except in the case of 2-(octahydro-1-azocinyl)ethylamine which gave XX.

A preliminary report by Halliday and co-workers on structure–activity relationships for the compounds described here has already appeared.[11] These materials were evaluated for hypotensive action in the normotensive anesthetized dog and rat and for adrenolytic effectiveness in the dog. In addition to the two reports mentioned,[4,11] other and more detailed descriptions of biological activities can be found elsewhere.[12] Furthermore, a summary publication on structure–activity relationships and mechanism of action of the more potent compounds will appear.[13] These studies reveal that a *sym*-N,N′-bis(2-pyridylalkyl)ethylenediamine skeleton is necessary for maximum adrenolytic potency. That is, all of the compounds listed in Table II in addition to II, III, IV, V, VIII, IX, and XIII, are substantially less adrenolytic than I at comparable doses. Compounds I, VI, and VII are of similar adrenolytic potency in that 10 mg./kg. (calculated as amount of base administered intravenously) usually reversed the pressor response to 2 γ/kg. of epinephrine in the normotensive anesthetized dog. Branching the ethylenediamine chain markedly increased adrenolytic potency. Compared to I, the branched compounds X and XI are roughly 2 and 10 times, respectively, more potent adrenolytic agents. Presently available data indicate that branching caused no changes in the quality of biological activity.

Experimental[14]

N,N′-Bis[α-(2-pyridyl)ethyl]ethylenediamine (I).—A mixture of 121 g. (1.0 mole) 2-acetylpyridine and 37 g. (0.50 mole) of 81% aqueous ethylenediamine in 400 ml. of benzene was heated at reflux for 5 hr. while 23 ml. of water was collected in a Dean-Stark apparatus. After cooling to room temperature, the precipitate was collected, washed with benzene, and dried. A mixture of this material and 0.4 g. of PtO_2 in 200 ml. of ethanol was reduced under 3 atm. (3.09 kg./cm.^{2}) of hydrogen. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a sirup. Distillation provided 120 g. (89%) of product.

1,2-Bis(2-pyrrolylcarboxaldimino)ethane.—To a solution of 28 g. (0.29 mole) of pyrrole-2-carboxaldehyde in 100 ml. of benzene was added 12 ml. of 72% aqueous ethylenediamine. After heating at reflux with stirring for 8 hr., the mixture was cooled. The precipitate was collected, washed with benzene, and dried to afford 26.8 g. (87%) of product, m.p. 175–179°.

Anal. Calcd. for $C_{12}H_{14}N_4$: N, 26.15. Found; N, 26.18.

N,N′-Bis(2-pyrrolylmethyl)ethylenediamine Dihydrochloride (VI).—A mixture of 26.8 g. (0.125 mole) of the Schiff base and 0.3 g. of PtO_2 in 200 ml. of ethanol was reduced under 3 atm. (3.09 kg./cm.^{2}) of hydrogen. The catalyst was removed by filtration and excess ethereal hydrogen chloride was added to the cooled filtrate. The precipitate was collected and recrystallized from methanol to provide 6.7 g. (19%) of product.

N,N′-Bis[α-(2-pyridyl)ethyl]ethylenediamine[15] (VII).—A solution of 21 g. (0.20 mole) of 2-vinylpyridine, 6.1 g. (0.090 mole) of 88% aqueous ethylenediamine, and 12 g. (0.20 mole) of glacial acetic acid in 100 ml. of ethanol was heated at reflux for 6 hr. The reaction mixture was concentrated *in vacuo* and the residue was treated with excess aqueous sodium hydroxide. This mixture was extracted twice with tetrahydrofuran, and the combined and dried organic layers were distilled to afford 10.8 g. (46%) of product.

N,N′-Bispicolylhydrazine Diacetate (VIII).—A mixture of 21 g. (0.10 mole) of 2-pyridinealdazine,[9] 24 g. (0.40 mole) of glacial acetic acid, and 0.5 g. of PtO_2 in 200 ml. ethanol was reduced under 3 atm. of hydrogen. The catalyst was separated by filtration, and the filtrate was concentrated to dryness. Trituration of the residue with ether followed by recrystallization from acetonitrile afforded 4.9 g. (15%) of product.

