and acetone cyanohydrin in the usual manner[3]), and 1-piperidinocyclohexanenitrile[5] with phenyllithium according to the above procedure gave the following compounds in 80–84% yield.

1-(2-Imino-1,1-dimethyl-2-phenylethyl)dimethylamine, bp 95–96° (2 mm). *Anal.* Calcd for $C_{12}H_{18}N_2$: N, 14.72. Found: N, 14.50.

1-(2-Imino-1,1-dimethyl-2-phenylethyl)morpholine, bp 115–120° (0.2 mm), mp 45–47° (hexane). *Anal.* Calcd for $C_{14}H_{20}N_2O$: N, 12.06. Found: N, 12.13.

1-(1-Benzimidoylcyclohexyl)piperidine, bp 148–151° (0.2 mm), mp 88–90° (hexane). *Anal.* Calcd for $C_{18}H_{26}N_2$: N, 10.36. Found: N, 10.24.

1-[2-Imino-1,1-dimethyl-2-(*p*-chlorophenyl)ethyl]piperidine.—A solution of 115 g (0.6 mole) of *p*-chlorobromobenzene in 600 ml of ether was stirred and cooled to −15° in an ice–salt bath and treated dropwise, over a period of 15 min, with 380 ml of 1.6 *N* *n*-butyllithium in hexane (0.6 mole) while maintaining the temperature at −7 to −12°. The pale yellow solution was stirred for an additional 30 min at −10° and then was treated with a solution of 76.0 g (0.5 mole) of α-piperidinoisobutyronitrile in 300 ml of ether. A yellow-orange precipitate began to separate from the mixture after about 30 min. After standing for 4 days at room temperature, the mixture was added to a cold NH_4Cl solution and processed in the manner described for **Ia** to give 96.2 g (73%) of pale yellow product, bp 155–158° (0.5 mm).

Anal. Calcd for $C_{15}H_{21}ClN_2$: N, 10.58. Found: N, 10.73.

1-(1,1-Dimethyl-2-phenacetylimino-2-phenylethyl)piperidine Hydrochloride (4).—A stirred solution of 40.0 g (0.17 mole) of **Ia** in 200 ml of benzene was maintained at 15–20° during the dropwise addition of a solution of 27.0 g (0.17 mole) of freshly distilled phenacetyl chloride in 100 ml of benzene. The mixture was refluxed for 1 hr, cooled, and filtered to give 62.5 g (93%) of product, mp 160–165°. After two crystallizations from 250-ml portions of isopropyl alcohol, the material weighed 39.3 g, mp 168–170°, λ_{max}^{Nujol} 5.85 and 5.98 μ (C=O and C=N).

1-(β-Amino-α,α-dimethylphenethyl)piperidine.—A solution of 29.9 g (0.13 mole) of **Ia** in 100 ml of ethanol was treated with 0.9 g of PtO_2. The mixture was placed in a Parr apparatus under 3 atm of hydrogen and heated to 50°. The theoretical quantity of hydrogen was consumed in 6 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 25.1 g (82%) of colorless product, bp 105–107° (0.1 mm), mp 56–59°. After crystallization from hexane, it melted at 61.5–63°.

Anal. Calcd for $C_{15}H_{24}N_2$: N, 12.06. Found: N, 11.83.

The HCl salt is **14** and the phenacetyl derivative is **15**.

The dimethylamino analog (above) was hydrogenated in a similar manner to give 64% yield of the amine, bp 87–89° (0.5 mm). The HCl salt is **16**.

2-Methyl-2-piperidinopropiophenone Hydrochloride (17).—To 170 ml of cold concentrated HCl was added 34.9 g (0.15 mole) of **Ia**; the mixture was refluxed for 24 hr, cooled, and treated with a solution of 100 g of NaOH in 130 ml of water. The product was extracted with ether and the combined ethereal solutions were dried ($MgSO_4$). After evaporation of the solvent, the residue was fractionated to give 31.8 g (91%) of pale yellow liquid, bp 100–101° (0.2 mm) [lit.[6] bp 110–112° (0.5 mm)]. This base was converted to the HCl salt in the usual manner (see preparation of **Ia**).

