68 (1 H, s, 8-hydroxyl), 4.14 (2 H, t, $J = 7.1$ Hz, C(1) methylene), 3.20 (2 H, t, $J = 7.5$ Hz, C(3) methylene), 2.72 (2 H, m, C(2) methylene), 2.07 and 2.04 (6 H, 2 s, 7-methyl and acetamido methyl); mass spectrum (EI mode), m/z 260 (P^+), 242 ($\text{P}^+ - \text{H}_2\text{O}$), 217 ($\text{P}^+ - \text{acetyl}$).

6-Acetamido-5,6-dihydroxy-7-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (20). A solution of 30 mg (0.11 mmol) of 1a in 10 mL of methanol was shaken under 50 psi of H_2 for 25 min in the presence of 8 mg of 5% Pd on charcoal. After addition of 3 drops of concentrated HCl to the reaction, the catalyst was removed by filtering through Celite, and the filtrate was concentrated to a solid. Recrystallization of the solid by dissolution in a minimal amount of methanol followed by addition of ethyl acetate afford 20 as the HCl salt: 32 mg (97%) yield; TLC (chloroform/methanol [6:4]) $R_f = 0.57$; IR (KBr pellet) 3337, 3150, 1650, 1505, 1299 cm^{-1} ; ^1H NMR (dimethyl sulfoxide- d_6) δ 9.39 (2 H, s, 5,8-dihydroxy), 9.03 (1 H, s, amide proton), 4.45 (2 H, t, $J = 6.9$ Hz, C(1) methylene), 3.22 (2 H, t, $J = 7.5$ Hz, C(3) methylene), 2.72 (2 H, quintet, $J = 7.6$ Hz, C(2) methylene), 2.10 and 2.08 (6 H, 2 s, 7-methyl and acetamido methyl); mass spectrum (EI mode), m/z 261 (P^+), 243 ($\text{P}^+ - \text{H}_2\text{O}$), 279 ($\text{P}^+ - \text{ketene}$).

Acknowledgment. The research was supported by an award from the National Cancer Institute (PHS no. 1 R01 CA36876-05).

Registry No. 1a, 123567-03-3; 1b, 123567-28-2; 1c, 123567-24-8; 1d, 123567-25-9; *syn-2a*, 123592-95-0; *anti-2a*, 123567-29-3; *syn-2b*, 123593-07-7; *anti-2b*, 123567-30-6; 3, 123567-04-4; 4, 123567-05-5; 4 deacetylated derivative, 123567-31-7; 5, 123567-06-6; 6, 123567-07-7; 6 deacetylated derivative, 123567-20-4; 6 phenyl carbonate analogue, 123567-21-5; 7c-2HCl, 123567-08-8; 7d-2HCl, 123567-22-6; 8, 123567-09-9; 9c, 123567-10-2; 9d, 123567-23-7; 10, 123567-11-3; 11, 123567-12-4; 12, 123567-13-5; 13, 123567-14-6; 14, 123567-15-7; 15a, 123567-16-8; 15b, 123567-26-0; 16a, 123567-17-9; 16b, 123567-27-1; 19, 123567-18-0; 20-HCl, 123567-19-1; 3-bromo-4-nitrotoluene, 40385-54-4; pyrrolidine, 123-75-1; ethylenimine, 151-56-4; 5-bromo-2,4-dinitrotoluene, 5411-53-0.

A Novel and Versatile Synthesis of 1-Alkyl-, 1-Aryl-, 1-(Alkylamino)-, or 1-Amido-Substituted and of 1,2,6-Trisubstituted Piperidines from Glutaraldehyde and Primary Amines or Monosubstituted Hydrazines¹

Alan R. Katritzky* and Wei-Qiang Fan

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received October 27, 1989

Various primary amines and 1-mono- and 1,1-disubstituted hydrazines were converted into the corresponding N-substituted piperidines in good to excellent yields via the products of double condensations with benzotriazole and glutaraldehyde. Reduction of the 2,6-bis(benzotriazolyl) N-substituted piperidines 4 and 7 with sodium borohydride in tetrahydrofuran afforded N-substituted piperidines. The benzotriazole moieties were also replaced by alkyl groups by reaction with Grignard reagents to produce 1,2,6-trisubstituted piperidines.

Many N-substituted piperidines and their 2,6-dialkyl derivatives are pharmacologically active and form an essential part of the molecular structure for important drugs.² For example, the 1-piperidino group is a feature of the antihistaminic agent and the spasmolytic benzhexol,³

of narcotic analgesics,⁴ of postganglionic parasympathetic agonists,⁵ and of oral anesthetics.⁶ Many 1,2,6-trialkyl-piperidine alkaloids have been isolated from both animal and plant species.^{7,8}

(1) The Chemistry of Benzotriazole. See: Katritzky, A. R.; Urogdi, L.; Meyence, A. J. Chem. Soc., Chem. Commun. 1989, 337. Katritzky, A. R.; Hughes, C. V. Chem. Scr. 1989, 29, 27, and refs 24-28.

(2) Coutts, R. T.; Casy, A. F. In *Pyridine and its Derivatives*; Abramovitch, R. A., Ed.; Interscience: John Wiley & Sons: New York, 1974; Part 4, p 492.

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(4) Reynolds, A. K.; Randall, L. O. *Morphine and Allied Drugs*; University of Toronto Press: Toronto, 1957; p 269.

(5) Hermans, B.; van Daele, P.; van de Westeringh, C.; van der Eycken, C.; Boey, J.; Dockx, J.; Janssen, P. A. J. J. Med. Chem. 1968, 11, 797.

(6) McElvain, S. M. J. Am. Chem. Soc. 1927, 49, 2835.

(7) MacConnel, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron*, 1971, 27, 1129.

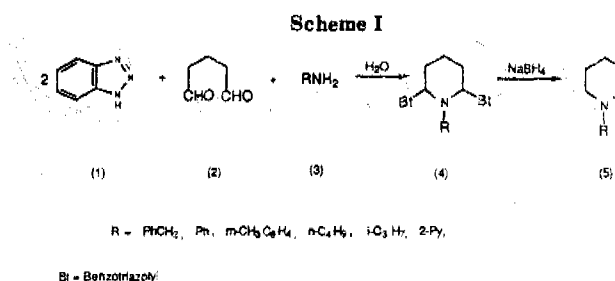
(8) Hootele, C.; Colau, B.; Halin, F. *Tetrahedron Lett.* 1980, 21, 5063.

