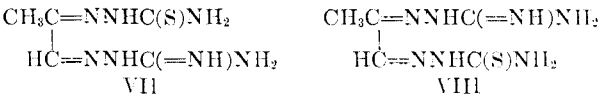
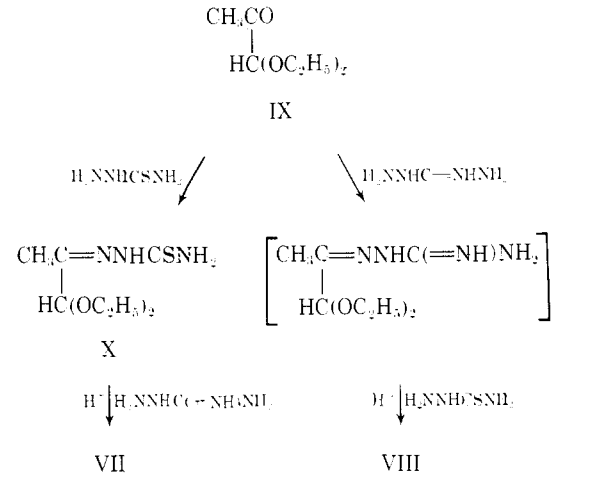


VII VIII

Pyruvaldehyde diethyl acetal (IX), the key intermediate for the synthesis of VII and VIII, was prepared from pyruvaldehyde according to the method of Braude and Evans.[15] Addition of thiosemicarbazide to an ethanol solution of IX readily formed pyruvaldehyde diethylacetal thiosemicarbazone (X), which reacted with an equivalent amount of aminoguanidine in the presence of hydrochloric acid to yield VII. When compound IX was first allowed to react with aminoguanidine followed by reaction with thiosemicarbazide in the presence of acid, the other isomer (VIII) was obtained.



IX

X

VII VIII

A semicarbazone analog of VII, pyruvaldehyde 1-guanylhydrazone 2-semicarbazone, was prepared from IX in a manner similar to that described for the preparation of VII.

Preliminary antitumor screening results[16] of VII and VIII with doses ranging between 15–480 mg/kg in BDF_1 mice indicated that replacement of either imino group by sulfur in VI results in the loss of activity against leukemia L1210.

Experimental Section[17]

Pyruvaldehyde Diethyl Acetal Thiosemicarbazone (X).—To a solution of 29.2 g (0.2 mole) of pyruvaldehyde diethyl acetal[15] (IX) in 250 ml of absolute ethanol was added, in one portion, 18.2 g (0.2 mole) of thiosemicarbazide. The reaction mixture was stirred for 15 hr at room temperature. The resulting solid was collected by filtration and washed with absolute ethanol. The product, weighing 31 g (71% yield), was satisfactory for use in the following experiment. For purposes of characterization a small portion was recrystallized from a mixture of ethanol and water to give a product which melted at 128–130°, resolidified, then slowly decomposed above 160°; $\lambda_{max}^{pH\ 1}$ 301 mμ (ε 14,200); $\lambda_{max}^{pH\ 9}$ 234 mμ (ε 8100), 267 mμ (ε 21,200).

Anal. Calcd $C_8H_{17}N_3O_2S$: C, 43.8; H, 7.81; N, 19.2 Found: C, 43.7; H, 7.81; N, 19.4.

Pyruvaldehyde 1-Guanylhydrazone 2-Thiosemicarbazone Hydrochloride (VII).—A solution of aminoguanidine hydrochloride [prepared by the addition of excess HCl to a suspension of 13.6 g (0.1 mole) of aminoguanidine bicarbonate in 150 ml of water] was added to a suspension of 22 g (0.1 mole) of X in 300 ml of ethanol. The mixture was stirred at room temperature for 2 hr after which time the insoluble material was removed by filtration and the filtrate was refrigerated overnight. The solid which separated was collected and the filtrate was concentrated at room temperature. Absolute ethanol (about 5 vol) was added to the concentrate and the solution was cooled overnight. In this manner a second crop of product was obtained. The combined solids were washed with absolute ethanol and dried at 56° (0.01 mm) for 15 hr to give 17 g (69% yield) of product: mp 223–224° dec, $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 47,700), $\lambda_{max}^{pH\ 9}$ 332 mμ (ε 44,800).