The ketones **19** and **20** were obtained in the same manner by hydrolysis of the corresponding imino compounds.

Appetite Depressant Test Procedure.—Mice were deprived of food (water *ad libitum*) for about 18 hr. Aqueous solutions of the test drugs were administered orally to groups of mice (10/dose) and after 15 min they were offered food pellets (Rockland Mouse Diet) for a period of 1 hr. The amount of food consumed during this period was then determined. The anorectic activity, expressed in milligrams per kilogram, is the approximate dose which caused a 50% decrease in the normal food intake. A similar test procedure was used when a compound was tested in dogs.

Acknowledgments.—The authors are indebted to A. Szabo, C. F. Turk, and J. Williams for the preparation of some of the compounds and to J. Alicino and his associates for the analyses reported herein.

(5) A. Katz and P. Merkel, *J. Prakt. Chem.*, **113**, 49 (1926).

(6) C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

5-(3-Dimethylaminopropyl)-2,8-diaza-10,11-dihydro-5H-dibenzo[*b*,*f*]azepine

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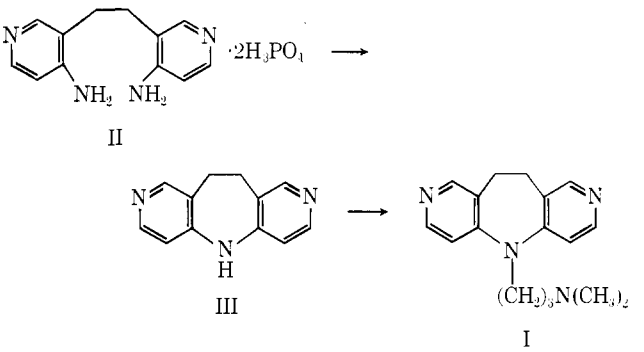
To study the biological effects of replacement of the aromatic rings by pyridine rings in the antidepressant drug, 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[*b*,*f*]azepine,[1] the diaza compound I was prepared as shown in Chart I.

CHART I



Pyrolysis of 4,4′-diamino-3,3′-dipicolyl[2] as the diphosphate salt (II) at temperatures in the range of 300°[3] gave the tricyclic amine III, which was converted into I by alkylation with dimethylaminopropyl chloride and sodium hydride. The latter was characterized as the tetrahydrochloride and dimaleate salts.

The nmr spectrum of I,[4] measured in $CDCl_3$ with TMS as internal standard on the Varian A-60, is consistent with the assigned structure and shows: (a) the protons at positions 1 and 9 of the ring, being the least shielded are furthest downfield, show a singlet at δ 8.31 (2 H); (b) the doublets centered at δ 8.26 (2 H) and 6.95 (2 H) are assigned to the protons at positions 3,7 and 4,6 of the ring, respectively; (c) the bridge protons at C-10 and -11 appear as a singlet at δ 3.11 (4 H); (d) the triplets centered at δ 3.92 (2 H) and 2.30 (2 H) and the quintet at 1.77 (2 H) are the α, γ, and β protons, respectively, of the propyl side chain; (e) the strong singlet at δ 2.18 corresponds to the six protons of the $N(CH_3)_2$ group.

Compound I was remarkably inactive in most biological testing procedures. The compound at an oral dose of 10 mg/kg did not antagonize tetrabenazine-induced sedation[5] in mice. The standard[1] had an ED_{50} of 0.5 mg/kg in this test procedure. At oral doses of 2–15 mg/kg in the cat, no significant behavioral changes were noted. The ED_{50} *in vitro*

(1) Imipramine: W. Schindler and F. Häfliger, *Helv. Chim. Acta*, **37**, 472 (1954).

(2) E. C. Taylor, A. J. Crovetti, and N. E. Boyer, *J. Am. Chem. Soc.*, **79**, 3549 (1957).

(3) W. Schindler and F. Häfliger, U. S. Patent 2,764,580 (1956).

(4) The author is indebted to Mr. Milton D. Yudis of the Physical Organic Chemistry Department of the Schering Corp. for the interpretation of the nmr data.