Table I. Preparation of the N-Substituted 2,6-Bis(benzotriazolyl)piperidines

no.	N-substituent	solvent	yield (%)	mp (°C)	calcd			found		
					C	H	N	C	H	N
4a	PhCH ₂	H ₂ O	91	61–63	70.42	5.62	23.96	70.74	5.69	23.47
4b	Ph	H ₂ O	85	155–158	69.87	5.32	24.81	69.52	5.66	24.50
4c	<i>m</i> -CH ₃ C ₆ H ₄	H ₂ O	80	145–148	70.42	5.62	23.96	70.74	5.87	23.62
4d	<i>n</i> -C ₄ H ₉	H ₂ O	75	<i>a</i>						
4e	<i>i</i> -C ₃ H ₇	H ₂ O	82	<i>a</i>						
4f	2-pyridyl	H ₂ O-EtOH	79	48–51	66.67	5.05	28.28	66.49	4.97	28.46
7a	PhNH	H ₂ O-EtOH	86	65–67	67.32	5.37	27.32	67.64	5.19	27.06
7b	(CH ₃) ₂ N	H ₂ O	73	<i>a</i>						
7c	PhCONH	EtOH	95	169–171	65.68	5.02	25.47	65.34	5.00	25.08
7d	CH ₃ CONH	EtOH	86	178–181	60.64	5.32	29.81	60.59	5.48	30.22
7e	CH ₃ CH ₂ O ₂ CNH	EtOH	94	183–186	59.11	5.42	27.59	58.98	5.52	27.65
7f	(CH ₃) ₂ CO ₂ CNH	EtOH	97	186–190	60.83	5.99	25.81	61.01	5.82	25.49
7g	PhCH ₂ O ₂ CNH	EtOH	93	192–195	64.10	5.13	23.93	63.92	5.31	23.65

^a Sticky oil, used as such in further reactions.

Many alternative methods are available for synthesizing N-substituted piperidines.⁹ Cyclization with the formation of a bond between a carbon atom and a heteroatom is the usual heterocyclization that forms a six-membered heterocyclic ring system. Thus, the most familiar approach to piperidines is from a 1-pentanamine derivative with a leaving group on carbon 5.¹⁰ Such methods utilize various 1,5-disubstituted pentanes as the starting materials. The preparation of a suitable starting material is often a major problem that restricts application, particularly in the preparation of 1,2,6-trisubstituted piperidines. N-Alkyl-substituted piperidines have also been made by the reduction of N-acylpiperidines or N-substituted 2-oxopiperidines,¹¹ but, once again, this suffers from the limited availability of the starting materials. Double reductive Mannich condensation of a dicarbonyl compound with an amine provided an alternative route for the preparation of N-substituted heterocycles with five- and six-membered rings.¹² Thus, Watanabe reported the synthesis of N-substituted piperidines from the reductive amination of glutaraldehyde and primary amines with tetracarbonylhydride as a reducing reagent,¹³ sodium cyanoborohydride has also been used as the reducing reagent.¹⁴ However, this method is inapplicable to 1,2,6-trisubstituted piperidines or to N-(alkylamino)- and N-(alkylamido)-piperidines. The reaction of glutaraldehyde with primary amines with sodium hydrogen sulfite followed by potassium cyanide gave N-alkyl-2,6-dicyanopiperidines,¹⁵ decyanidation of which by heating with sodium borohydride in isopropyl alcohol afforded the N-alkylpiperidines. Reaction of N-benzyl-2,6-dicyanopiperidine anions with alkyl halides, and then decyanidation, gave 2-alkyl- and 2,6-dialkyl-N-benzylpiperidines.¹⁶ N-Alkylation of C-substituted piperidines, often obtained by the reduction of pyridine derivatives, was an alternative route to 1,2,6-trisubstituted piperidines.^{7,17} Other methods previously



used have included catalytic or hydride reduction of substituted imines,¹⁸ intramolecular amination of olefins in the presence of mercuric ion,¹⁹ and catalytic reaction of butadiene with Schiff bases by Pd(NO₃)₂Ph₃P.²⁰ These methods are limited by the availability of the starting materials and reagents and sometimes by the severe conditions.

Relatively few N-(alkylamino)- and N-amido-substituted piperidines have been reported. They were previously prepared by the reduction of N-nitrosopiperidines with zinc dust or lithium aluminum hydride²¹ to N-amino-piperidines, which were then subjected to reductive alkylation with aldehydes and sodium cyanoborohydride²² or to acylation with an acyl or sulfonyl chloride.²³

The present paper describes novel syntheses of a variety of N-alkyl-, N-aryl-, N-(alkylamino)-, N-(acylamino)-, and N-[(alkoxycarbonyl)amino]piperidines and their corresponding 2,6-disubstituted derivatives by double condensations of benzotriazole and glutaraldehyde with primary amines or unsymmetrically substituted hydrazines and subsequent reduction by sodium borohydride or reaction with Grignard reagents.

Recent publications from our laboratory have demonstrated the versatile synthetic utility of benzotriazole.^{24–28}

(9) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, p 395.

(10) Drake, N. L.; Van Hook, J.; Garman, J. A.; Hayes, R.; Johnson, R.; Kelley, G. W.; Melamed, S.; Peck, R. M. *J. Am. Chem. Soc.* 1946, 68, 1529.

(11) Raucher, S.; Klein, P. *Tetrahedron Lett.* 1980, 21, 4061.

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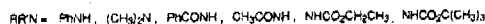
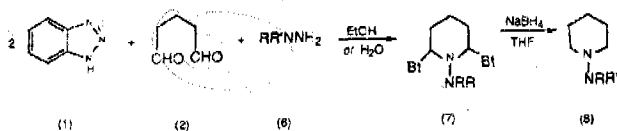
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Scheme II



The products formed from benzotriazole (1), amines (amides and hydrazines) and aldehydes, have been used as intermediates for the monoalkylation of aromatic and of heteroaromatic amines,²⁴ for the conversion of secondary aliphatic to tertiary aliphatic amines,²⁵ and for the alkylation of amides and thioamides²⁶ and of hydrazines.²⁷ We now demonstrate the utility of benzotriazole in forming N-substituted piperidines.