Anal. Calcd for $C_5H_{11}N_7S \cdot HCl \cdot 0.5H_2O$: C, 24.3; H, 5.31; Cl, 14.4; N, 39.7; S, 13.0. Found: C, 24.3; H, 5.60; Cl, 14.6; N, 40.0; S, 12.9.

The corresponding sulfate salt was similarly prepared: mp 236–237° dec.

Anal. Calcd for $C_5H_{11}N_7S \cdot 0.5H_2SO_4 \cdot 0.5H_2O$: C, 23.2; H, 5.05; N, 37.8; S, 18.6. Found: C, 23.4; H, 5.02; N, 38.0; S, 18.8.

Pyruvaldehyde 1-Guanylhydrazone 2-Semicarbazone Hemisulfate.—A mixture of 7.5 g (0.1 mole) of semicarbazide and 14.6 g (0.1 mole) of IX in 100 ml of absolute ethanol was stirred at room temperature for 18 hr. There was then added 100 ml of an acidic solution of aminoguanidine sulfate [prepared from 13.6 g (0.1 mole) of aminoguanidine bicarbonate and excess sulfuric acid]. After being stirred overnight at room temperature the solid from the reaction mixture was collected by filtration, yielding 17.5 g (72.0% yield) of a white solid, mp 221–222° dec, $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 33,500), $\lambda_{max}^{pH\ 9}$ 294 mμ (ε 25,500).

Anal. Calcd for $C_5H_{11}N_7O \cdot 0.5H_2SO_4 \cdot 0.5H_2O$: C, 24.7; H, 5.37; N, 40.3. Found: C, 24.7; H, 5.60; N, 40.4.

Pyruvaldehyde 2-Guanylhydrazone 1-Thiosemicarbazone Hydrochloride. (VIII).—To a stirred suspension of 14.6 g (0.1 mole) of IX and 9.0 g of sodium acetate in 200 ml of absolute ethanol was added, at room temperature, 11.0 g (0.1 mole) of aminoguanidine hydrochloride. After being stirred at room temperature for 18 hr, the reddish colored mixture was chilled and there was then added 25 ml of concentrated HCl, 50 ml of water, and finally, 9.1 g (0.1 mole) of thiosemicarbazide. With the addition of acid the reddish color of the reaction mixture disappeared. The mixture was stirred at 0° for 2 hr, then at room temperature for 1 hr, during which time the thiosemicarbazide slowly dissolved and a white solid gradually separated. The product was isolated by filtration. Purification was effected by dissolving in water then filtering to remove a small amount of insoluble material. The filtrate was evaporated at room temperature *in vacuo* to yield the desired product. The product (21.0 g, 82% yield) was dried at 25° (0.05 mm) for 15 hr, then allowed to equilibrate with atmospheric moisture: mp 248° dec, $\lambda_{max}^{pH\ 1}$ 305 mμ (ε 50,500), $\lambda_{max}^{pH\ 9}$ 335 mμ (ε 43,600).

Anal. Calcd for $C_5H_{11}N_7S \cdot HCl \cdot H_2O$: C, 23.5; H, 5.53; N, 38.4. Found: C, 23.6; H, 5.90; N, 38.1.

Acknowledgment.—The authors wish to express their appreciation to Mr. Leland R. Lewis, Mr. John R. Gravatt, and Mrs. Margaret Rounds for the analytical and instrumental measurements.

(15) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3324 (1955).

(16) Biological testing work was carried out by contract screeners of CCNSC of the National Cancer Institute.

(17) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

Some Congeners and Analogs of Dipyridamole

DANIEL KAMINSKY, WILSON B. LUTZ, AND SAM LAZARUS

The Warner-Lambert Research Institute, Morris Plains, New Jersey

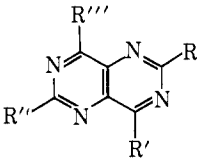
Received January 6, 1966

Since 2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido[5,4-*d*]pyrimidine (dipyridamole) (Ia, R = R″ = $(HOCH_2CH_2)_2N$; R′ = R‴ = piperidino) is a potent coronary vasodilator,[1] we were prompted to

(1) (a) R. Kadatz, *Arzneimittel-Forsch.*, **9**, 39 (1959); (b) G. Brabner, F. Kaindl, and O. Krapp, *ibid.*, **9**, 45 (1959); (c) T. Hoekerts and G. Bogelmann, *ibid.*, **9**, 47 (1959); (d) H. J. Bretschneider, A. Frank, U. Bernard, K. Kochsiek, and F. Scheler, *ibid.*, **9**, 49 (1959); (e) H. Spitzbarth, *ibid.*, **9**, 59 (1959).