(5) For a review of this procedure, see V. G. Vernier, H. M. Hanson, and C. A. Stone in "Psychosomatic Medicine," J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, Chapter 80.

antihistaminic activity (guinea pig ileum) of I was greater than 40 μg/l., whereas the standard drug had an ED_{50} of 14 μg/l.[6]

Experimental Section[7]

4,4'-Diamino-3,3'-dipicolyl Diphosphate (II).—The diamino compound (10 g), mp 245–250°,[2] was dissolved in ethanol and 85% H_3PO_4 was added dropwise until no further precipitation occurred. The crude product was filtered, air dried, and used directly in the next step; yield 14.8 g.

2,8-Diaza-10,11-dihydro-5H-dibenzo[*b,f*]azepine (III).—The diphosphate (**II**, 32.0 g) was heated at 295–305° for 4 hr. After cooling, the black solid was suspended in water and the mixture was made strongly basic with NaOH (50%) solution. The crude product was filtered and air dried; yield 12.2 g (75%). A small sample was sublimed at a bath temperature of 280–285° and the light yellow sublimate was recrystallized from dilute ethanol; mp 200–202°.

Anal. Calcd for $C_{12}H_{11}N_3 \cdot 0.5H_2O$: C, 69.88; H, 5.87; N, 20.38. Found: C, 69.50; H, 5.54; N, 20.58.

5-Dimethylaminopropyl-2,8-diaza-10,11-dihydro-5H-dibenzo-[*b,f*]azepine (I).—A mixture of 10 g (0.05 mole) of the amine III, 2.6 g of NaH (50% in mineral oil) and 150 ml of xylene was heated under reflux with stirring for 2 hr. A solution of 6.6 g of dimethylaminopropyl chloride in 50 ml of xylene was added, and the mixture was refluxed with stirring for 15 hr. Dilute (10%) HCl was added, and the organic layer was separated and discarded. The acid solution was made basic with NH_4OH and extracted with $CHCl_3$. The solvent was removed and the product was distilled, bp 206–210° (0.2 mm), yield 7.0 g (48%).

Anal. Calcd for $C_{17}H_{22}N_4$: C, 72.30; H, 7.85; N, 19.84. Found: C, 71.98; H, 8.12; N, 19.36.

The **dimaleate** salt was prepared and recrystallized from ethanol–ether; mp 156–157°.

Anal. Calcd for $C_{17}H_{22}N_4 \cdot 2(C_4H_4O_4)$: C, 58.36; H, 5.88; N, 10.89. Found: C, 57.98; H, 5.94; N, 10.98.

The **tetrahydrochloride** was recrystallized from absolute ethanol–ether; mp 223–224° dec.

Anal. Calcd for $C_{17}H_{22}N_4 \cdot 4HCl$: C, 47.67; H, 6.12; N, 13.08. Found: C, 47.60; H, 6.37; N, 13.07.

(6) Biological data reported herein was obtained by Drs. F. E. Roth and R. Taber of the Biological Research Division of Schering Corp.

(7) Microanalysis by Mr. E. Connor of these laboratories. All melting points are uncorrected. Conditions for maximum yield were not studied.

2-Phenylindolizines

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As a part of a continuing investigation of aminoalkyl derivatives of heterocyclic compounds, we have prepared for pharmacological study the 2-phenylindolizines and their 5,6,7,8-tetrahydro derivatives listed in Table I. The indolizines were obtained by treating the quaternary salts formed from 2-bromoacetophenone and the appropriately substituted pyridines with sodium bicarbonate.[1] To avoid difficulty at the quaternization step, the compounds with an aminoalkyl group were made by reducing an alkyl carbamate group with lithium aluminum hydride after the indolizine ring had been formed. Most of the indolizines were unstable to light and air and darkened rapidly. However, the quaternary salts of the tertiary alkyl bases were relatively stable. No bisquaternary salt was formed, even with excess alkyl halide.

The indolizines were not hydrogenated with palladium or platinum catalysts but were reduced easily to the 5,6,7,8-tetrahydro compounds with Raney nickel at room temperature. The tetrahydro derivatives were somewhat more stable than the parent compounds, and salts of the aminoalkyl compounds were obtained.