Results and Discussion

Glutaraldehyde and Amine Double Condensation with Benzotriazole. The preparation of condensation products from aldehydes, benzotriazole, and primary or secondary amines has usually been carried out in ethanolic solution²⁹ or by the Dean-Stark method.²⁵ Recently, we reported that benzotriazole reacts with various amines and formaldehyde or acetaldehyde in water at 20 °C, to afford the condensation products in high yield.³⁰ We have now found that this simple procedure can be easily applied to glutaraldehyde. Thus, benzotriazole (1) was first mixed with water, and the appropriate primary amine (3) and was stirred for 10 min at 20 °C. When aqueous glutaraldehyde (2) (25%) was slowly added, a solid began to form immediately. The essentially pure product was obtained after filtration and washing with water. A variety of both aromatic and aliphatic primary amines were employed; the 2,6-bis(benzotriazolyl) N-substituted piperidines (4) were produced in excellent yields (Scheme I). The results are listed in Table I.

When monosubstituted and unsymmetrically disubstituted hydrazines (phenylhydrazine (6a) and *N,N*-dimethylhydrazine (6b)) were used as the amine component, the *N*-(alkylamino)piperidine derivatives 7a and 7b were obtained. This method can also be applied to acylhydrazines (benzoylhydrazine (6c) and acetylhydrazine (6d)) and alkyl carbazates (ethyl carbazate (6e), *tert*-butyl carbazate (6f), and benzyl carbazate (6g)) to prepare the corresponding *N*-(acylamino)- or *N*-[(alkoxycarbonyl)amino]piperidine derivatives 7c-g. For the three alkyl carbazates, ethanol was used as the solvent for the condensation instead of water. The yields of the expected 2,6-bis(benzotriazolyl)-*N*-(acylamino)- or -[(alkoxycarbonyl)amino]-substituted piperidines were excellent under mild conditions (Scheme II). The results are summarized in Table I. These double condensations can be carried out on a large scale, and the procedure is very simple.

The novel bis(benzotriazole)-substituted piperidines 4 and 7 prepared by double condensation were characterized by elemental analyses. Their spectra (both ¹H and ¹³C NMR), however, are too complicated to be assigned due to the many possible isomers. *N*-(Aminoalkyl)benzotriazoles generally exist as two isomers³¹ (i.e., 1-benzo-

Table II. Preparation of the N-Substituted Piperidines by Reduction

no.	N-substituent	yield (%)	mp (bp), °C/pressure, mm Hg			ref
			exptl	lit.		
5a	PhCH ₂	78	oil	49/0.1		13
5b	Ph	80	oil	99/0.2		13 ^a
5c	<i>m</i> -CH ₃ C ₆ H ₄	68	oil	a		32
5d	<i>n</i> -C ₄ H ₉	59	80/10	70/34		13
5e	<i>i</i> -C ₃ H ₇	55	145-148/760	149-150/756		33
5f	2-pyridyl	64	oil ^b	138-139/4		34
8a	PhNH	87	oil	c		
8b	(CH ₃) ₂ N	79	oil	d		22
8c	PhCONH	82	193-195	195-197		23
8d	CH ₃ CONH	84	105-106	107-108		23
8e	CH ₃ CH ₂ O ₂ CNH	88	79-80	e		
8f	(CH ₃) ₃ CO ₂ CNH	85	80-81	f		
8g	PhCH ₂ O ₂ CNH	90	101-102	g		

^a Hydrochloride: mp 202-204 °C (lit.³² mp 206-206.5 °C).

^b Picrate: mp 134-136 °C (lit.³⁴ mp 136-137 °C). ^c Anal. Calcd for C₁₁H₁₆N₂: C, 75.00; H, 9.09; N, 16.91. Found: C, 74.67; H, 8.89; N, 16.98. ^d No boiling point was given. ^e Anal. Calcd for C₈H₁₀N₂O₂: C, 55.81; H, 9.30; N, 16.28. Found: C, 55.85; H, 9.45; N, 16.73. ^f Anal. Calcd for C₁₀H₁₂N₂O₂: C, 60.00; H, 10.00; N, 14.00. Found: C, 60.29; H, 9.72; N, 14.58. ^g Anal. Calcd for C₁₃H₁₈N₂O₂: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.79; H, 7.85; N, 12.64.

triazolyl and 2-benzotriazolyl) together with the *cis* and *trans* forms of 2,6-disubstituted piperidines. This allows six possible forms of N-substituted 2,6-bis(benzotriazolyl)piperidines. Their ¹H and ¹³C NMR spectra are correspondingly complex (one example is given in the Experimental Section).

Preparation of N-Substituted Piperidines by Reduction. We have already reported^{24,25} that benzotriazole moieties in various reaction products of benzotriazole and aldehyde with an amine or an amide can be replaced smoothly by a hydrogen atom from sodium borohydride. We now demonstrate that 2,6-bis(benzotriazolyl) N-substituted piperidines 4 and 7, derived from the double condensations described above, are smoothly reduced to N-substituted piperidines 5 and 8 by sodium borohydride under mild conditions (Schemes I and II). The benzotriazole formed during the reduction is easily separated by extraction with alkali. Thus, our sequence, double condensation of benzotriazole, glutaraldehyde with amines or hydrazines, and then subsequent reduction by sodium borohydride, provides a novel synthetic route to piperidines with a variety of N-substituents.

The results listed in Table II indicate that the benzotriazole products 7, which contain an *N*-amino or *N*-amido group, are generally reduced even more easily and in higher yields than adducts 4, reflecting the facilitation of departure of the benzotriazole moiety by electron-donating α -effect of the *N*-amino group. Therefore, our present method is particularly suitable for the preparation of the *N*-(alkylamino)- and *N*-(acylamino)piperidines. The simple procedure and mild reaction conditions of both the double condensation and reduction afford excellent yields. The previously available methods usually need at least three steps from piperidine (nitrosation, reduction, and then alkylation or acylation) and give lower overall yields.