TABLE I

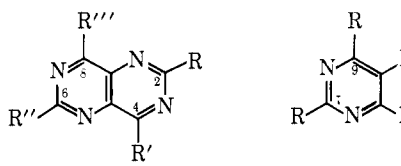
PYRIMIDO[5,4-*d*]PYRIMIDINES



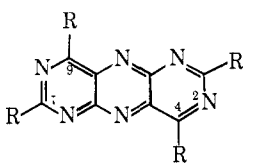
No.	R	R′	R″	R‴	Mp, °C	Recrystn solvent[a]	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
Ie	Cl	Piperidino	Cl	Piperidino	245–246[b]	A	$C_{16}H_{22}Cl_2N_6$	52.32	52.44	5.49	5.58	22.88	22.96
If	Cl	4-Hydroxy-piperidino	Cl	4-Hydroxy-piperidino	237–239	A	$C_{16}H_{20}Cl_2N_6O_2$	48.13	47.96	5.05	4.81		
Ig	Cl	4-Methyl-piperazino	Cl	4-Methyl-piperazino	208–210	B	$C_{16}H_{22}Cl_2N_8$	48.36	48.55	5.58	5.77	28.20	27.89
Ij	Piperidino	4-Methyl-piperazino	Piperidino	4-Methyl-piperazino	158–159	C	$C_{26}H_{42}N_{10}$	63.12	63.12	8.56	8.76	28.32	28.29
Ik	Morpholino	4-Methyl-piperazino	Morpholino	4-Methyl-piperazino	239–241	B	$C_{24}H_{38}N_{10}O_2$	57.81	57.91	7.68	7.60		
Il	4-Methyl-piperazino	4-Methyl-piperazino	4-Methyl-piperazino	4-Methyl-piperazino	153–155	D	$C_{26}H_{44}N_{12}$	59.51	59.30	8.45	8.51	32.04	31.84

[a] A = 2-ethoxyethanol, B = isopropyl alcohol, C = petroleum ether, D = ethyl acetate. [b] K. Thomae [British Patent 807,826 (1959)] reports this melting point.

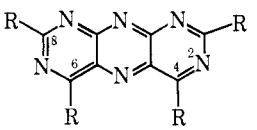
prepare several derivatives of pyrimido[5,4-*d*]pyrimidine (I), pyrimido[4,5-*g*]pteridine (II), and pyrimido[5,4-*g*]pteridine (III) for pharmacological evaluation.



I



II



III

The derivatives of I were prepared from 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine (Ib, R = R′ = R″ = R‴ = Cl). Reactions under varying conditions with heterocyclic amines yielded the 4,8-diamino (I, R′ = R‴ = Cl), 4,6,8-triamino (I, R = Cl), and the 2,4,6,8-tetraamino compounds. The 4,8-diamino compounds were prepared by reaction of Ib in dimethylformamide solution with 2 molar equiv of the appropriate amine at ambient temperatures. One triamino monochloro compound (Ic, R = Cl; R′ = R″ = R‴ = piperidino) was prepared by allowing Ib to react with an excess of piperidine at temperatures below 100°. Tetraamino compounds were prepared by refluxing either the monochloro compound (Ic), one of the 2,6-dichloro compounds, or Ib with a large excess of the desired amine.

The substituted pyrimidopteridines (II and III) were prepared by treatment of the corresponding tetrachloro compounds with an excess of the appropriate amines at elevated temperatures.

The pharmacological testing of these compounds (method of Boxill, *et al.*[2]) proved disappointing, and no definite evidence of coronary-dilator activity could be found.

(2) G. C. Boxill, M. Ben, I. W. Hillyard, and M. R. Warren, *J. Pharmacol. Exptl. Therap.*, **137**, 198 (1962).