Pharmacology.[2]—The compounds were screened for their effects on the central nervous system in mice[3] and in some instances in cats. In mice (orally) the tertiary aminoalkylindolizines (**2**, **8**, Table I), were stimulants at 1–5 mg/kg, depressants at higher doses, and lethal (convulsions) at 100 mg/kg. Compound **6** produced a locomotor depression at 1 mg/kg which was pronounced at 30 mg/kg, and it was lethal at 100 mg/kg. The secondary amine **4** was less active, exhibiting slight to marked ataxia at 10–100 mg/kg, and it was lethal at 300 mg/kg. The 5,6,7,8-tetrahydro derivatives **12** and **13** had an action similar to that of the parent compounds but were less active and less toxic. The carbamate **3** and its tetrahydro derivative **11** produced a slight depression only, at 30–100 mg/kg, and were nonlethal at 1000 mg/kg. The dimethylamide **7** was a stimulant at 10–30 mg/kg, a depressant at higher doses, and lethal at 1000 mg/kg.

In cats (orally) **6** produced stimulation at 1–10 mg/kg, while **7** and **8** at 4–30 mg/kg caused stimulation followed by emesis.

Experimental Section[4]

Pyridylalkylamine Carbamates.—A solution of 0.5 mole of the aminoalkylpyridine and 10 g of pyridine in 300 ml of $CHCl_3$ was stirred and kept below 40° while 0.6 mole of ethyl chloroformate was added. After several hours 50 ml of water was added and the mixture was kept overnight. Strong NaOH solution was added with cooling until the mixture was strongly basic, and the $CHCl_3$ was separated, dried briefly (K_2CO_3), filtered, and distilled.

2-(3-Aminopropyl)pyridine.—3-(2-Pyridyl)propionitrile (52 g) in 400 ml of ethanol saturated with NH_3 was hydrogenated at 70–75° with 10 g of Raney nickel under 100 kg/cm² of hydrogen. The product was distilled.

2-(3-Methylaminopropyl)pyridine.—2-(3-*N*-Carbethoxyaminopropyl)pyridine (27.5 g) added dropwise to 10 g of $LiAlH_4$ in 500 ml of ether was stirred and refluxed for 6 hr. The cooled mixture was decomposed by the successive addition of 9 ml of water, 9 ml of 15% NaOH, and 27 ml of water, and after 1 hr the precipitate was filtered and washed by slurrying it with more ether. The solution was dried (K_2CO_3), filtered, and distilled.

N,N-Dimethyl-4-(2-pyridyl)butyramide.—4-(2-Pyridyl)butyric acid was heated in a metal bath at 210–220° (air condenser) and dimethylamine was passed through the molten mixture until the acid carbonyl had disappeared from the infrared spectrum of the melt (1.5–2 hr). The residue was dissolved in benzene, filtered, and distilled, bp 119–121 (1 mm),[5] yield 70%.

N-Phenacylpyridinium Bromides.—Molar equivalents of the pyridine and 2-bromoacetophenone were refluxed in benzene for 14–20 hr. The benzene was decanted from the quaternary salt

(1)(a) D. E. Ames, T. F. Grey, and W. A. Jones, *J. Chem. Soc.*, 620 (1959); (b) O. Westphal, K. Jann, and W. Heffe, *Arch. Pharm.*, **294**, 37 (1961); (c) V. S. Venturella, *J. Pharm. Sci.*, **52**, 868 (1963); **53**, 107 (1964); **53**, 1166 (1964).

(2) We are indebted to Dr. S. Irwin (Department of Psychiatry, The University of Oregon Medical School, Portland, Ore.) and the Biological Division of the Schering Corp. for this data.

(3) S. Irwin in "Clinical Pharmacological Techniques," J. H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Inc., Chicago, Ill., 1964, Chapter 4.

(4) Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. The physical constants of pyridine intermediates are in Table II.

(5) J. Ernest and J. Pitha, *Chem. Listy*, **51**, 543 (1957), give bp 106° (0.5 mm).