Anal. Calcd. for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.7; H, 8.3; N, 29.0.

4-Amino-2-(*n*-dodecylamino)-5,6,7,8-tetrahydroquinazoline (**VII**) was synthesized according to procedure C from N^1-(*n*-dodecyl)dicyandiamide[29] and cyclohexanone at 166–178° for 24 hr. Crystallization from ethanol (Darco) afforded a 61% yield after reduction of solvent volume. Two more crystallizations from 95% ethanol gave colorless prismatic needles, m.p. 98–100°, dried for 24 hr. at room temperature: λ_{max} in mμ (ϵ), at pH 1, 227 (20,490), 283 (5480), at pH 10, 235 (13,790), 294 (6330).

Anal. Calcd. for $C_{20}H_{36}N_4$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.76; H, 10.70; N, 16.76.

2,6-Diamino-4,5-pentamethylenepyrimidine (**VIII**) was prepared by procedure C from dicyandiamide and cycloheptanone for 4 hr. at 175–190°; the reaction mixture was triturated with petroleum ether. Crystallization from methanol gave a 51% yield and three further crystallizations from methanol afforded the analytical sample: m.p. 216–217°; λ_{max} in mμ (ϵ), at pH 1, 280 (7630), at pH 10, 235 (9880), 289.5 (7640).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.40; H, 8.10; N, 31.60.

2,6-Diamino-4,5-hexamethylenepyrimidine (**IX**). **Procedure D.**—Dicyandiamide (0.63 g., 7.5 mmoles) and cyclooctanone (0.63 g., 5 mmoles) in 2.5 ml. of 2-(2-ethoxyethoxy)ethanol was heated for 5 hr. at 180–202° in a V-shaped flask equipped with an air condenser and an immersion thermometer. A clear solution was obtained in 5 min. and solid started to deposit 1 hr. later. The reaction mixture was cooled to room temperature, dissolved in 50 ml. of acetone, and filtered. The filtrate was evaporated to dryness and the residue was triturated with a mixture of acetone and ether. The off-white crystalline solid that resulted was collected; yield 0.83 g. (87%). A solution of 0.69 g. of the crude solid in 35 ml. of absolute methanol was treated with Darco and concentrated to 2 ml. After overnight refrigeration, the crystalline solid was collected and washed with benzene; yield 0.33 g. (42%). For analysis this solid was crystallized once more from absolute methanol and twice from a minimal volume of 50% ethanol: colorless prismatic plates; m.p. 191–193°; λ_{max} in mμ (ϵ) at pH 1, 221 (16,820), 278 (7690), at pH 10, 233 (9760), 287 (7820).

Anal. Calcd. for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.40; H, 8.40; N, 29.08.

2,6-Diamino-4,5-heptamethylenepyrimidine (**X**), prepared by procedure D from cyclononanone and dicyandiamide for 5 hr. at 192–203°, crystallized in 49% yield from 95% ethanol (Darco) after concentration. For analysis this product was crystallized three more times from 95% ethanol and twice from 50% ethanol; the colorless prismatic plates, dried for 17 hr. at 50°, had m.p. 189–192°; λ_{max} in mμ (ϵ), at pH 1, 277 (6640), at pH 10, 232 (8620), 287 (6500).

Anal. Calcd. for $C_{11}H_{18}N_4$: C, 64.04; H, 8.79; N, 27.16. Found: C, 63.75; H, 8.72; N, 27.04.

2,6-Diamino-4,5-octamethylenepyrimidine (**XI**), synthesized by procedure D from cyclodecanone and dicyandiamide for 17 hr. at 190–202°, was obtained in 49% yield on crystallization from 50% ethanol (Darco) after concentration. Two more crystallizations from 50% ethanol afforded prismatic plates, m.p. 207–210°, dried for 65 hr. at 50°: λ_{max} in mμ (ϵ), at pH 1, 277 (7770), at pH 10, 230 (9810), 287 (7790).

Anal. Calcd. for $C_{12}H_{20}N_4$: C, 65.42; H, 9.15; N, 25.43. Found: C, 64.98; H, 9.18; N, 25.24.