Experimental Section[3]

2,4,6,8-Tetrachloropyrimido[5,4-*d*]pyrimidine was prepared by the method of Fischer and co-workers.[4] The crude product was freshly sublimed before use to yield material, mp 256–258°.

2,6-Dichloro-4,8-bis(4β-hydroxyethyl-1-piperazinyl)pyrimido[5,4-*d*]pyrimidine (Id, R = R″ = Cl; R′ = R‴ = 4-β-hydroxyethyl-1-piperazinyl).—A mixture of 12 g (0.046 mole) of 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine (Ib), 12 g (0.092 mole) of N-(β-hydroxyethyl)piperazine, and 200 ml of dimethylformamide was stirred for 1 hr and 90 ml of 1 *N* NaOH was added. The mixture was stirred for 2 hr, 200 ml of water was added, and the mixture was filtered to yield 15.8 g (90.3%) of yellow product, mp 226–234°. Two recrystallizations from 2-ethoxyethanol yielded yellow crystals, mp 237–238°.

Anal. Calcd for $C_{18}H_{26}Cl_2N_8O_2$: C, 47.27; H, 5.73; Cl, 15.50. Found: C, 47.51; H, 6.02; Cl, 15.45.

Using a similar procedure compounds Ie–g were prepared (see Table I).

2-Chloro-4,6,8-tripiperidinopyrimido[5,4-*d*]pyrimidine (Ic).—A mixture of 5.4 g (0.02 mole) of 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine (Ib), 17 g (0.2 mole) of piperidine, and 50 ml of ethanol was refluxed for 24 hr. The alcohol was removed under vacuum, and the residue was heated for an additional 36 hr on a steam bath. Trituration with 250 ml of water and filtration yielded 7.9 g (95%) of yellow solid, mp 120–122°. Several recrystallizations from isopropyl alcohol gave the analytical sample, mp 124–125°.

Anal. Calcd for $C_{21}H_{30}ClN_7$: C, 60.63; H, 7.27; Cl, 8.52. Found: C, 60.85; H, 7.38; Cl, 8.57.

2-(4-Methyl-1-piperazinyl)-4,6,8-tripiperidinopyrimido[5,4-*d*]pyrimidine (Ih).—A mixture of 4 g (0.01 mole) of Ic and 10 g (0.1 mole) of N-methylpiperazine was refluxed for 6 hr. The excess N-methylpiperazine was removed under vacuum (85–90° (*ca.* 15 mm)], and the residue was triturated with water and dried to yield 4.7 g of yellow solid, mp 132–140°. Three recrystallizations from petroleum ether (bp 38–53°) gave 3.6 g (72%) of fluorescent yellow crystals of Ih, mp 141–143°.

Anal. Calcd for $C_{26}H_{41}N_9$: C, 65.10; H, 8.62; N, 26.28. Found: C, 65.32; H, 8.74; N, 26.20.

Compounds Ij–Il (see Table I) were prepared similarly from Ig and the appropriate amines.

2,4,7,9-Tetrachloropyrimido[4,5-*g*]pteridine (II, R = Cl).—To a solution of 40 g of 5-aminouracil and 84 g of KOH in 1200 ml of water cooled to 0–5° was added a solution of 310 g of potassium ferricyanide in 2 l. of water cooled to *ca.* −5°. After 15 min a crude potassium salt was collected, and the filter cake was washed repeatedly with methanol and ether. The dry orange solid (29.2 g) was used without further purification.

A mixture of 12.8 g of the crude potassium salt, 130 ml of $POCl_3$, and 32.5 g of P_2O_5 was kept at reflux for *ca.* 60 hr. Vola-

(3) Melting points are corrected and were obtained using a Thomas–Hoover Uni-Melt apparatus.

(4) F. G. Fischer, J. Roch, and W. P. Neumann, *Ann.*, **631**, 147 (1960).

tiles were removed under vacuum to yield 18.1 g of crude tetrachloro compound containing inorganic salts. A 0.5-g sample sublimed at 0.02 mm (bath temperature 220–230°) gave 150 mg of orange sublimate. An analytical sample was prepared by subliming crude material three times at 0.02 mm (bath temperature 220–290°). The compound did not melt below 360°. The chlorine value was low, possibly due to the extreme ease with which the compound reacts with moisture. It reacts violently with the common primary and cyclic secondary amines.

