A Study of Some Pyridopyrazines and Pyridopyrimidines

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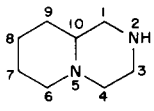
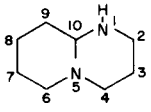
The *d*- and *l*-forms of 2*H*-octahydropyrido[1,2-*a*]pyrazine (I) have been prepared and their absolute configurations established. These configurations were confirmed by an optical rotary dispersion study. The infrared spectra of 2*H*-octahydropyrido[1,2-*a*]pyrazine (I), 1*H*-octahydropyrido[1,2-*a*]pyrimidine (II) and 2*H*-octahydropyrido[1,2-*c*]pyrimidine (III) were compared with the infrared spectrum of quinolizidine. All of these spectra showed the Bohlmann bands characteristic of a *trans* ring structure. A few derivatives of these ring systems have been prepared.

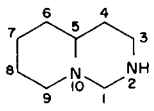
Hypotensive activity was reported in 1966 for a series of disubstituted 2*H*-octahydropyrido[1,2-*a*]pyrazines (1). The present study was undertaken to determine if this activity existed in the parent system (I) and whether optical activity had any effect on biological activity. In addition, two related systems, 1*H*-octahydropyrido[1,2-*a*]-pyrimidine (II) and 2*H*-octahydropyrido[1,2-*c*]pyrimidine (III), were prepared and alkylated to determine whether the relative position of the non-bridgehead nitrogen atom was a major factor in the biological activity. We were also interested in ascertaining whether the Bohlmann infrared bands, for *trans* ring fusion, were present in all three series.



I



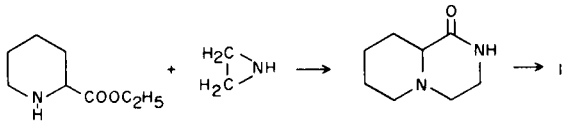
II



III

The 2*H*-octahydropyrido[1,2-*a*]pyrazine (I) was prepared from ethyl 2-piperidinecarboxylate by condensation with ethylenimine (Scheme I) and reduction of the resulting lactam with lithium aluminum hydride (2). The *d*,*l*-free base (I) was then alkylated, in acetone solution in the presence of triethylamine, with benzhydryl bromide and diethylaminoethyl chloride to form 2-benzhydryl-2*H*-octahydropyrido[1,2-*a*]pyrazine and 2-(2-diethylamino-ethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine, respectively. The 2-(2-aminoethyl) derivative was prepared by alkylating I with chloroacetonitrile (3), and subsequently reducing the nitrile with lithium aluminum hydride.

SCHEME I



Two guanidine derivatives were prepared by reacting 2*H*-octahydropyrido[1,2-*a*]pyrazine and 2-(2-aminoethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine, respectively, with 1-guanyl-3,5-dimethylpyrazole nitrate (4) to give 2-guanyl-2*H*-octahydropyrido[1,2-*a*]pyrazine and 2-(guanidino-ethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine.

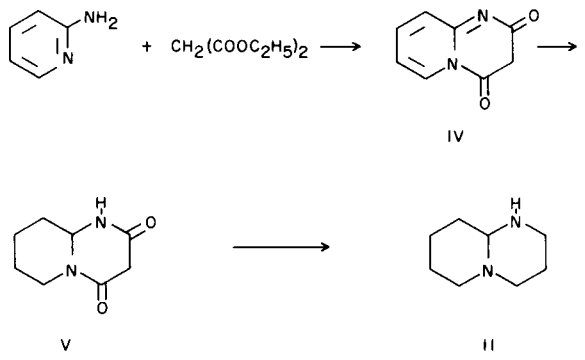
Although the parent compound (I) was prepared in 1960 (2), only the *d*,*l*-form has been reported up to now. 2-Piperidinecarboxylic acid (pipecolic acid) was resolved with tartaric acid as early as 1896 (5) and the absolute configurations of the isomers were reported in 1950 (6). Since the configuration of the asymmetric center in pipecolic acid should be retained in the 2*H*-octahydropyrido[1,2-*a*]pyrazine-1-one, a method was available for determining the configuration of the asymmetric center at position 10 in the lactam. We converted the *d*- and *l*-forms of ethyl pipecolate to the corresponding *d*- and *l*-forms of 2*H*-octahydropyrido[1,2-*a*]pyrazine-1-one. According to the reported configurations (6), the *d*-form of pipecolic acid has the S-configuration and presumably this configuration is retained as the asymmetric center in 2*H*-octahydropyrido[1,2-*a*]pyrazine-1-one. As a check on this assumption, an optical rotatory dispersion study of the *d*-lactam was made which revealed a Cotton curve with a steeply ascending positive tail. When an amine with an

asymmetric center adjacent to the nitrogen atom contains a chromophore absorbing above 200 mμ, the sign of the steeply ascending or descending tail may be used to assign absolute configuration (7). In the present case the positive tail is indicative of the S-configuration.