2,6-Diamino-4,5-tridecamethylenepyrimidine (**XII**) was obtained by procedure D from cyclopentadecanone and dicyandiamide for 8 hr. at 196–203°. Crystallization from 95% ethanol (Darco) gave a 24% yield after concentration. Two more crystallizations from 95% ethanol afforded colorless prismatic plates, m.p. 235–236°, dried for 24 hr. at 45°: λ_{max} in mμ (ϵ), at pH 1, 278 (8230), at pH 10, 232 (10,430), 289 (8170).

Anal. Calcd. for $C_{17}H_{30}N_4$: C, 70.30; H, 10.41; N, 19.29. Found: C, 70.08; H, 10.49; N, 19.15.

2,4-Diaminoquinazoline (**XIII**) **by Dehydrogenation of II.**—An intimate mixture of 2,4-diamino-5,6,7,8-tetrahydroquinazoline (1 g., 6.1 mmoles) and 10% palladium on carbon (1 g.) was heated in a metal bath at 280–300° (bath temperature) for 3 hr. During the reaction a slow stream of nitrogen was passed continuously through the reaction vessel. The cooled reaction mixture was transferred directly to a sublimation apparatus and fractionally sublimed. The light yellow fraction subliming at 140–160° (0.5 mm.) was collected. Resublimation at 140–160° (0.05 mm.) afforded light yellow prismatic crystals: yield 150 mg. (15%); m.p. 250–252° (lit.[19] m.p. 259°); λ_{max} in mμ (ϵ) at pH 1, 226 (39,010), 230 infl. (37,350) 247 infl. (13,000), 315 (4860), 322 infl. (4010), at pH 10, 231 (44,740), 266 (8770), 273 sh (7800), 332 (4470).

Anal. Calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.14; H, 5.15; N, 34.79.

Acknowledgment.—The assistance of Mrs. Deborah M. Brun and Miss Gail Mulligan is gratefully acknowledged. The infrared and ultraviolet absorption spectra were done by Dr. James H. Gunnerson and Mr. Michael Botchan. The authors are indebted to Dr. Sisir K. Sengupta for his contributions to this work.

(29) E. J. Modest, D. H. Trites, and G. E. Foley, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 22-O.

Hexahydro-1-methyl-4-phenyl-4-acetoxyazepine and the Demjanov Rearrangement of 1-Methyl-4-phenylpiperidine-4-methylamine*

JULIUS DIAMOND,[1a] WILLIAM F. BRUCE,[1b] AND FLOYD T. TYSON[1c]

Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania, and Department of Chemistry, Temple University, Philadelphia 22, Pennsylvania

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The preparation of hexahydro-1-methyl-4-phenyl-4-acetoxyazepine has been accomplished by the lead tetraacetate acetoxylation of hexahydro-1-methyl-4-phenylazepine. Three other possible methods of preparation were explored, including the Ziegler method, the amide degradation, and the Demjanov rearrangement of 1-methyl-4-phenylpiperidine-4-methylamine. The latter method did not yield the desired product, but gave instead, without ring enlargement, a mixture of 1-methyl-4-benzylpiperidinol and 1-methyl-4-benzyl-1,2,5,6-tetrahydropyridine.