Anal. Calcd for $C_9Cl_4N_6$: C, 29.84; Cl, 44.05; N, 26.10. Found: C, 29.66; Cl, 43.10, 43.37; N, 25.91.

2,4,7,9-Tetrapiperidinopyrimido[4,5-*g*]pteridine (II, R = piperidino).—To 50 ml of dry piperidine was added, with vigorous stirring, 6.0 g of crude 2,4,7,9-tetrachloropyrimido[4,5-*g*]pteridine (containing about 70% of inert material.) After the initial exothermic reaction had subsided, the mixture was kept at reflux for 2 hr and allowed to stand over the weekend. The mixture was stirred with ether, and the solids were filtered, washed with ether, and dried. The purple solid was leached with 100 ml of boiling water, filtered, and washed with ligroin to give 4.2 g of crude product, mp 345–348°. An analytical sample was prepared by dissolving the compound in 60 ml of boiling CH_2Cl_2, adding 60 ml of cyclohexane, distilling 60 ml of the mixed solvent, and cooling to give small purple-red needles, mp 349–351.5°.

Anal. Calcd for $C_{29}H_{40}N_{10}$: C, 65.09; H, 7.80; N, 27.11. Found: C, 65.27; H, 7.87; N, 26.84.

2,4,7,9-Tetra(4-hydroxypiperidino)pyrimido[4,5-*g*]pteridine (II, R = 4-hydroxypiperidino).—To 8.73 g (86.5 mmoles) of 4-hydroxypiperidine, at a temperature just above the melting point, was added 1.45 g (4.5 mmoles) of 2,4,7,9-tetrachloropyrimido[4,5-*g*]pteridine, and the mixture was stirred at 110–120° overnight. Pure diethylene glycol dimethyl ether (5 ml) was added, and heating was continued for 4 hr. Hot water (25 ml) was added, and the product was filtered from the cooled solution. The dark purple solid weighed 2.62 g (93%) and melted at 318–327°. Recrystallization from dimethylformamide and then from methanol raised the melting point to 335–336° (sealed, evacuated capillary). The analytical sample was sublimed (with difficulty) at 260–280° (0.001 mm) to yield a red powder, mp 343–344° (sealed, evacuated capillary).

Anal. Calcd for $C_{29}H_{40}N_{10}O_4$: C, 57.91; H, 6.94; N, 24.14. Found: C, 57.75; H, 7.20; N, 23.93.

2,4,7,9-Tetra(diethanolamino)pyrimido[4,5-*g*]pteridine (II, R = diethanolamino).—A mixture of 50 g of diethanolamine and 3.0 g of crude 2,4,7,9-tetrachloropyrimido[4,5-*g*]pteridine was warmed on the steam bath with thorough agitation; a vigorous exothermic reaction occurred. After heating at 90–95° for 18 hr, the excess diethanolamine was removed under high vacuum (*ca.* 1 mm) and the dark red residue was triturated with 150 ml of ice–water and filtered. The crude product was dissolved in dilute acetic acid and filtered, and the filtrate was made alkaline with aqueous NH_3. The product separated as small red needles which, when dry, weighed 0.86 g (16%), mp 225–226° (sealed, evacuated capillary). Recrystallization from water and then from diethanolamine–water (1:2) raised the melting point to 239–240° (sealed, evacuated capillary).

Anal. Calcd for $C_{24}H_{40}N_{10}O_8$: C, 48.31; H, 6.76; N, 23.48. Found: C, 48.42; H, 6.96; N, 23.26.

2,4,6,8-Tetrachloropyrimido[5,4-*g*]pteridine (III, R = Cl). A mixture of 7.15 g (0.0288 mole) of 2,4,6,8-tetrahydroxypyrimido[5,4-*g*]pteridine,[5] 25 g (0.12 mole) of PCl_5, and 70 ml of $POCl_3$ was refluxed for 3 hr. The mixture was cooled and filtered. The filter cake was washed with ether and dried to yield 7.30 g (82%) of product, mp >360°. The analytical sample was prepared by sublimation [160° (*ca.* 0.001 mm)].

Anal. Calcd for $C_9Cl_4N_6$: C, 29.85; Cl, 44.07; N, 26.10. Found: C, 29.68; Cl, 43.84; N, 26.13.