The N-substituted piperidines were characterized by their ¹H and ¹³C NMR (Tables III and IV) and by com-

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Table III. ¹H NMR Spectral Data of the N-Substituted Piperidines (CDCl₃, δ)

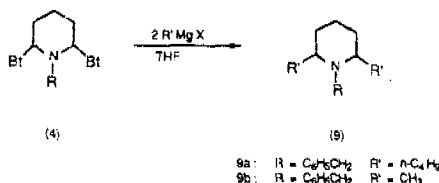
no.	2,6-CH ₂ (4 H, t)	3,5-CH ₂ (4 H, m)	4-CH ₂ (2 H, m)	N-substituent
5a	2.46	1.70	1.55	7.42 (s, 5 H), 3.55 (s, 2 H)
5b	2.85	1.60	1.45	6.35–7.15 (m, 5 H)
5c	3.10	1.68	1.55	7.0–7.20 (m, 1 H), 6.40–6.80 (m, 3 H), 2.32 (s, 3 H, CH ₃)
5d	2.50	a	a	2.40 (t), 1.70–1.40 (m, 10 H), 0.90 (t, J = 7 Hz, 3 H, CH ₃)
5e	2.80	1.80	1.55	3.50 (m, 1 H), 1.00 (d, J = 7 Hz, 6 H, CH ₃)
5f	3.60	1.80	1.58	8.30 (d, J = 5 Hz, 1 H), 7.52 (m, 1 H), 6.55–6.95 (m, 2 H)
8a	2.32	1.85	1.45	7.05–7.43 (m, 2 H), 6.60–7.00 (m, 3 H), 4.18 (s, 1 H, NH)
8b	2.75	1.68	1.40	2.58 (s, 6 H, CH ₃)
8c	2.85	1.78	1.45	7.80 (d, J = 8 Hz, 2 H), 7.35–7.55 (m, 3 H), 7.03 (s, 1 H, NH)
8d	2.70	1.70	1.55	6.65 (s, 1 H, NH), 2.05 (s, 3 H, CH ₃)
8e	2.78	1.70	1.40	5.95 (s, 1 H, NH), 4.15 (q, J = 6.5 Hz, 2 H, CH ₂), 1.25 (t, 3 H, CH ₃)
8f	2.70	1.68	1.40	5.60 (s, 1 H, NH), 1.45 (s, 9 H, <i>t</i> -Bu)
8g	2.73	1.68	1.38	7.34 (s, 5 H, C ₆ H ₅), 5.78 (s, 1 H, NH), 5.12 (s, 2 H, CH ₂)

^aOverlapped by the N-substituent signal.

Table IV. ¹³C NMR Spectral Data of the N-Substituted Piperidines (CDCl₃, δ)

no.	2,6-C	3,5-C	4-C	N substituent
5a	54.2	25.7	24.2	138.4, 128.9, 127.8, 126.6, 63.6 (CH ₂)
5b	53.7	25.4	23.9	141.1, 128.9, 128.3, 126.5
5c	50.5	26.3	24.5	138.1, 128.9, 128.5, 119.9, 117.2, 113.5, 21.8
5d	48.3	23.7	22.8	44.5 (CH ₂), 25.1, 22.5, 17.5
5e	48.9	23.3	22.3	51.1 (CH), 18.1 (CH ₃)
5f	44.7	23.9	23.1	158.1, 146.3, 135.7, 110.8, 105.5
8a	57.2	26.5	23.9	148.0, 128.8, 119.2, 113.5
8b	48.0	25.6	24.0	38.6 (CH ₃)
8c	57.0	25.3	22.2	165.2 (CO), 134.0, 131.3, 128.4, 127.0
8d	55.1	25.7	22.6	168.0 (CO), 28.9 (CH ₃)
8e	57.0	25.1	22.7	155.0 (CO), 60.3 (CH ₂), 14.5 (CH ₃)
8f	56.8	25.2	23.0	155.0 (CO), 80.0 (C), 28.5 (CH ₃)
8g	57.4	25.3	23.0	155.2 (CO), 136.2, 128.4, 128.3, 128.0, 66.6 (CH ₂)

Scheme III

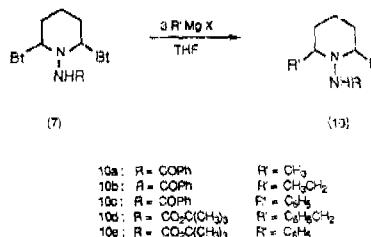


parison with data of authentic specimens (Table II).

Preparation of 1,2,6-Trisubstituted Piperidines by Grignard Reaction. Reaction of 2,6-bis(benzotriazolyl)-N-benzylpiperidine (4a) with 2.2 equiv of Grignard reagent in a mixture of tetrahydrofuran and diethyl ether gave the 2,6-dialkyl-N-benzylpiperidines (9a and 9b) in moderate yields (Scheme III). This procedure should be potentially applicable to other benzotriazole adducts. The configurations of 9a and 9b were examined by ¹H NMR. In the trans isomer, the benzyl methylene protons are nonequivalent because the trans isomer (even when rapidly ring interconverting) is chiral and should be an AB system. By contrast, the corresponding equivalent CH₂ protons of the cis isomer will appear as a singlet.^{16,17,35} In our reaction, only a singlet benzyl methylene signal at δ 3.70 is observed for both 9a and 9b. Accordingly, we consider the product to have the cis configuration.

Once again, similar to the reduction, the Grignard reactions of the N-amino- or N-amido-substituted benzotriazole adducts 7 are easier than those of the N-alkyl or N-aryl analogues 4. Thus, reactions of compounds 7c, 7e, and 7f with 3.3 equiv of Grignard reagents proceeded smoothly, leading to the corresponding symmetrical 2,6-disubstituted N-amidopiperidines 10a–f, respectively. The yields were generally good, and no products of partial reaction were detected in these transformations (Scheme

Scheme IV



IV). The results, show that this two-step reaction sequence, double condensation and subsequent Grignard reaction, is widely applicable for the preparation of 2,6-disubstituted N-amido-substituted piperidines. Benzotriazole, the side product, was easily removed by washing with aqueous alkali in a simple workup.

The 1,2,6-trisubstituted piperidines 10 were characterized by their ¹H and ¹³C NMR spectra and by analyses (Experimental Section). Examination of the NMR (particularly ¹³C NMR) spectra of products 10 shows that only one of the two possible cis/trans isomers is isolated after recrystallization from aqueous ethanol. Presumably, the other isomer either is formed in smaller amount and remains in solution or is not produced at all, just as with the 2,6-dialkyl-N-benzylpiperidines.

Conclusions

The present work demonstrates the synthetic utility of benzotriazole in building up a piperidine ring, the ease of double addition of benzotriazole and glutaraldehyde with amines or hydrazines, and the ease by which the benzotriazole moiety is replaced by a hydrogen atom or by an alkyl group. This method possesses the advantages of simple procedure, mild conditions, easy availability of starting materials, and good yields. It is particularly useful in preparing N-(alkylamino)- and N-(acylamino)-

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piperidines and their relatively inaccessible 2,6-disubstituted derivatives.