N,N′-Bis[α-(2-piperidyl)ethyl]ethylenediamine (XIII).—A mixture of 27 g. (0.10 mole) of I, 66 ml. of 6 *N* hydrochloric acid, and 5 g. of 5% rhodium-on-alumina in 150 ml. of ethanol was reduced under 3 atm. of hydrogen. The catalyst was removed by filtration and the filtrate concentrated to a sirup which was treated with excess aqueous sodium hydroxide. This mixture was extracted with ether, then tetrahydrofuran, and the combined organic layers were dried over potassium carbonate. Distillation provided 20.1 g. (71%) of product.

N-*t*-Butyl-N-[α-(2-pyridyl)ethyl]amine (XIV).—*t*-Butylamine (53 g., 0.72 mole) and 14 g. (0.075 mole) of 2-(α-bromoethyl)-pyridine[10] in 100 ml. of ethanol were heated in a citrate bottle for 0.5 hr. at 100°. After cooling and removal of solvent by distillation, 4.2 g. (0.075 mole) of potassium hydroxide dissolved in 75 ml. ethanol was added, and the mixture was filtered to remove inorganic salt. The filtrate was concentrated and the residue was distilled to provide 4.5 g. (34%) of crude product.

N-[α-(2-Pyridyl)ethyl]piperidine (XV).—To a boiling solution of 34 g. (0.40 mole) of piperidine in benzene was added a solution of 8.8 g. (0.047 mole) of 2-(α-bromoethyl)pyridine in benzene over 0.5 hr. Heating at reflux was continued for an additional 3 hr. After cooling, the mixture was filtered and the filtrate was distilled to afford 7.3 g. (81%) of product.

[α-(2-Pyridyl)ethyl]trimethylammonium Bromide (XVI).—A solution of 47 g. (0.80 mole) of trimethylamine and 15 g. (0.080 mole) of 2-(α-bromoethyl)pyridine in 100 ml. ethanol was heated in a pressure bottle for 3 hr. at 100°. The solvent was evaporated and the residue was recrystallized from acetonitrile to provide 11.3 g. (58%) of material.

N-[β-(2-Pyridyl)ethyl]piperidine (XIX).—A solution of 21 g. (0.20 mole) of 2-vinylpyridine, 12 g. (0.20 mole) of glacial acetic acid, and 17 g. (0.20 mole) of piperidine in 85 ml. of ethanol was heated at reflux for 8 hr. The solvent was removed by evaporation and the residue was treated with excess aqueous potassium hydroxide. This mixture was extracted three times with ether. The combined and dried organic layers were concentrated and the residue was distilled to yield 29.5 g. (77%) of XIX.

N-[α-(2-Pyridyl)ethyl]-β-(octahydro-1-azocinyl)ethylamine (XX).—A solution of 15 g. (0.12 mole) of 2-acetylpyridine in 50 ml. of ethanol was added to a stirred solution of 19.5 g. (0.12 mole) of 2-(octahydro-1-azocinyl)ethylamine[16] in 100 ml. of ethanol during 10 min. An exothermic reaction ensued. After stirring for an additional 0.5 hr., 0.5 g. of PtO_2 was added, and the mixture was reduced under 3 atm. of hydrogen. The exothermic reduction was completed in 0.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to a residue which was distilled to give 16.2 g. (52%) of product.

(11) R. P. Halliday, W. J. Kinnard, and J. P. Buckley, Abstracts of Papers, American Pharmaceutical Association Annual Meeting, Miami Beach, Florida, May 12–17, 1963.

(12) (a) R. P. Halliday, M.S. Thesis, University of Pittsburgh, 1960; (b) R. P. Halliday, Ph.D. Thesis, University of Pittsburgh, 1962.

(13) J. P. Buckley, personal communication.

(14) Melting points are corrected. Boiling points are uncorrected. Most analyses were performed under the direction of Mr. E. Kluchesky in the Analytical and Control Department, Lakeside Laboratories, Inc.

(15) A recent report suggests that this reaction affords the unsymmetrical product: E. Profft and S. Lojack, *Rev. Chim. Roumaine*, **7**, 405 (1963). *Index Chemicus*, **9**, 29485 (1963).