2,4,6,8-Tetrapiperidinopyrimido[5,4-*g*]pteridine (III, R = piperidino).—To 5.25 g (0.062 mole) of piperidine, cooled in an ice bath, was added 2 g (0.0062 mole) of 2,4,6,8-tetrachloropyrimido[5,4-*g*]pteridine in small portions with stirring. An additional 5.25 g of piperidine was added, and the mixture was heated on a steam bath overnight. The cooled mixture was ground with water, and the crude product obtained by filtration was recrystallized from ethanol to yield 1.45 g (45%) of material melting at 315–318°. The product was chromatographed on alumina and eluted with acetone. Evaporation of the acetone and washing with petroleum ether gave the analytical sample, yellow needles, mp 326–327°.

Anal. Calcd for $C_{29}H_{40}N_{10}$: C, 65.08; H, 7.81; N, 27.11. Found: C, 64.86; H, 7.89; N, 26.98.

Acknowledgment.—We are grateful to Mr. Arnold Lewis and his group for the analyses and Mr. Robert Puchalski for the infrared and ultraviolet spectra.

(5) E. C. Taylor, *J. Am. Chem. Soc.*, **77**, 2246 (1955).

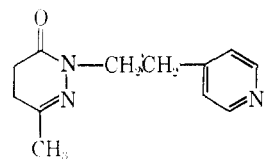
Synthesis and Pharmacological Activity of a Series of 2-Substituted Pyridazinones

JULIAN G. MICHELS, GEORGE C. WRIGHT, AND GABRIEL GEVER

The Norwich Pharmacal Company, Norwich, New York

Received February 9, 1966

In the course of our investigations into the chemistry and pharmacology of certain pyridazinones, 4,5-dihydro-6-methyl-2-[2-(4-pyridyl)ethyl]-3-pyridazinone (I)[1a] was prepared. This compound was found to have



I

the interesting property of potentiating, in laboratory animals, the action of drugs that affect the central nervous system, such as pentobarbital, hexobarbital, chloral hydrate, chlorpromazine, mephenesin, strychnine, and diphenylhydantoin.[1b] Although I itself has no detectable action on the central nervous system, its administration along with the above named drugs greatly increases the duration of their action at a given dose level or enables a decrease in the dose required to give a desired effect. In view of this property of I, it became of interest to prepare a series of related structures in an endeavor to correlate structure with activity.

The compounds prepared are shown in Tables I and II. All of the compounds in Table I were prepared by reaction of the appropriately substituted hydrazine with levulinic acid. Of these substituted hydrazines, 2-(4-pyridyl)ethyl-,[1a] 2-hydroxyethyl-,[2] 2-cyanoethyl-,[3] phenethyl-,[4] 2-dimethylaminoethyl-,[5] 4-pyridylmethyl-,[6] 4-pyridyl-,[7] 2-(2-pyridyl)ethyl-,[8] and 2-(4-morpholinyl)-ethylhydrazine[9] have been previously described. Certain properties of the hydrazines prepared in the present work are given in Table III. These hydrazines were prepared by one of the following three methods.

(1) (a) G. Gever and J. G. Michels, U. S. Patent 3,012,032 (1961); (b) R. H. Boller, W. T. Rockfold, J. A. Buzard, and I. J. Stern, *J. Pharmacol. Exptl. Therap.*, **134**, 95 (1961).

(2) S. Gabriel, *Ber.*, **47**, 3032 (1914).

(3) U. Hoffmann and K. Jacobi, German Patent 598,185 (1934); U. S. Patent 1,992,615 (1935).

(4) E. Votocek and O. Leminger, *Collection Czech. Chem. Commun.*, **4**, 271 (1932).

(5) W. Ward and G. Gever, U. S. Patent 2,726,241 (1955).

(6) Y. Takeda, Y. Maejima, and H. Namekata, *Japan. J. Tuberc.*, **2**, 184 (1954).

(7) E. Koenigs, W. Weiss, and A. Zscharn, *Ber.*, **59B**, 316 (1926).

(8) A. N. Kost, S. I. Sobinov, E. V. Vinogradova, and V. Kozler, *Zh. Obshch. Khim.*, **33**, 3606 (1963).

(9) A. Halpern, U. S. Patent 3,086,975 (1963).