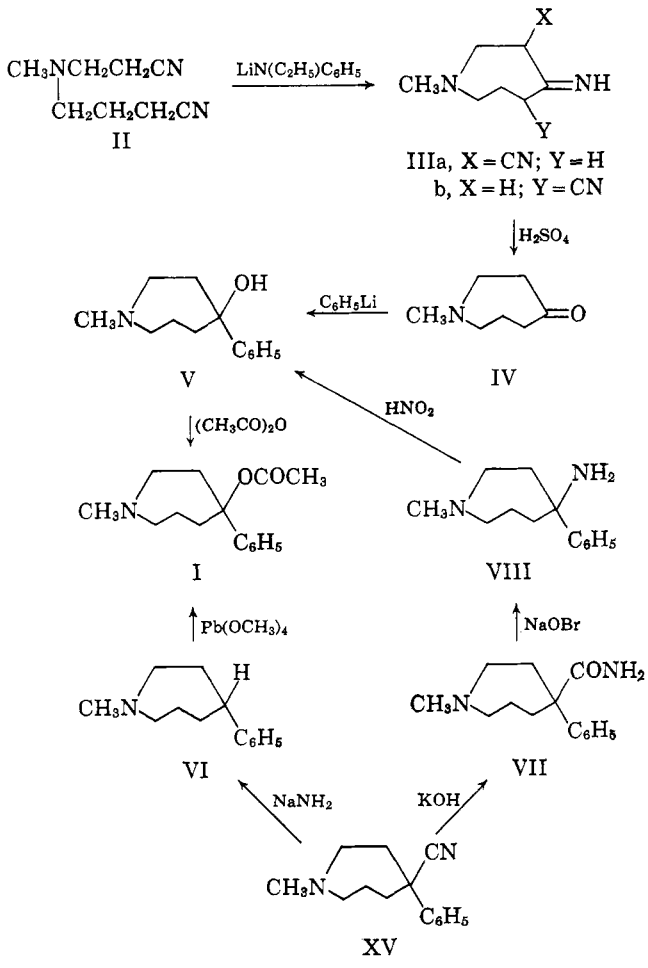
The potent hexahydroazepine analgesic proheptazine was made from a hexahydroazepinone which was secured by ring closure of the appropriate cyano ester.[2] Attempts to use this route to make the corresponding hexahydroazepine IV without the 3-methyl group were unsuccessful. We have, however, obtained this hexahydroazepinone in low yield by the Ziegler method and found it to be unstable, darkening rapidly at room

* To Professor Louis F. Fieser.

(1) (a) Taken in part from a thesis submitted by J. D. to the graduate school of Temple University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1955. (b) To whom inquiries may be sent at Wyeth Laboratories. (c) Department of Chemistry, Temple University.

(2) J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Med. Chem.*, **7**, 57 (1964); L. B. Mellett and L. A. Woods, *Fortschr. Arzneimittelforsch.*, **5**, 248 (1963).

SCHEME I



temperature and unsuitable for preparations involving more than small quantities. Since we wished to make a sufficient amount of the prototype of proheptazine for analgesic tests, several alternative methods for preparing it were explored (Scheme I).

Method 1. Cyclization of N-(2-Cyanoethyl)-N-(3-cyanopropyl)methylamine (II).—Compound II, prepared from 3-methylaminopropionitrile and 4-chlorobutyronitrile,[3] was cyclized by the method of Ziegler.[4] A mixture of lithium salts of hexahydro-1-methyl-3-(or 5)-cyano-4-iminoazepines (IIIa and b) resulted, from which upon treatment with acetic acid in ether the separate isomeric imines were obtained. By heating the mixture of lithium salts in 70% aqueous sulfuric acid, the mixed imines were hydrolyzed and decarboxylated in 28% yield to hexahydro-1-methyl-4-azepinone (IV), an unstable oil. With phenyllithium, IV gave the lithium salt of hexahydro-1-methyl-4-phenyl-4-azepinol (V), which was treated *in situ* with acetic anhydride to form the desired acetate I in 23% yield. In addition to low over-all yield, this method suffers from the unstable nature of IV, which becomes more serious with larger amounts.

Method 2. Acetoxylation of Hexahydro-1-methyl-4-phenylazepine (VI).—Decyanation of hexahydro-1-methyl-4-phenyl-4-cyanoazepine (XV),[5,6] best by the action of fresh sodamide,[7] gave VI, which was acetoxylated with lead tetraacetate to produce I in 21% yield. The reaction proceeded with the evolution of carbon dioxide and a combustible gas; 57% of the starting compound VI was recovered. The conversion yield of I by this method was therefore about 46%.

Assuming that lead tetraacetate reacts by a free-radical mechanism with compounds containing an activated hydrogen,[8] we postulate that the reaction of VI with lead tetraacetate may proceed by the following route, accounting for the experimental observations: $Pb(OCOCH_3)_4 \rightarrow Pb(OCOCH_3)_2 + 2CH_3COO\cdot \rightarrow CH_3\cdot + CO_2$; $2CH_3\cdot \xrightarrow{fast} C_2H_6$; $CH_3\cdot + VI \rightarrow VI(-H)\cdot + CH_4$; $VI(-H)\cdot + Pb(OCOCH_3)_4 \rightarrow I + CH_3COO\cdot + Pb(OCOCH_3)_2$; $VI(-H)\cdot + CH_3COO\cdot \rightarrow I$.