(16) R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

3,6-Disubstituted Pyridazines[1]

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Since maleic hydrazide was first shown to regulate plant growth[2,3] there has been much interest in deriva-

(1) Contribution No. 228 from Research Center, United States Rubber Company.

(2) D. L. Schoene and O. L. Hoffmann, *Science*, **109**, 588 (1949).

(3) O. L. Hoffmann and D. L. Schoene (to U. S. Rubber Company), U. S. Patent 2,614,916 (Oct. 21, 1962).

TABLE I

3,6-DISUBSTITUTED PYRIDAZINES

Compd. no.	3-Substituent	6-Substituent	Empirical formula	M.p., °C.	Carbon, %, Calcd.	Carbon, %, Found	Hydrogen, %, Calcd.	Hydrogen, %, Found	Chlorine, %, Calcd.	Chlorine, %, Found	Nitrogen, %, Calcd.	Nitrogen, %, Found
I	*i*-C_3H_7NH	Cl	$C_7H_{10}ClN_3$	110–112	48.99	48.86	5.87	6.11	20.66	20.64	24.48	24.13
II	*sec*-C_4H_9O	Cl	$C_8H_{11}ClN_2O$	34–36	51.47	51.59	5.94	6.37	19.00	18.85	15.01	15.04
III	*n*-C_4H_9NH	Cl	$C_8H_{12}ClN_3$	110.9–111.5	51.75	51.68	6.52	6.58	19.10	18.93	22.63	22.41
IV	C_6H_5NH	Cl	$C_{10}H_8ClN_3$	191.2–192.2	58.40	58.48	3.92	3.98	17.24	17.16	20.43	20.21
V	$C_6H_{11}NH$[a]	Cl	$C_{10}H_{14}ClN_3$	167.2–168.2	56.73	56.63	6.66	6.70	16.75	16.54	19.85	19.76
VI	$CH_2{=}CHCH_2O$	*i*-C_3H_7NH	$C_{10}H_{13}N_3O$	80.0–81.5	62.15	61.78	7.82	7.92	...	...	21.75	21.77
VII	$(n\text{-}C_4H_9)_2N$	Cl	$C_{12}H_{20}ClN_3$	57–58	59.61	59.86	8.34	8.53	14.67	14.46	17.38	17.31
VIII	*i*-C_3H_7NH	C_6H_5S	$C_{13}H_{15}N_3S$	119.3–120.3[b]	63.64	63.51	6.16	6.22	...[c]	...[c]	17.13	16.80
IX	C_6H_5NH	*i*-C_3H_7NH	$C_{13}H_{16}N_4$	175.0–175.6[d]	68.39	68.37	7.06	7.25	...	...	24.54	24.60
X	2-MBT[e]	2-MBT[e]	$C_{18}H_{10}N_4S_4$	180.5–182.5	52.86	52.80	2.46	2.64	...[f]	...[f]	13.67	13.39
XI	$C_8H_{11}N_2$[g]	$C_8H_{11}N_2$[g]	$C_{20}H_{24}N_6$	234–236	68.94	69.00	6.94	6.94	...	...	24.12	24.07

[a] Cyclohexyl. [b] Picrate m.p. 175.2–177.2°. [c] % Calcd., for sulfur: 13.07; Found: 13.14. [d] Picrate m.p. 212.6–215.1°. [e] 2-Benzothiazolylthio. [f] % Calcd., for sulfur: 31.19; Found: 31.34. [g] 4-Dimethylaminoanilino.

tives of this compound,[4-8] usually prepared *via* 3,6-dichloropyridazine.[6,8] During a program of making new derivatives of maleic hydrazide we have also used 3,6-dichloropyridazine to prepare the 3,6-disubstituted pyridazines listed in Table I. Some of these pyridazines have now been found to show strong inhibition of the tomato blight fungus *Alternaria solani*. Although observations of inhibition of the growth of plant fungi cannot be extrapolated exactly to fungi which are parasitic to animals, a study of compounds which show antifungal activity in plants may serve as a guide for researches on therapeutic fungicides.[9]

It is well established that the first chlorine atom of 3,6-dichloropyridazine is displaced by nucleophiles much more easily than is the second.[5-8] This effect undoubtedly arises from the fact that all the nucleophiles thus far reported are electron-releasing when substituted on the pyridazine ring and so counteract the activating (electron-withdrawing) effect of the heterocyclic nitrogen atoms. Hence, the preparation of an unsymmetrical 3,6-diaminopyridazine is best carried out using the low-boiling amine in the first, easy step and the high boiling amine in the second, more difficult step.