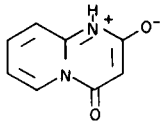
The *d*- and *l*-forms of 2*H*-octahydropyrido[1,2-*a*]-pyrazine-1-one were reduced with lithium aluminum hydride and alkylated with 2-diethylaminoethyl chloride to give the *d*- and *l*-forms of 2-(2-diethylaminoethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine (8).

The 1*H*-octahydropyrido[1,2-*a*]pyrimidine (II) was prepared by condensing 2-aminopyridine with diethylmalonate (9). The resulting 1*H*-3,4-dihydropyrido[1,2-*a*]-pyrimidine-2,4-dione (IV) (10) was hydrogenated over platinum to form 1*H*-octahydropyrido[1,2-*a*]pyrimidine-2,4-dione (V) (10) and the latter was reduced with lithium aluminum hydride to II. (See Scheme II).

SCHEME II



It has been reported (11) that compound IV exists predominantly in a Zwitterion form.



Alkylation of II proved unusually difficult and only the benzhydryl and 2-diethylaminoethyl derivatives were obtainable from direct alkylation methods. The low yields in this sequence of reactions were probably due to the instability of the octahydropyridopyrimidine nucleus. Hexahydropyrimidine is known to be unstable (12) and presumably, since this nucleus is present in II, it too would be rather unstable.

The 2*H*-octahydropyrido[1,2-*c*]pyrimidine (III) was prepared from 2-(2-aminoethyl)piperidine (13) by condensation with formaldehyde. Compound III was alkylated with benzhydryl bromide and 2-diethylaminoethyl chloride in acetone-triethylamine to give 2-benzhydryl- and 2-(diethylaminoethyl)-2*H*-octahydropyrido[1,2-*c*]pyrimidine, respectively. The 2-(2-aminoethyl)-2*H*-octahydropyrido[1,2-*c*]pyrimidine was prepared by alkylating 2-(2-aminoethyl)piperidine with chloroacetonitrile in toluene solution in the presence of anhydrous potassium carbonate, and reducing the resulting cyanomethyl derivative with lithium aluminum hydride.

The three ring systems, I, II, and III, dealt with in this study, may be considered to be aza derivatives of quinolizidine. In the latter, it has been estimated that the *trans* ring-fusion is preferred over the *cis* ring-fusion by 4.4 kcal/mole at room temperature (14). From published work on other heterocyclic systems (15), it appeared reasonable to consider only the all-chair form of 2*H*-octahydropyrido-[1,2-*a*]pyrazine (I). Two forms of this are possible, *trans* and *cis*. The unshared electron pair of the bridgehead nitrogen and the hydrogen of the bridgehead carbon may be situated *trans* or *cis* to each other. Bohlmann had suggested, from a study of alkaloids possessing the quinolizidine nucleus, that a group of bands in their infrared spectra between 2700-2800 cm^{-1} indicated a *trans* ring structure. The absence of such bands was taken as evidence for a *cis* ring-fusion (16). Wiewiorowsky and Skolik carried out a more rigorous evaluation of the Bohlmann bands which supports Bohlmann's suggestion (17).

In the present work, the infrared spectra of compounds I, II, and III were compared with the infrared spectrum of an authentic sample of quinolizidine (Table I). These data indicate that compounds I, II, and III exist predominantly in the *trans* ring-fused conformation.

A nuclear magnetic resonance study, over a temperature range of -60° to + 150°, for quinolizidine showed no variation in the spectra.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover capillary melting-point apparatus. The values are uncorrected.

The Perkin-Elmer Model 521 Recording Spectrophotometer was used for the infrared spectra.

The nuclear magnetic spectra were obtained at 60 MHz on a Varian Associates spectrometer. Model HR-60, using 5-10% solutions in appropriate solvents with tetramethylsilane as an internal standard.

The optical rotations were measured on a Hilger Polarimeter and are accurate to ± 2°.