Experimental Section

Melting points were determined on a Kofler hot-state apparatus and are uncorrected. The ^1H NMR (300-MHz) spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as the internal standard. ^{13}C NMR spectra were taken on Varian VXR-300 (75-MHz) and JEOL JNM FX-100 (25-MHz) instruments. Elemental analyses were carried out in this department. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone immediately before use.

Double Condensation. Typical Procedure. Benzotriazole (40 mmol), the appropriate amine or hydrazine (20 mmol), and distilled water (200 mL) were stirred vigorously for 10 min at 20 °C. Glutaraldehyde (20 mmol, 25% aqueous solution; Aldrich) was slowly added to the reaction mixture, and the stirring was continued for 1-2 h at room temperature. The products were filtered off, washed with water, and dried under vacuum.

For acylhydrazines and alkyl carbazates the procedure is similar, except ethanol was used as the solvent instead of water.

2,6-Bis(benzotriazolyl)-N-[(ethoxycarbonyl)amino]piperidine (7e): ^1H NMR (DMSO- d_6) δ 8.10-8.70 (m), 7.62-7.98 (m), 7.02 (m), 6.30 (m), 4.28 (d), 3.82 (m), 3.05-3.40 (m), 2.85 (d), 2.25-2.75 (m), 1.22-1.60 (m), 0.80-1.00 (m); ^{13}C NMR δ 155.5, 154.6, 145.6, 145.5, 132.3, 127.2, 126.8, 124.0, 123.8, 119.2, 118.9, 117.9, 117.7, 113.0, 111.3, 72.8, 60.0, 58.7, 29.8, 29.5, 20.7, 14.7, 14.5.

Reduction of Benzotriazole Adducts. Typical Procedure. Adduct 4 or 7 (5 mmol) suspended in THF (30 mL) was stirred at room temperature with sodium borohydride (0.6 g, 15 mmol) overnight. The reaction was quenched with water, and the product was extracted with hexane or diethyl ether. The extract was dried (MgSO_4), and the solvent evaporated under reduced pressure to obtain N-substituted piperidines. In some cases, the products were purified by column chromatography (silica gel) or recrystallization from aqueous ethanol.

Reaction with Grignard Reagents. Typical Procedure. To the Grignard reagent prepared from magnesium turnings (11 mmol for 4 and 16.5 mmol for 7) and alkyl or aryl halide in diethyl ether (30 mL) was added the benzotriazole adduct (4 or 7) (5 mmol) in tetrahydrofuran dropwise under nitrogen. After the addition was complete, the reaction mixture was refluxed for 2 h, then poured in ice-water containing NH_4Cl , and extracted with diethyl ether. The organic layer was washed with NaOH (2 $\times$ 30 mL, 1 N) and water (2 $\times$ 30 mL) and dried over MgSO_4 . Evaporation of the solvent gave the crude products, which were purified by crystallization or by column chromatography.

2,6-Dibutyl-N-benzylpiperidine (9a): oil (45%); ^1H NMR (CDCl_3) δ 7.20-7.50 (m, 5 H), 3.70 (s, 2 H, PhCH_2), 2.85 (m, 2 H,

CH), 1.00-1.80 (m, 18 H), 0.82 (t, 6 H, CH_3); ^{13}C NMR δ 143.5, 128.4, 127.7, 125.8, 63.2, 51.6, 34.6, 29.1, 27.3, 23.8, 22.9, 14.0. MS (m/e) for $\text{C}_{20}\text{H}_{33}\text{N}$, calcd 287.4874, found 287.4392.

2,6-Dimethyl-N-benzylpiperidine (9b): oil (48%); ^1H NMR (CDCl_3) δ 7.15-7.45 (m, 5 H), 3.72 (s, 2 H, PhCH_2), 2.90 (m, 2 H, CH), 1.75-1.45 (m, 6 H), 0.98 (d, 6 H, CH_3). MS (m/e) for $\text{C}_{14}\text{H}_{21}\text{N}$, calcd 203.1675, found 203.1651.

2,6-Dimethyl-N-(benzoylamino)piperidine (10a): 70%; mp 176-178 °C (lit.²³ mp 179-180 °C); ^1H NMR (CDCl_3) δ 7.75-7.25 (m, 5 H), 7.00 (s, 1 H, NH), 2.95 (m, 2 H, CH), 1.95-1.55 (m, 6 H), 1.00 (d, J = 6.5 Hz, 6 H, CH_3).

2,6-Diethyl-N-(benzoylamino)piperidine (10b): 72%; mp 152-154 °C; ^1H NMR (CDCl_3) δ 7.76-7.25 (m, 5 H), 7.00 (s, 1 H, NH), 2.90 (m, 2 H, CH), 1.95-1.05 (m, 10 H), 0.90 (t, 6 H, J = 6 Hz, CH_3); ^{13}C NMR δ 166.7 (CO), 135.1, 130.9, 128.7, 126.8, 66.5 (CH), 26.7, 25.9, 23.0, 17.0. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}$: C, 73.81; H, 9.29; N, 10.75. Found: C, 74.11; H, 9.11; N, 10.48.

2,6-Diphenyl-N-(benzoylamino)piperidine (10c): 49%; mp 126-128 °C; ^1H NMR (CDCl_3) δ 7.75 (m, 2 H), 7.45-7.05 (m, 13 H), 4.57 (m, 2 H, CH), 2.00 (m, 4 H), 1.75 (m, 2 H); ^{13}C NMR δ 165.9 (CO), 141.2, 137.1, 130.9, 128.7, 128.0, 127.2, 126.5, 126.2, 36.8, 25.5, 23.7. Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}$: C, 80.89; H, 6.74; N, 7.87. Found: C, 81.21; H, 6.43; N, 7.52.

2,6-Dibenzyl-N-[(tert-butoxycarbonyl)amino]piperidine (10d): 52%; mp 115-117 °C; ^1H NMR (CDCl_3) δ 7.40-7.15 (m, 10 H), 6.00 (s, 1 H, NH), 3.24 (m, 2 H, CH), 2.75 (d, J = 7 Hz, 4 H, CH_2), 2.05 (m, 4 H), 1.75 (m, 2 H), 1.25 [s, 9 H, $\text{C}(\text{CH}_3)_3$]; ^{13}C NMR 154.6, 137.1, 129.3, 127.5, 126.6, 78.0 (C), 60.2 (CH), 34.2 (CH_2), 28.3, 26.9, 18.5. Anal. Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_2$: C, 75.79; H, 8.42; N, 7.37. Found: C, 75.52; H, 8.71; N, 7.05.