The reaction is initiated by the thermal decomposition of lead tetraacetate to acetate radicals and their subsequent decomposition to methyl radicals, which then abstract a hydrogen from VI to form the hexahydro-1-methyl-4-phenyl-4-azepine radical, VI (−H). Since a large percentage of VI was recovered, we conclude that the reactivity of the hydrogen atom at the 4 position of VI is relatively low and that the reaction of VI with methyl radicals is slow; the predominating termination reaction is the more rapid dimerization of methyl radicals.

Method 3. Degradation of Hexahydro-1-methyl-4-phenylazepine-4-carboxamide (VII).—Partial hydrolysis of nitrile XV[6] gave the amide VII. By treatment with bromine and aqueous sodium hydroxide, this was converted to hexahydro-1-methyl-4-phenyl-4-aminoazepine (VIII). Upon reaction with nitrous acid, this amine gave, without change in ring size, hexahydro-1-methyl-4-phenyl-4-azepinol (V). The structure of this product is shown by its conversion by means of acetic anhydride to the same acetate ester (I) which was obtained by methods 1 and 2. The acetate ester (I), which itself is an oil, was identified in all three cases by conversion to its methiodide and comparison by mixture melting point determinations.

Method 4. Demjanov Rearrangement of 1-Methyl-4-phenylpiperidine-4-methylamine (IX).—Since cycloalkylmethylamines such as cyclobutylmethylamine and cyclohexylmethylamine are known to undergo ring expansion on treatment with nitrous acid to give the corresponding alcohol in yields up to 60%,[9] we investigated the reaction of 1-methyl-4-phenylpiperidine-4-methylamine[10] (IX) with nitrous acid. We found (Scheme II) that none of the desired azepinol (V) could be isolated; instead, IX underwent rearrangement without ring enlargement to produce chiefly 1-

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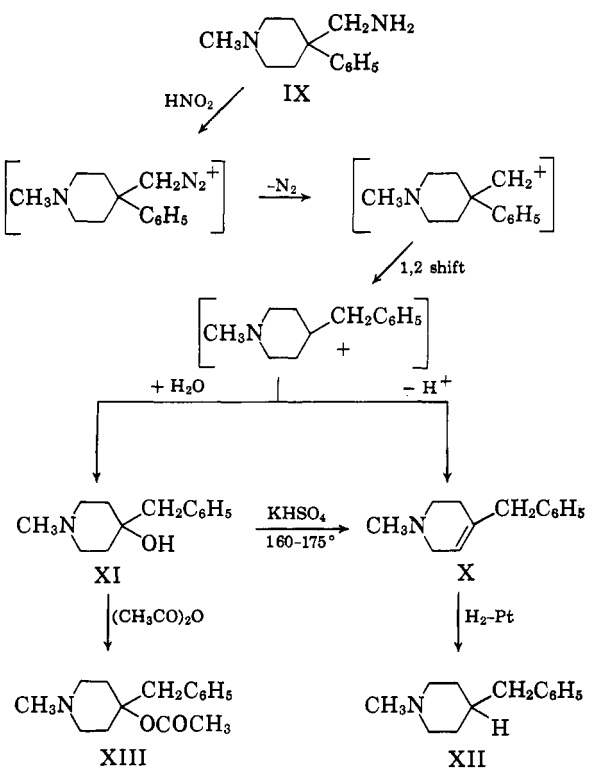
(7) J. Diamond, W. F. Bruce, and F. T. Tyson, *ibid.*, **22**, 399 (1957).

(8) W. A. Waters in "Organic Chemistry," Vol. 4, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 1185–1189.