TABLE I

	Quinolizidine	2*H*-Octahydropyrido[1,2-*a*]pyrazine (I)	
neat	2793 cm^{-1}	neat	2800 cm^{-1}
	2758		2754
	2735		2742
	2674		2670
$CHCl_3$	2800	$CHCl_3$	2804
	2760		2760
	2728		2747
	2672		2670
1*H*-Octahydropyrido[1,2-*a*]pyrimidine (II)		2*H*-Octahydropyrido[1,2-*c*]pyrimidine (III)	
neat	2790 cm^{-1}	neat	2800 cm^{-1}
	2745		2761
	2730		2726
	2671		2670
$CHCl_3$	2802	$CHCl_3$	2810
	2756		2771
	2735		2730
	2670		2685-2670

Preparation of *d*- and *l*-Ethyl 2-Piperidinecarboxylate.

2-Piperidinecarboxylic acid was resolved with *d*-tartaric acid to get the *d*-form of the acid and with *l*-tartaric acid to get the *l*-form of 2-piperidinecarboxylic acid (5). *d*-Acid, m.p. 275-276° $[\alpha]_D^{25°}$ + 27.7° (*c* 4.4, HOH); *l*-acid, m.p. 275-276° $[\alpha]_D^{25°}$ -20.3° (*c* 4.9, HOH) (18) [Lit. (5) m.p. 267°, $[\alpha]_D^{19°}$ + 26.2° (*c* 3.1, HOH), $[\alpha]_D^{20°}$ -20.3 [*c* 2.85, HOH)].

The two acids were converted to their ethyl esters by treatment with ethyl alcohol and sulfuric acid (19). *d*-Ester, yield 68%, b.p. 83-85°/7 mm., $[\alpha]_D^{25°}$ + 21.3° (*c* 4.5, HOH); *l*-ester, yield 65%, b.p. 83-85°/7 mm., $[\alpha]_D^{25°}$ -20.8 (*c* 4.6, HOH). [No lit. values available].

Preparation of *d*- and *l*-2*H*-octahydropyrido[1,2-*a*]pyrazine-1-one.

These compounds were prepared from the *d*- and *l*-esters by treatment with ethylenimine by the method of Freed and Day (2). *d*-2*H*-octahydropyrido[1,2-*a*]pyrazine-1-one, yield 42%, m.p. 149-151°, $[\alpha]_D^{25°}$ + 118.7° (*c* 3.0, HOH); *R.D.* $[\alpha]_{255}$ + 853°, $[\alpha]_{231}$ -303°, $[\alpha]_{228}$ 0° (*c* 0.059, HOH); *l*-2*H*-octahydropyrido-[1,2-*a*]pyrazine-1-one, yield 40%, m.p. 149-151°, $[\alpha]_D^{25°}$ -93.8° (*c* 3.8, HOH). [No lit. values available].

Anal. Calcd. for *d*-$C_8H_{14}N_2O$: C, 62.25; H, 9.14; N, 18.15. Found: C, 62.12; H, 9.24; N, 18.01.

Anal. Calcd. for *l*-$C_8H_{14}N_2O$: C, 62.25; H, 9.14; N, 18.15. Found: C, 62.32; H, 9.04; N, 18.12.

Preparation of 2-Benzhydryl-2*H*-octahydropyrido[1,2-*a*]pyrazine.

A solution of 5.3 g. (0.0214 mole) of benzhydryl bromide, 5 ml. of water and 50 ml. of acetone was added dropwise to a stirred, refluxing solution of 3.0 g. (0.0214 mole) of 2*H*-octahydropyrido-[1,2-*a*]pyrazine, 4.34 g. (0.0428 mole) of triethylamine and 50 ml. of acetone. The mixture was refluxed for 24 hours. Approximately half of the solvent was removed and the remaining solution was made basic with sodium hydroxide (5%). The basic solution was extracted with chloroform. Evaporation of the chloroform gave an oil which was converted to its hydrochloride salt with dry hydrogen chloride in acetone solution. The hydrochloride was recrystallized from a mixture of methanol and 2-propanol, yield 56%, m.p. 245-246° dec.

Anal. Calcd. for $C_{21}H_{28}Cl_2N_2$: C, 66.48; H, 7.44; N, 7.38; Cl, 18.69. Found: C, 66.30; H, 7.52; N, 7.24; Cl, 18.51.

Preparation of 2-(2-Diethylaminoethyl)-2*H*-octahydropyrido-[1,2-*a*]pyrazine.