In the present work it was reasoned that a nucleophile, such as cyanide ion, which would be electron-withdrawing as a substituent should not show the usual lowered rate for displacement of the second chlorine. However, our attempts to prepare a cyanopyridazine by treatment of 3,6-dichloropyridazine with sodium cyanide in refluxing 80% ethanol[10] or with cuprous cyanide in pyridine[11] were unsuccessful. Reaction of 3,6-dichloropyridazine with sodium dibutyl phosphite by the method of Kosolapoff[12] gave only recovered starting materials and a small amount of material which decomposed upon attempted distillation (100°, 0.05 mm.).

In a test of the fungicidal activity of 3,6-disubstituted pyridazines, tomato plants were sprayed to run-off with aqueous suspensions (2000 p.p.m.) of the compounds listed in Table I. The treated plants and untreated control plants were inoculated with an aqueous suspension of *Alternaria solani* spores and kept in a greenhouse for 3 days after which they were scored by comparing the number of disease lesions of the treated plants with those of the untreated plants. The control of fungus on the treated plants was as follows: III, 98%; V, 94%; IV, 87%; IX, 80%; XI, 50%.

In a post-emergence herbicide test, seeds of both broad-leaf and grassy species of weeds were planted in boxes and allowed to grow for about 2 weeks, after which the weeds were sprayed to run-off with 2000 p.p.m. aqueous suspensions of I or VIII. Ten days later the pyridazines were evaluated for weed-controlling ability on the basis of 0% for untreated weeds and 100% for complete absence of weeds. Compound I gave 95% control of broadleaf weeds and 80% control of grassy weeds; VIII gave 95% control of broadleaf weeds and 60% control of grassy weeds.

In a pre-emergence herbicide test, seeds of broadleaf and grassy weeds were planted in pots in a sand–soil mixture and the pots were then sprayed with an aqueous suspension of I at a rate of 5 pounds/acre of the chemical. Three weeks after planting, the control of broadleaf weeds was 98% and the control of grassy weeds 95%.

Experimental[13]

3-Chloro-6-isopropylaminopyridazine.—A solution of 149 g. (1.00 mole) of 3,6-dichloropyridazine in 500 ml. of reagent benzene

(4) (a) E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.*, **81**, 6511 (1959), and references cited therein; (b) E. A. Steck, *J. Org. Chem.*, **24**, 1597 (1959).

(5) (a) J. Druey, *Angew. Chem.*, **70**, 5 (1958); (b) J. Druey (to Ciba), U. S. Patent 2,764,584 (September 25, 1956).

(6) (a) M. M. Rogers and J. P. English (to American Cyanamid), U. S. Patent 2,671,086 (March 2, 1954); (b) M. M. Rogers and J. P. English (to American Cyanamid), U. S. Patent 2,712,011 (June 28, 1955).

(7) (a) N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 778 (1955); (b) T. Itai and H. Igeta, *ibid.*, **75**, 966 (1955).

(8) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

(9) See, for example, J. F. Grove, *Quart. Rev.* (London), **17**, 2 (1963).

(10) H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931).

(11) J. E. Caben, C. A. Dornfeld, and G. H. Coleman, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 212.

(12) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

(13) All melting points are corrected.

was treated with 180 ml. (2.10 moles) of isopropylamine. The solution was refluxed for 132 hr. During this time the temperature of the solution rose from 59 to 75° and there precipitated 59.5 g. (62%) of white plates of isopropylamine hydrochloride, m.p. 155–158°; reported[14] 148–150°. The solution was evaporated to give a tan crystalline precipitate which was dissolved in 120 ml. of concentrated hydrochloric acid and reprecipitated into 2 l. of water containing 120 g. of sodium hydroxide. The tan granular precipitate was separated by filtration, washed with water and dried to give 108 g. (62%) of product, m.p. 107–110°; **picrate,** m.p. 174–176°.