(9) N. Demjanov and L. Lushnikov, *J. Russ. Phys. Chem. Soc.*, **35**, 261 (1903); *Chem. Zentr.*, **I**, 828 (1903); N. Demjanov, *J. Russ. Phys. Chem. Soc.*, **36**, 168 (1904); *Chem. Zentr.*, **I**, 1214 (1904); O. Wallach, *Ann.*, **353**, 318 (1907); *Chem. Zentr.*, **II**, 236 (1907); *Nachr. Ges. Wiss. Gottingen*, 65 (1907); *Chem. Zentr.*, **II**, 54 (1907); L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, **9**, 399 (1926); R. Kotani, *J. Org. Chem.*, **30**, 350 (1965).

(10) F. F. Blicke and E. P. Tsao, *J. Am. Chem. Soc.*, **75**, 5417 (1953).

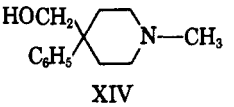
SCHEME II



methyl-4-benzyl-1,2,5,6-tetrahydropyridine (X),[11] but in addition 1-methyl-4-benzyl-4-piperidinol (XI).

The structure of X was established by catalytic hydrogenation to the known 1-methyl-4-benzylpiperidine (XII)[12] and by the absence of a large absorption maximum in the 2500-Å. region characteristic of styrene-type structures: λ_{max}^{EtOH} 2525 Å. (ϵ_{max} 530), compared with styrene λ_{max}^{hexane} 2500 (ϵ_{max} 14,700).[13] Further support for the structure assigned to X lies in the fact that in structures with six-membered rings, a double bond exocyclic to the ring makes the structure less stable than the isomeric cyclohexene.[14]

The structure of XI was established by mild heating of the compound with fused potassium bisulfate (160–175°), which dehydrated it to X, identified through its methiodide. Acetylation of XI yielded a solid acetate XIII which differed from its oily isomer I, and gave a methiodide which melts 24° lower than that of I. Preparation of another isomer for comparison with XI was accomplished by the reduction of meperidine by lithium aluminum hydride to give a known solid product, 1-methyl-4-phenylpiperidine-4-methanol (XIV),[15] which would have been expected if the reaction with nitrous acid proceeded without rearrangement. This material melted 60° higher than XI and a mixture melting point was depressed below either, showing that the two are different compounds.



XIV

Experimental[16]

N-(2-Cyanoethyl)-N-(3-cyanopropyl)methylamine (II).[3]—A solution of 61.8 g. (0.60 mole) of 4-chlorobutyronitrile in 50 ml. of *n*-butyl alcohol was slowly added over 4 hr. to a rapidly stirred mixture of 55.4 g. (0.66 mole) of 3-methylaminopropionitrile, 95.4 g. (0.9 mole) of anhydrous sodium carbonate, and 5 g. (0.03 mole) of potassium iodide at reflux. The mixture was stirred and refluxed a total of 17 hr. and cooled, and the inorganic solid was filtered and washed with ether. The combined filtrate and washings were extracted with excess 6 *N* hydrochloric acid. The acid extract was washed with ether, made basic with potassium carbonate, and extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, and distilled to give 68 g. (75%) of a colorless liquid, b.p. 135–140° (0.4 mm.), $n^{26}D$ 1.4543, d^{26}_4 0.965.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79; equiv. wt., 151.2. Found: C, 63.14; H, 8.46; N, 27.90; equiv. wt., 155.

The picrate, formed from saturated picric acid in methanol and crystallized from acetone–methanol, melted at 144–145°.

Anal. Calcd. for $C_{14}H_{16}N_6O_7$: C, 44.21; H, 4.24; N, 22.10. Found: C, 44.5; H, 4.66; N, 22.0.

Hexahydro-1-methyl-3-cyano-4-iminoazepine (IIIa) and Hexahydro-1-methyl-5-cyano-4-iminoazepine (IIIb).—A clear yellow ethereal solution of lithium N-ethylanilide was prepared by dissolving 4.2 g. (0.6 g.-atom) of lithium shot in a solution of 90.8 g. (0.75 mole) of N-ethylaniline and 44.8 g. (0.35 mole) of naphthalene in 1 l. of absolute ether. To this solution, stirred and refluxed with vigor, was added, over 7 hr., a solution of 30.2 g. (0.2 mole) of II in 500 ml. of absolute ether. A white precipitate (a) formed and was collected on a filter, washed with absolute ether, and suspended in 300 ml. of ether. To this stirred and cooled suspension was added dropwise 12 g. (0.2 mole) of glacial acetic acid in 200 ml. of ether. After 30 min., the suspended solid (b) was collected on a filter and washed with ether. The filtrate and washings were combined and distilled to give 6.7 g. of yellow liquid, b.p. 120–132° (0.4 mm.), which crystallized on standing. Trituration with cold benzene gave, after filtration, 4.5 g. of a mixture of IIIa and IIIb, m.p. *ca.* 110–125°.