2*H*-Octahydropyrido[1,2-*a*]pyrazine (*d*- and *l*-forms) was alkylated with 2-diethylaminoethyl chloride hydrochloride by the above procedure. The product was converted to its hydrochloride in a similar manner also. *d*-Isomer, yield 55%, m.p. 253.5-255° dec., $[\alpha]_D^{25°}$ + 8.4° (*c* 5.3, HOH); *l*-isomer, yield 58%, m.p. 253.5-255° dec., $[\alpha]_D^{25°}$ -12.0° (*c* 4.2, HOH).

Anal. Calcd. for *d*-$C_{14}H_{32}Cl_3N_3$: C, 48.21; H, 9.25; N, 12.05;

Cl, 30.49. Found: C, 48.42; H, 9.33; N, 11.95; Cl, 30.46.

Anal. Calcd. for *l*-$C_{14}H_{32}Cl_3N_3$: C, 48.21; H, 9.25; N, 12.05; Cl, 30.49. Found: C, 48.13; H, 9.40; N, 11.91; Cl, 30.51.

Preparation of 2-Cyanomethyl-2*H*-octahydropyrido[1,2-*a*]pyrazine.

A solution of 12.5 g. (0.1655 mole) of chloroacetonitrile in 50 ml. of dry toluene was added dropwise to a stirred refluxing mixture of 22.2 g. (0.1585 mole) of 2*H*-octahydropyrido[1,2-*a*]-pyrazine, 43.8 g. (0.317 mole) of anhydrous potassium carbonate and 200 ml. of dry toluene. Refluxing was continued for 1 hour after the addition. The toluene was removed by filtration and concentrated *in vacuo*. The concentrate was added to ice water, extracted with ether and the ether evaporated to give a brown powder. The product was recrystallized from petroleum ether (30-60°), yield 48% colorless needles, m.p. 60.5-62°.

Anal. Calcd. for $C_{10}H_{17}N_3$: C, 66.94; H, 9.56; N, 23.44. Found: C, 66.82; H, 9.40; N, 23.65.

Preparation of 2-(2-Aminoethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine.

A solution of 13.5 g. (0.0755 mole) of 2-cyanomethyl-2*H*-octahydropyrido[1,2-*a*]pyrazine in 100 ml. of dry ether was added dropwise to a stirred suspension of 4.0 g. (0.105 mole) of lithium aluminum hydride in 200 ml. of dry ether. The mixture was refluxed for 24 hours, 16 ml. of water was added and the mixture was filtered. The precipitate was extracted with ether and evaporation of the ether gave an oil. The latter was fractionally distilled to yield 69% of the desired product, b.p. 92° (0.23 mm), $n_D^{26.5°}$ 1.5021.

Anal. Calcd. for $C_{10}H_{21}N_3$: C, 65.53; H, 11.55; N, 22.92. Found: C, 65.45; H, 11.68; N, 22.79.

Preparation of 2-(2′-guanidinoethyl)-2*H*-octahydropyrido[1,2-*a*]-pyrazine nitrate.

A mixture of 6.2 g. (0.388 mole) of 2-(2-aminoethyl)-2*H*-octahydropyrido[1,2-*a*]pyrazine, 3.4 g. (0.0169 mole) of 1-guanyl-3,5-dimethylpyrazole nitrate (4.20) and 100 ml. of absolute ethanol was refluxed for 2 hours and stirred for an additional 19 hours in a carbon dioxide free atmosphere. After removing the solvent *in vacuo*, the residual oil was triturated with dry ether until a solid was obtained. The solid was recrystallized from ethanol-ether, yield 88.3%, m.p. 143-144.5°.

Anal. Calcd. for $C_{11}H_{24}N_6O_3$: C, 45.82; H, 8.39; N, 29.14. Found: C, 45.94; H, 8.54; N, 29.27.

Preparation of 2-Guanyl-2*H*-octahydropyrido[1,2-*a*]pyrazine sulfate.

A mixture of 7 g. (0.05 mole) of 2*H*-octahydropyrido[1,2-*a*]-pyrazine, 5.03 g. (0.025 mole) of 1-guanyl-3,5-dimethylpyrazole nitrate and 100 ml. of dry ethanol was stirred for 10 hours and then refluxed for 2.5 hours. After removing the solvent *in vacuo*, the residual oil was triturated with 15 ml. portions of dry ether until the oil solidified. The solid was dissolved in 25 ml. of water and passed through an Amberlite SO_4 (IRA-400) ion exchange column. The eluant was concentrated *in vacuo* and the resulting solid was recrystallized from water-methanol, yield of sulfate, 63%, m.p. 314-317° dec.