3-Anilino-6-isopropylaminopyridazine.—A solution of 85.5 g. (0.500 mole) of 3-chloro-6-isopropylaminopyridazine in 300 ml. of reagent xylene was treated with 93 g. (1.00 mole) of purified aniline and the solution refluxed for 18 hr. The dark solution so obtained was treated with 100 ml. of concentrated hydrochloric acid to give a dense tan precipitate of amine hydrochlorides. The amine salts were separated from the xylene by filtration and extracted three times with mixtures of 250 ml. of chloroform and 250 ml. of 5% sodium hydroxide. The combined chloroform extracts were evaporated to give a dark semisolid residue of unreacted aniline and 3-chloro-6-isopropylaminopyridazine. The residue from the extraction was dried to give 90 g. (79%) of light tan granular solid, m.p. 177–178°. This was recrystallized from 750 ml. of 95% ethanol to give a first crop of 57.3 g. (50%) of material as shining yellow plates, m.p. 175.0–175.6°.

Evaporation of the mother liquor gave a residue which was recrystallized from 180 ml. of 95% ethanol to give a second crop, weight 17.5 g., m.p. 173.7–174.7°. The total yield was 74.8 g. (66%).

The infrared spectrum showed peaks for two types of N–H bond (3330 and 3190 cm.$^{-1}$), aryl hydrogen (3050 cm.$^{-1}$), alkyl hydrogen (2980 and 2920 cm.$^{-1}$), 3,6-disubstituted pyridazine (855 and 838 cm.$^{-1}$), and monosubstituted benzene (754 and 693 cm.$^{-1}$), as well as a complex of C–N and C–C stretching peaks in the 1700–1300 cm.$^{-1}$ region.

3,6-Bis(2-benzothiazolylthio)pyridazine.—Sodium ethoxide was prepared by dissolving 11.5 g. (0.500 g.-atom) of sodium in 500 ml. of absolute ethanol. To the ethoxide solution was added 83.5 g. (0.500 mole) of recrystallized 2-mercaptobenzothiazole. The resulting clear yellow solution was treated with 37.3 g. (0.250 mole) of 3,6-dichloropyridazine in 250 ml. of absolute ethanol and the mixture refluxed for 36 hr. After cooling the mixture to room temperature, the white precipitate was separated by filtration. Washing with two 200-ml. portions of ethanol and two 200-ml. portions of water followed by drying gave 56.2 g. (55%) of product, m.p. 176–178°.

(14) A. Skita and F. Keil, *Ber.*, **61**, 1682 (1928).

Nitrogen Substituted Phenoxazines

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Only a few 10-substituted phenoxazines were described in the literature[2] prior to the publication of Gilman's[3] facile preparation of phenoxazine in 1957. We wish to report a number of 10-substituted phenoxazines, which, it was hoped, would have interesting biological properties due to their analogy to the phenothiazines and which have not been reported elsewhere.[4]

From 1-bromo-3-chloropropane and phenoxazine in a solution of sodium amide we prepared 10-(3-chloropropyl)phenoxazine[4m] (**1**) which we treated with diallylamine, N-(2-hydroxyethyl)piperazine, and N-(2-aminoethyl)morpholine to form compounds **2**, **3**, and **4**, respectively. Compound **5** was prepared from phenoxazine and N,N-diallyl 2-chloroacetamide. Two more phenoxazine derivatives (**6** and **7**) were prepared from the dimethylamino alkylation of 2-acetylphenoxazine.[4a,c,n]

Phenoxazine was acylated with chloroacetyl chloride and 2-chloropropionyl chloride to give compounds **8** and **9**, respectively. We refluxed various amines with the appropriate chloroacylphenoxazine; the basic products were converted then to the hydrochlorides and the methyl halides (**10–15**). By a similar method, **16** was prepared from 2-acetylphenoxazine.

We prepared phenoxazine-10-carbonyl chloride[4f,o] (**17**) by reacting phenoxazine with phosgene at atmospheric pressure. This was then converted to the ethyl ester **18** and a basic ester **19** which was isolated as the methiodide. In addition, the unsubstituted hydrazide **20** was formed.