The solid (b) was dissolved in a small amount of water saturated with sodium sulfate, and the solution was extracted with chloroform. The extract was dried and distilled, yielding 4.6 g. of yellow oil, b.p. 130–140° (0.5 mm.), which on standing also crystallized. Trituration with cold benzene and filtration afforded 3.1 g. of additional IIIa and IIIb mixture, m.p. *ca.* 110–125°. The combined solids, 7.6 g. (25.3%), were crystallized from benzene to give the higher melting, less soluble isomer as fine white needles, m.p. 140–142°.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79. Found: C, 63.64; H, 8.56; N, 25.79.

Concentration of the filtrate separated the more soluble isomer, m.p. 108–109°.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79. Found: C, 63.53; H, 8.68; N, 25.74.

These two compounds slowly evolved ammonia on standing (no doubt due to the action of atmospheric moisture) to give the corresponding β-ketonitriles, accounting for the low nitrogen analyses. No attempt was made to assign them definitive structures, since in the next step both yielded the same product.

Hexahydro-1-methyl-4-azepinone (IV).—The lithium salts, 32 g. (a above) from another run, added in small portions to a solution of 136 ml. of 98% sulfuric acid in 105 ml. of water at 5°, gave a solution which was heated at 120–130° for 5 hr., when carbon dioxide evolution ceased. This material was made basic by adding solid sodium carbonate in small portions. The product was extracted from solution with chloroform, dried over potassium carbonate, filtered, and distilled, yielding 7 g. (27.6%) of a colorless liquid, b.p. 115–120° (45 mm.), $n^{23}D$ 1.4893, d^{23}_4 0.963, yield 7 g. (27.6%). This material rapidly darkened on standing and was not analyzed.

The picrate from methanol, recrystallized from acetone–methanol, decomposed at 171–172°.

(11) A referee pointed out that X would be expected from IX without ring enlargement in view of R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.*, **24**, 336 (1959).

(12) S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, **71**, 896 (1949).

(13) W. H. Rodebush and I. Feldman, *ibid.*, **68**, 896 (1946).

(14) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 445.

(15) B. Elpern, *J. Am. Chem. Soc.*, **76**, 281 (1954).

(16) All melting points were determined in a Hirshberg-type apparatus with a 75-mm. immersion thermometer and are corrected.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.53; N, 15.72. Found: C, 44.0; H, 4.55; N, 15.68.

Hexahydro-1-methyl-4-phenyl-4-aminoazepine (VIII).—A solution of sodium hypobromite was prepared from 40 g. (0.25 mole) of bromine and 30 g. (0.75 mole) of sodium hydroxide in 250 ml. of water at 5°. To this solution was added in one lot, with stirring, 50 g. (0.2 mole) of hexahydro-1-methyl-4-phenylazepine-4-carboxamide (VII).[7] The temperature rose spontaneously to 46° with solution of most of the solid. The mixture was then heated at 84–90° for 0.5 hr., cooled, saturated with sodium carbonate, and extracted with chloroform. The chloroform solution was extracted with aqueous hydrochloric acid, the acid extract was made basic with sodium hydroxide, and the base was extracted by chloroform. The extract was dried over potassium carbonate, filtered, and distilled to give a pale yellow liquid (VIII), 12.9 g. (26.5%), b.p. 112–114 (0.3 mm.), $n^{27}D$ 1.5495, d^{27}_4 1.02.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71; MR (at the sodium D line), 64.1. Found: C, 76.00; H, 9.33; N, 13.28; MR 63.5.

The monopicrate, m.p. 168–169°, was formed in ether.