Anal. Calcd. for $C_9H_{20}N_4O_4S$: C, 38.56; H, 7.19; N, 19.92; S, 11.44. Found: C, 38.50; H, 7.34; N, 19.81; S, 11.26.

Preparation of 1*H*-Octahydropyrido[1,2-*a*]pyrimidine.

A mixture of 24 g. (0.632 mole) of lithium aluminum hydride in 1000 ml. of dry dioxane was stirred and refluxed in a Soxhlet apparatus in order to extract 30 g. (0.179 mole) of 1-*H*-octahydropyrido[1,2-*a*]pyrimidine-2,4-dione (10) slowly into the reaction vessel. The mixture was refluxed for 16 hours, until complete solution had been reached, and then 98 ml. of water was slowly added with stirring. The precipitate was removed, dried and extracted with ether. After drying (sodium sulfate), the ether was removed and the residue was distilled *in vacuo*, yield 42%, b.p. 85° (11 mm.), $n_D^{25°}$ 1.4940.

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.51; H, 11.50; N, 19.98. Found: C, 68.40; H, 11.62; N, 19.83.

The monohydrochloride was prepared in dry ethanol-ether solution, m.p. 172.5-175° dec.

Anal. Calcd. for $C_8H_{17}ClN_2$: C, 54.38; H, 9.70; N, 15.85; Cl, 20.06. Found: C, 54.26; H, 9.75; N, 15.85; Cl, 20.09.

Preparation of *l*-Diethylaminoethyl-1*H*-octahydropyrido[1,2-*a*]-pyrimidine.

A mixture of 10.5 g. (0.075 mole) of 1*H*-octahydropyrido-[1,2-*a*]pyrimidine, 12.9 g. (0.075 mole) of diethylaminoethyl chloride hydrochloride and 16.2 g. (0.160 mole) of triethylamine in 100 ml. of acetone was stirred and refluxed for 24 hours. After cooling, the triethylamine hydrochloride was removed by filtration and the solvent removed *in vacuo*. The residual oil was distilled *in vacuo*, yield 27%, b.p. 121-123° (1.1 mm), $n_D^{25°}$ 1.4889.

Anal. Calcd. for $C_{14}H_{19}N_3$: C, 70.24; H, 12.21; N, 17.55. Found: C, 70.14; H, 12.15; N, 17.38.

Preparation of 2-Benzhydryl-2*H*-octahydropyrido[1,2-*c*]pyrimidine.

A mixture of 2*H*-octahydropyrido[1,2-*c*]pyrimidine (13) (10 g., 0.075 mole), 17.65 g. (0.0715 mole) of benzhydryl bromide and 14.5 g. (0.143 mole) of triethylamine in 100 ml. of acetone was refluxed for 24 hours. After cooling, the solid was removed and extracted with water. The water insoluble residue was recrystallized from ethanol-water, yield 50%, m.p. 110-111.5°.

Anal. Calcd. for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.23; H, 8.71; N, 8.93.

The dihydrochloride was prepared and recrystallized from methanol-diethylether, m.p. 296-297° dec.

Anal. Calcd. for $C_{21}H_{28}Cl_2N_2$: C, 66.50; H, 7.40; N, 7.40; Cl, 18.70. Found: C, 66.34; H, 7.50; N, 7.57; Cl, 18.62.

Preparation of 2-Diethylaminoethyl-2*H*-octahydropyrido[1,2-*c*]-pyrimidine.

A mixture of 10 g. (0.0715 mole) of 2*H*-octahydropyrido-[1,2-*c*]pyrimidine, 12.3 g. (0.0715 mole) of diethylaminoethyl chloride hydrochloride, 15.2 g. (0.15 mole) of triethylamine and 100 ml. of acetone was refluxed for 24 hours. The mixture was cooled and the triethylamine hydrochloride removed by filtration. The filtrate was concentrated to an oil which was distilled *in vacuo*, yield 40% (yellowish oil) b.p. 101-107° (0.3 mm), $n_D^{25°}$ 1.4848.

Anal. Calcd. for $C_{14}H_{29}N_3$: C, 70.24; H, 12.21; N, 17.55. Found: C, 70.11; H, 12.05; N, 17.73.

Preparation of 2-Cyanomethyl-2*H*-octahydropyrido[1,2-*c*]pyrimidine.