2,6-Diphenyl-N-[(tert-butoxycarbonyl)amino]piperidine (10e): 75%; mp 168-170 °C; ^1H NMR (CDCl_3) δ 7.58 (d, J = 8 Hz, 4 H), 7.40-7.20 (m, 6 H), 5.95 (s, 1 H, NH), 4.22 (m, 2 H, CH), 2.00 (m, 4 H, CH_2), 1.78 (m, 2 H), 1.25 (s, 9 H); ^{13}C NMR δ 154.0 (CO), 140.8, 127.4, 127.3, 126.1, 78.3 (C), 62.4 (CH), 28.2, 27.4, 18.8. Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 74.60; H, 8.23; N, 7.91.

Registry No. 1, 95-14-7; 2, 111-30-8; 3 (R = PhCH_2), 100-46-9; 3 (R = Ph), 62-53-3; 3 (R = $n\text{-CH}_3\text{C}_6\text{H}_4$), 108-44-2; 3 (R = $n\text{-C}_4\text{H}_9$), 109-73-9; 3 (R = $i\text{-C}_4\text{H}_9$), 75-31-0; 3 (R = 2-Py), 504-29-0; 4a, 126216-53-3; 4b, 126216-55-5; 4c, 126216-57-7; 4d, 126255-29-6; 4e, 126216-59-9; 4f, 126216-61-3; 5a, 2905-56-8; 5b, 4096-20-2; 5c, 71982-24-6; 5d, 4945-48-6; 5e, 766-79-0; 5f, 68654-52-4; 6a, 100-63-0; 6b, 57-14-7; 6c, 613-94-5; 6d, 1068-57-1; 6e, 4114-31-2; 6f, 870-46-2; 7a, 126216-63-5; 7b, 126216-65-7; 7c, 126216-67-9; 7d, 126216-69-1; 7e, 126216-71-5; 7f, 126216-73-7; 7g, 126216-75-9; 8a, 126216-44-2; 8b, 49840-60-0; 8c, 5454-07-9; 8d, 31507-04-7; 8e, 4663-84-7; 8f, 126216-45-3; 8g, 126216-46-4; 9a, 126216-47-5; 9b, 4209-63-6; 10a, 100875-43-2; 10b, 126216-48-6; 10c, 126216-49-7; 10d, 126216-50-0; 10e, 126216-51-1; $\text{H}_2\text{NNHCOOCH}_2\text{Ph}$, 5331-43-1.

A Novel Method for the Synthesis of Symmetrical Vicinal Tertiary and Secondary Diamines¹

Alan R. Katritzky,*[§] Wei-Qiang Fan,[§] and Cong Fu[†]

Department of Chemistry, University of Florida, Gainesville, Florida 32611, and Department of Chemistry, Hangzhou University, Hangzhou, Zhejiang 310028, People's Republic of China

Received October 27, 1989

A variety of symmetrical vicinal tertiary and secondary diamines are readily prepared in good to excellent yields by either Grignard reaction or reduction of the glyoxal bisproducts with benzotriazole and secondary or primary amines.

Vicinal diamino compounds are of importance in medicinal chemistry,² in metal chelation,³ and in polyaza macrocyclic and cryptate chemistry.⁴ They are also useful

synthetic intermediates, particularly in the formation of heterocyclic rings.⁵

[§] University of Florida.

[†] Hangzhou University.

(1) The Chemistry of Benzotriazole. See: (a) Katritzky, A. R.; Fan, W. Q. *J. Org. Chem.*, previous paper in this issue. (b) Katritzky, A. R.; Urogi, L.; Mayence, A. *J. Chem. Soc., Chem. Commun.* 1989, 337.

United States Patent Office

3,542,776

Patented Nov. 24, 1970

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3,542,776

MORPHOLINOISONICOTINAMIDES

William Dvornch, Radnor, and Harvey E. Alburn, West Chester, Pa., assignors to American Home Products Corporation, New York, N.Y., a corporation of Delaware

No Drawing. Continuation-in-part of application Ser. No. 589,820, Oct. 27, 1966, which is a continuation-in-part of application Ser. No. 392,920, Aug. 28, 1964. This application Oct. 25, 1967, Ser. No. 677,859

Int. Cl. C07d 87/24

U.S. Cl. 260-247.2

6 Claims

ABSTRACT OF THE DISCLOSURE

This invention relates to new isonicotinic acid hydrazides and more particularly to isonicotinic acid hydrazide derivatives of periodate oxidized pyrimidine and 6-amino-purine ribosides. The compounds are useful for blocking the auto-immune processes in warm-blooded animals.

This application is a continuation-in-part of U.S. Ser. No. 589,820, filed Oct. 27, 1966, and now abandoned which is in turn a continuation-in-part of U.S. Ser. No. 392,920, filed on Aug. 28, 1964 and now abandoned.

The immune response, production of antibodies, is the means by which immunity to infectious disease is generated, and is an expression of an animal body's biochemical integrity. Malfunctions of the natural defense mechanism are known collectively as immunopathies. Immunopathies are characterized by an altered response to external foreign substances such as the manifestation of atopy or an allergy. Immunopathies also include auto-immune phenomena. The animal body is normally tolerant to its own tissues and does not treat them as foreign substances. A breakdown of the tolerance to an animal body's own tissues is the basis of auto-immune diseases.

In addition to the immunopathies, normal functioning of the immune response can be disadvantageous in other ways, for example, by causing rejection of transplanted tissues or organs. Suppression of the immune response can be of major therapeutic importance in particular instances.

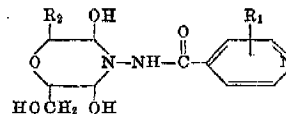
Suppression of the immune response was initially observed after X-ray and cortisone treatment, and is also achieved by treatment with chemical compounds of three major classifications: alkylating agents (nitrogen mustards), purine antimetabolites (6-mercaptopurine) and the folic acid antagonists (methotrexate). Remarkable success in the treatment of auto-immune diseases, and prolongation of homografts with the foregoing anti-auto-immune compounds has stimulated research into this area of increasing interest and practical importance. The treatment of auto-immune diseases and prolonging homograft survival by selectively suppressing the immune response of an adult animal to a specific foreign substance is of major importance.