Anal. Calcd. for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.84; H, 5.31; N, 16.56.

Hexahydro-1-methyl-4-phenyl-4-azepinol (V).—A solution of 15.3 g. (0.075 mole) of VIII in 9 g. of glacial acetic acid and 75 ml. of water was mixed with a solution of 5.5 g. (0.08 mole) of sodium nitrite in 25 ml. of water. A slow evolution of gas occurred. The solution was allowed to stand at room temperature for 0.5 hr., then was heated at 85° for 2 hr., when gas evolution practically ceased. It was diluted with an equal volume of water, extracted with ether, made basic with sodium hydroxide, and again extracted with ether. This ether extract was dried over potassium carbonate, filtered, and distilled to give 7.0 g. (46%), b.p. 120–122° (0.3 mm.), $n^{26}D$ 1.5515. In the following reaction series this proved to be V.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.59; H, 9.26; N, 7.29.

In addition, a small unidentified forerun was obtained: 3.7 g., b.p. 102–106° (0.3 mm.), $n^{26}D$ 1.5532, picrate m.p. 187–189°.

Hexahydro-1-methyl-4-phenyl-4-acetoxyazepine (I). A. From Hexahydro-1-methylazepinone-4 (IV) by Reaction with Phenyllithium and Acetylation.—A solution of phenyllithium was prepared from 1 g. (0.15 g.-atom) of lithium shot and 12.6 g. (0.08 mole) of bromobenzene in 50 ml. of absolute ether under nitrogen. To this solution was added dropwise with stirring 6 g. (0.47 mole) of IV in 50 ml. of benzene. The reaction mixture was refluxed 2 hr., cooled to 5°, and 8 ml. (0.08 mole) of acetic anhydride in 25 ml. of benzene was added dropwise with stirring. The resulting mixture was refluxed 2 hr., cooled, and extracted with dilute hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide, and extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, and distilled to give 2.7 g. (23.4%) of I, b.p. 120–125° (0.3 mm.), $n^{29}D$ 1.5375. The methiodide, m.p. 215–217° dec., was formed in acetone, and a mixture melting point determination with the analyzed methiodide formed in B, m.p. 218–219° dec., showed no depression (215–217° dec.).

B. From Hexahydro-1-methyl-4-phenylazepine (VI) by Acetoxylation with Lead Tetraacetate.—Compound VI[6] (57 g., 0.30 mole) was added to 300 ml. of glacial acetic acid and the solution was stirred and heated to 85° under nitrogen. To this solution was added 146.4 g. (0.33 mole) of lead tetraacetate in portions and at a rate which held the temperature of the reaction between 85 and 100°. The exit gas, passed through barium hydroxide test solution, gave a white precipitate which dissolved in dilute acetic acid with evolution of gas. The exit gas, freed of carbon dioxide by passage through 20% sodium hydroxide, burned with a blue flame.

After gas evolution became negligible (0.5 hr. after the lead tetraacetate addition had been completed), about 200 ml. of acetic acid was distilled out of the reaction mixture under reduced pressure. The residue was cooled, and a cold solution of 78.4 g. (0.8 mole) of sulfuric acid in 300 ml. of water was added. The precipitated lead sulfate was collected on a filter, and the filtrate was poured into ice-cold saturated sodium carbonate solution and extracted with chloroform. The chloroform extract was dried over potassium carbonate, filtered, and distilled to give two fractions. (1) Compound VI was recovered in 33-g. yield, b.p. 100–110° (0.5 mm.), $n^{26.5}D$ 1.5290 (57%, b.p. 106–110° at 0.8 mm., $n^{27}D$ 1.5290[6]). (2) Compound I was produced in 15.5-g. yield, b.p. 147–152° (0.3 mm.), $n^{27}D$ 1.5273, apparent yield 20.9%. The methiodide, m.p. 218–219° dec., was formed in acetone.

Anal. Calcd. for $C_{16}H_{24}INO_2$: C, 49.37; H, 6.21; I, 32.60; N, 3.60. Found: C, 49.38; H, 6.54; I, 32.60; N, 3.38.