A solution of 2.2 g. (0.0294 mole) of chloroacetonitrile in 25 ml. of dry toluene was added dropwise to a stirred refluxing mixture of 7.9 g. (0.0572 mole) of anhydrous potassium carbonate and 4.0 g. (0.0286 mole) of 2*H*-octahydropyrido[1,2-*c*]pyrimidine in 100 ml. of dry toluene. The mixture was refluxed for 1 hour, cooled and diluted with ice water. The organic layer was separated and the aqueous layer made basic with potassium carbonate and extracted with ether. The organic layers were combined and the

solvents removed. The resulting gum was recrystallized from petroleum ether (30-60°), yield 76%, m.p. 66.5-68°.

Anal. Calcd. for $C_{10}H_{17}N_3$: C, 66.94; H, 9.56; N, 23.44. Found: C, 66.80; H, 9.73; N, 23.56.

Preparation of 2-(2-Aminoethyl)-2*H*-octahydropyrido[1,2-*c*]pyrimidine.

A solution of 7.0 g. (0.039 mole) of 2-cyanomethyl-2*H*-octahydropyrido[1,2-*c*]pyrimidine in 60 ml. of anhydrous ether was added dropwise to a stirred suspension of 2.06 g. (0.0543 mole) of lithium aluminum hydride in 150 ml. of anhydrous ether. After refluxing for 24 hours, 10 ml. of water was carefully added with stirring. The precipitate was removed and extracted with ether. The combined organic extracts were dried (sodium sulfate), the solvent was removed in a steam bath and the residual oil was distilled *in vacuo*, yield 63%, b.p. 109.5° (1.6 mm), $n_D^{25°}$ 1.5035.

Anal. Calcd. for $C_{10}H_{21}N_3$: C, 65.53; H, 11.55; N, 22.92. Found: C, 65.39; H, 11.35; N, 22.77.

REFERENCES

(1) A. D. Lourie and A. R. Day, *J. Med. Chem.*, 9, 311 (1966).

(2) M. E. Freed and A. R. Day, *J. Org. Chem.*, 25, 2108 (1960).

(3) D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, 6, 705 (1963).

(4) R. A. B. Bannard, A. A. Casselman, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, 36, 1541 (1958).

(5) F. Mende, *Ber.*, 29, 2887 (1896); H. C. Beyerman, *Rec. Trav. Chim.*, 78, 134 (1959).

(6) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950).

(7) J. C. Craig and S. K. Roy, *Tetrahedron*, 21, 401 (1965).

(8) These compounds, along with others are being tested. The results will be published elsewhere.

(9) A. E. Tschitschibabin, *Ber.*, 57, 1168 (1924).

(10) V. Boekelheide and J. Figueras, *J. Am. Chem. Soc.*, 71, 2587 (1949).

(11) A. R. Katritzky, F. D. Popp, and A. J. Waring, *J. Chem. Soc.*, B 565 (1966).

(12) A. W. Titherley and K. E. R. Branch, *ibid.*, 103, 330 (1913); G. E. K. Branch, *J. Am. Chem. Soc.*, 38, 2466 (1916).

(13a) K. Winterfield and W. Goebel, *Chem. Ber.*, 92, 637 (1959); (b) K. Winterfield and H. Schuler, *Arch. Pharm.*, 293, 203 (1960).

(14) H. S. Aaron, *Chem. Ind.*, 1338 (1965).

(15) M. Przyblyska and W. H. Barnes, *Acta. Cryst.*, 6, 377 (1953); J. W. Visser, J. Manassen, and J. W. DeVries, *ibid.*, 7, 288 (1954); J. M. Lindsey and W. H. Barnes, *ibid.*, 8, 227 (1955); M. Davis and D. Hassel, *Acta. Chem. Scand.*, 17, 1181 (1963).

(16) F. O. Bohlmann, *Angew. Chem.*, 69, 641 (1957); *Chem. Ber.*, 91, 2157 (1958); *ibid.*, 92, 1798 (1959).

(17) M. Wiewiorowski and J. Skolik, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, 10, 1 (1962).

(18) H. C. Beyerman, J. Eenshuistra and W. Eveleens, *Rec. Trav. Chim.*, 76, 415 (1957).

(19a) A. Camps, *Arch. Pharm.*, 240, 346 (1902); (b) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 437 (1931); (c) W. A. Rechow and D. S. Tarbell, *J. Am. Chem. Soc.*, 74, 4960 (1952).

(20) M. Fasold, F. Turba and W. Wirshing, *Biochem. Z.*, 335, 86 (1961); F. L. Scott and J. Reilly, *J. Am. Chem. Soc.*, 74, 4562 (1952).

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