Unfortunately, the group of compounds known to have a desirable anti-immune activity have undesirable side effects. The alkylating agents are known to be carcinogenic and mutagenic, while the purine analogues are potentially so. The toxicity of the folic acid antagonists and corticosteroids is well known.

It has now been discovered that the members of a class of new compounds are effective as anti-auto-immune agents. Thus, the invention, in its broadest concept, resides in the method of blocking an auto-immune process in warm-blooded animals, such as standard experimental animals, by administering to the animals, a therapeutical-

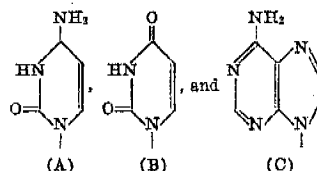
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ly active amount of a compound selected from the group having the following formula:



(I)

wherein R₁ is selected from the group consisting of hydrogen and methyl, and R₂ is selected from the group consisting of

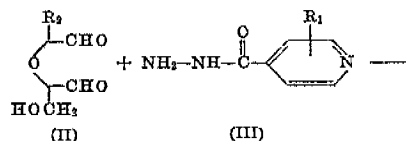


(A)

(B)

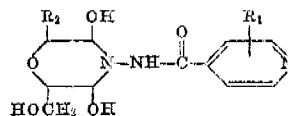
(C)

The new compounds of the present invention may be prepared by the treatment of periodate oxidized pyrimidines and 6-amino purine ribosides with isonicotinic acid hydrazides according to the following reaction sequence:



(II)

(III)



(I)

wherein R₁ and R₂ are defined as above. In carrying out the reaction, the appropriate periodate oxidation product (II) in an inert solvent such as water, dioxane, dimethylformamide, or the like, is treated with an equimolar amount of isonicotinic acid hydrazide (III) or an alkyl derivative thereof. The reaction mixture is allowed to stand for a period of from about one to ten hours, after which time crystals begin to form. The crystalline product (I) is then filtered off, washed and dried in a conventional manner. The product may be recrystallized if desired.

To prepare the periodate oxidation product used in the process of the present invention two to six moles of periodic acid in an aqueous solution are added to one mole of an appropriate pyrimidine or 6-amino purine riboside. The reaction is then conducted at a temperature of from about 5 to 35° C., in the absence of light, for a period of about ten minutes to fifty hours. The oxidation reaction normally proceeds smoothly. To separate and purify the desired product, the solution remaining after the oxidation step, is passed over a Dowex-1-acetate column and the column washed with water. The iodate-periodate-freese solution and the wash are then freeze-dried to afford the oxidation product in substantially quantitative yields.

The isonicotinic acid hydrazide used may be prepared according to the method described in U.S. Pat. 2,830,994, issued Apr. 15, 1958.

It is known that agents which are effective in auto-immune diseases are active also in preventing both the clinical and histopathologic changes which occur in experimental allergic encephalomyelitis (EAE). Such agents include the compounds thioguanine, Imuran, 6-mercaptopurine, cyclophosphamide, methotrexate and cortisone. Thus, the disease EAE may serve as a test standard, for

some demyelinating diseases, more notably multiple sclerosis, and for auto-immune processes in general. (cf. N. W. Brandiss, J. W. Smith, R. N. Friedman, "Suppression of Allergic Encephalomyelitis by Antimetabolites; Ann. N.Y. Acad. Sci., 122:356, 1965.)

EAE is characterized by a delayed cellular hypersensitivity which is tissue specific and results in clinical paralysis of the animal. Histopathological lesions of the spinal cord and brain caused by the disease resemble those in human demyelinating disease, and it is thus classified as an experimental auto-allergic or auto-immune disease. (cf. B. H. Waksman, "Experimental Allergic Encephalomyelitis and the 'auto-allergic' Diseases," I. Arch. Allerg. appl. Immunol., 14 (suppl.) 1, 1959; and I. R. Mackay and F. M. Burnet, "Auto-Immune Diseases, Pathogenesis, Chemistry and Therapy," Charles C. Thomas, Springfield, 1963.)

The surprising efficacy of the compounds of Formula I above in the treatment of EAE has indicated that they are active, non-toxic, immunosuppressive agents. In the practicing of the method of the invention, the compounds of Formula I may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound selected, the chosen route of administration, and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules, which may contain conventional excipients, or in the form of solutions; or they may be injected parenterally, that is intramuscularly, intravenously or subcutaneously. For parenteral administration, they may be used in the form of sterile solutions containing other solutes, for example, enough saline or glucose to make the solutions isotonic.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in the range of from about 20 to 200 milligrams per kilogram (mg./kg.) of body weight per day, although as aforementioned, variations will occur. In general, larger animals require smaller doses on an mg./kg. basis than do smaller animals.

The following examples are illustrative of the preparation of the compounds useful in the method of invention and of the exercising of the latter, but are not to be considered necessarily limitative thereof:

EXAMPLE I

The periodate oxidation product of adenosine in the amount of 5.31 grams (g.) equivalent to 20 millimoles (mmoles), is wet with 60 milliliters (ml.) of ethanol, dissolved in 200 ml. of water and admixed with 2.74 g. (20 mmoles) of isonicotinic acid hydrazide. After two to three hours the clear solution begins to deposit fine needle-like crystals, and the mixture is shaken to form a solid crystalline mass. The crystals are filtered off, washed with cold water, ethanol, and ether, and dried in vacuo over silica gel to give 6.66 g. of N-[2-(6-amino-9H-purin-9-yl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide trihydrate (73 percent of theoretical yield).

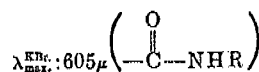
The above product precipitates from the reaction mixture in analytically pure form, but, if desired, it can be recrystallized from hot water at a concentration of 1.25 g. per 300 ml. It is slightly soluble in water (0.2 percent by weight) and soluble in 0.1 normal (N) hydrochloric acid, 0.1 N sodium hydroxide (solutions turn yellow

shortly), pyridine, acetic acid, dimethylacetamide, dimethylsulfoxide, and insoluble in the common organic solvents. It decomposes when heated in vacuo at 56° C. and gives no definite melting point when heated in a capillary tube.

Based on the formula $C_{16}H_{18}N_6O_5 \cdot 3H_2O$, it was calculated that the elemental analysis would be C, 42.10; H, 5.30; N, 24.53; H_2O , 11.85. The product was analyzed and the elemental analysis was found to be C, 42.11; H, 5.46; N, 24.31. The amount of water of hydration was found to be H_2O , 12.2—by the Abderhalden method and 12.6 by the Karl Fischer method. The result may be expressed.