Compounds **10**, **12**, and **13** were studied for anticholinergic and spasmolytic activity *in vitro* using acetylcholine ($1–5 \times 10^{-7}$) and histamine ($1–12.5 \times 10^{-6}$) induced spasms in the isolated guinea pig ileum preparation, and $BaCl_2$ ($1–10^{-3}$) induced spasms in the isolated rabbit ileum preparation. Compound **10** in a concentration of $1–5 \times 10^{-5}$ inhibited $BaCl_2$-induced spasms by 19% and in a concentration of $1–2 \times 10^{-7}$ inhibited acetylcholine-induced spasms by 10%. Compound **12** was not active against acetylcholine-induced spasms in a concentration of $1–2 \times 10^{-7}$, but inhibited $BaCl_2$-induced spasms by 30% in a concentration of $1–2.5 \times 10^{-7}$. Compound **13** inhibited $BaCl_2$-induced spasm by 40% in a concentration of $1–2.5 \times 10^{-7}$, acetylcholine-induced spasm by 20% in a concentration of $1–2.5 \times 10^{-8}$, and histamine-induced spasm by 30% at $1–2 \times 10^{-7}$.

The effects of compound **10**, **12**, and **13** on the mean arterial blood pressure of dogs anesthetized with pentobarbital (35 mg./kg. i.v.) was studied by means of a mercury manometer following intravenous administration of 10 mg./kg. Compound **10** produced a 70% decrease in mean arterial pressure, **12** produced a 60% decrease, and **13** produced a 36% decrease. The hypotensive activity of all three compounds was of short duration, returning to control level in less than 15 min.

Experimental

10-(3-Chloropropyl)phenoxazine (1).—To a solution of sodium amide in liquid ammonia, prepared from 3.9 g. (0.17 g.-atom) of

(1) Hazleton Laboratories, Falls Church, Virginia.

(2) K. Miescher and A. Marxer (to Ciba Pharmaceutical Prods, Inc.) U. S. Patent 2,485,212 (October 18, 1949).

(3) H. Gilman and L. O. Moore, *J. Am. Chem. Soc.*, **79**, 3485 (1957).

(4) (a) P. Müller, N. P. Buu-Hoi, and R. Rips, *J. Org. Chem.*, **24**, 37 (1959); (b) G. Frangatos, G. Kohan, and F. L. Chubb, *Can. J. Chem.*, **38**, 1021 (1960); (c) H. Vanderhaeghe, *J. Org. Chem.*, **25**, 747 (1960); (d) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *ibid.*, **26**, 1901 (1961); (e) H. Linde, *Arch. Pharm.*, **294**, 398 (1961); (f) M. Claesen and H. Vanderhaeghe, *J. Org. Chem.*, **26**, 4130 (1961); (g) H. Vanderhaeghe and L. Verlooy, *ibid.*, **26**, 3827 (1961); (h) V. G. Samolovova, T. V. Gortinskaja, and M. N. Shchukina, *Zh. Obshch. Khim.*, **30**, 1516 (1960); (i) V. G. Samolovova, T. V. Gortinskaja, and M. N. Shchukina, *ibid.*, **31**, 1492 (1961); (j) Smith Kline & French Laboratories, British Patent 825,312 (Dec. 16, 1959); *Chem. Abstr.*, **49**, 5840*g*; (k) Chas. Pfizer and Co., Inc. British Patent 850,334 (Oct. 5, 1960); (l) Smith Kline & French Laboratories, British Patent 875,348 (Aug. 16, 1961); (m) Recherche et Industrie Therapeutiques (R.I.T.) S.A., Belgian Patent 569,697 (Jan. 24, 1959); *Chem. Abstr.*, **54**, 586*d* (1960); (n) Belgian Patent 575,133 (July 27, 1959); *Chem. Abstr.* **54**, 5708*f* (1960); (o) Belgian Patent 577,565 (Oct. 10, 1959); (p) Smith Kline & French Laboratories, Belgian Patent Appl. 593,266 (July 22, 1960); (q) Recherche et Industrie Therapeutique (R.I.T.) S.A., Belgian Patent Appl. 594,542 (August 30, 1960); 594,543 (August 30, 1960).