Analysis.—Calc'd. for $C_{16}H_{18}N_6O_5 \cdot 3H_2O$ (percent): C, 42.10; H, 5.30; N, 24.53; H_2O , 11.85. Found (percent): C, 42.11; H, 5.46; N, 24.31; H_2O , 12.2—Abderhalden, 12.6—Karl Fischer.

For the product the wave length of maximum absorption in infrared illumination was found to be at 6.05 microns (μ) using a potassium bromide cell. The result may be expressed:



The wavelength of maximum absorption in ultra-violet illumination is 259 millimicrons (m μ) in a 0.1 N hydrochloric acid solvent, and the extinction coefficient is 20,500. The result may be expressed:

$$\lambda_{\text{max}}^{\text{UV}}: 259 \text{ m}\mu (\epsilon = 20,500).$$

EXAMPLE II

Following the procedure of the previous example, the periodate oxidation product of cytidine is treated with 2-methylisonicotinic acid hydrazide to afford N-[2-(4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]-2-methylisonicotinamide dihydrate.

Analysis.—Calc'd for $C_{16}H_{20}N_6O_6 \cdot 2H_2O$ (percent): C, 44.8; H, 5.6; N, 19.6; H_2O , 8.4. Found (percent): C, 45.5; N, 5.8; H_2O , 7.5—Abderhalden.

EXAMPLE III

According to the method of the previous examples, N-[2-(4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide is prepared by reacting the periodate oxidation product of cytidine with isonicotinic acid hydrazide (yield 72 percent).

Analysis.—Calc'd for $C_{15}H_{18}N_6O_5 \cdot 2\frac{1}{2}H_2O$ (percent): C, 42.58; H, 5.47; H_2O , 10.65. Found (percent): C, 42.89; H, 5.48; H_2O , 10.34—Abderhalden.

EXAMPLE IV

To prepare N-[3,5-dihydroxy-6-hydroxymethoxy-2-(1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)morpholino]-2-methylisonicotinamide dihydrate, the periodate oxidation product of uridine is reacted with 2-methylisonicotinic acid hydrazide according to Example I.

Analysis.—Calc'd for $C_{16}H_{18}N_6O_7 \cdot 2H_2O$ (percent): C, 44.74; H, 5.40; H_2O , 8.38. Found (percent): C, 44.76; H, 5.31; H_2O , 8.50—Abderhalden; 9.36—Karl Fischer.

EXAMPLE V

The use of the compounds in the blocking of an auto-immune process

Experimental allergic encephalomyelitis (EAE) in rats is characterized by clinical symptoms which occur 11 to 15 days after inoculation of the animal with an encephalitogenic emulsion consisting of isologous spinal cord emulsified in complete Freund's adjuvant. The symptoms initially consist of ataxia or paresis followed by flaccid paralysis of the hindquarters, urinary incontinence, fecal impaction and weight loss. These clinical symptoms are accompanied by hematologic changes consisting of increased polymor-

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phonuclear cells and decreased lymphocytes, the thymus and spleen are significantly reduced in weight and the adrenals are increased in weight. Table I below shows the protective effect of the test compound, N-[2-(6-amino-9H-purin-9-yl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide, against EAE compared with other drugs of known effectiveness. Twelve animals were used in the control group and in each of the drug-treated groups. The drugs were administered either orally or subcutaneously as shown. The dose is stated in milligrams per kilogram (mg./kg.) of the body weight of the host. The dose response for the test compound is shown.

TABLE I

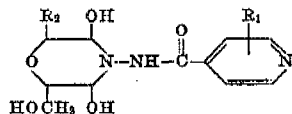
Drug	Dose, mg./kg.	Frequency	Total No. doses	Percent paralysis
Control				90-100
Cortisone	8.5 subcutaneous	Daily	13	0
6-mercaptopurine	60 oral	Alternate days	6	0
Methotrexate	0.25 oral	do	6	0
Cytosin	10 oral	do	6	0
Imuran	100 oral	do	6	0
Thioguanine	6 oral	do	6	0
Test compound	10 oral	do	6	100
Do	100 oral	do	6	42
Do	150 oral	do	6	0
Do	200 oral	do	6	0

The results in Table I above indicate that the test compound is active against EAE.

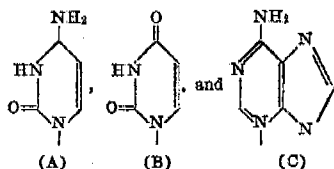
The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

What is claimed is:

1. A compound selected from the group consisting of those having the formula



wherein R₁ is selected from the group consisting of hydrogen and methyl and R₂ is selected from the group consisting of



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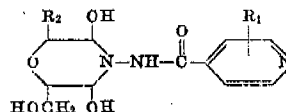
2. A compound as described in claim 1 which is: N-[2-(6-amino-9H-purin-9-yl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide.

3. A compound as described in claim 1 which is: N-[2-(4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]-2-methylisonicotinamide.

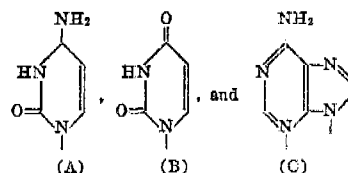
4. A compound as described in claim 1 which is: N-[2-(4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide.

5. A compound as described in claim 1 which is: N-[3,5-dihydroxy-6-(hydroxymethyl)-2-(1,2,3,4-tetrahydro-2,4-dioxo-1-pyrimidinyl)morpholino]-2-methylisonicotinamide.

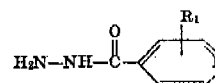
6. A process for preparing a compound selected from the group consisting of those having the formula:



wherein R₁ is selected from the group consisting of hydrogen and methyl and R₂ is selected from the group consisting of



which comprises reacting the product of periodate oxidation of a compound selected from the group consisting of 6-amino-9-β-D-ribofuranosyl-9H-purine, 4-amino-1-β-D-ribofuranosyl-2(1H)-pyrimidinone, and 1-β-D-ribofuranosyl-2,4-pyrimidinediol, with an isonicotinic acid hydrazide having the formula:



wherein R₁ is defined as above.

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3,164,590 1/1965 Lovell 260-247.2

50 ANNE MARIE T. TIGHE, Primary Examiner

U.S. Cl. X.R.

260-252, 260, 256.4; 424-248