The picrate, m.p. 183–183.5°, was formed in methanol–ether and recrystallized from acetone–ethanol.

Anal. Calcd. for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.18; H, 5.36; N, 12.10.

C. From Hexahydro-1-methyl-4-phenyl-4-azepinol (V) by Acetylation.—A solution of 1 g. (0.005 mole) of V (from VIII), 5 g. of acetic anhydride (0.05 mole), and 1 drop of concentrated sulfuric acid in 60 ml. of benzene was refluxed for 3 hr., cooled, and extracted with dilute hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide, and extracted with ether. The ether extract was dried over potassium carbonate, filtered, and concentrated to an oil, which was converted to the crystalline methiodide, which crystallized from acetone, m.p. 220–221° dec. The mixture melting point (220–221° dec.) with the methiodide from B (218–219° dec.) established that they were the same.

1-Methyl-4-benzyl-1,2,5,6-tetrahydropyridine (X) and 1-Methyl-4-benzyl-4-piperidinol-4 (XI).—A solution of 5.5 g. (0.08 mole) and sodium nitrite in 25 ml. of water was added to a solution of 15.3 g. of 1-methyl-4-phenylpiperidinemethylamine[10] (IX) in 75 ml. of water and 9 g. of acetic acid. A spontaneous exothermic reaction occurred with evolution of nitrogen. After the initial reaction began to subside (0.5 hr.), the mixture was heated at 100° for 2 hr., cooled, made basic with sodium hydroxide, and extracted with ether. The extract was dried over potassium carbonate and distilled, to give two fractions. (1) A 7.8-g. yield, b.p. 95–110° (0.25 mm.), was redistilled to give 6.3 g. of a colorless liquid (X), b.p. 84–86° (0.2 mm.), $n^{24}D$ 1.5369. A solution of X in ethanol showed a small ultraviolet absorption maximum at λ_{max}^{EtOH} 2525 Å. (ϵ_{max} 530). The base darkened rapidly on standing, even under nitrogen, and was not analyzed.

The methiodide, m.p. 161–163°, was formed in ether and recrystallized from methyl ethyl ketone.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.10; H, 6.12; I, 38.5; N, 4.25. Found: C, 51.36; H, 6.38; I, 38.1; N, 4.18.

The picrate, m.p. 132–134°, was formed in methanol–ether.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84; N, 13.46. Found: C, 55.25; H, 5.12; N, 13.93.

(2) A 4.5-g. yield, b.p. 114–118° (0.25 mm.), $n^{26}D$ 1.5391, partially crystallized on standing. The solid was triturated with *n*-hexane and filtered to give 2.5 g. (16.3%) of XI, m.p. 77–78°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.29; H, 9.50; N, 6.71.

The picrate, m.p. 161–163°, was formed in methanol–ether.

1-Methyl-4-benzylpiperidine (XII)[12] from X.—A mixture of 0.46 g. (0.0025 mole) of X and 0.05 g. of platinum oxide in 15 ml. of methanol was shaken with hydrogen at 25° near atmospheric pressure. About 93% of the theoretical amount of hydrogen, determined volumetrically, was absorbed after 6 hr. The filtrate from this mixture was concentrated and diluted with ether. Addition of methyl iodide and recrystallization from acetone–methyl ethyl ketone gave the methiodide, m.p. 205–206° (lit.[12] m.p. 206–207°).

Dehydration of 1-Methyl-4-benzyl-4-piperidinol (XI) to X.—An intimate mixture of 0.5 g. of XI and 2 g. of fused potassium bisulfate was heated at 160–175° and 20 mm. for 15 min. The mixture was cooled, dissolved in water, made basic with sodium hydroxide, and extracted with ether. The extract was dried over potassium carbonate, filtered, and mixed with a solution of methyl iodide in acetone; the methiodide, m.p. 160–162°, crystallized. A mixture with the methiodide of X, obtained by the action of nitrous acid on IX, melted at 160–162°, showing that the two samples were identical.

1-Methyl-4-benzyl-4-acetoxypiperidine (XIII).—A solution of 0.5 g. (0.0025 mole) of XI, 2.5 g. (0.025 mole) of acetic anhydride, and 1 drop of concentrated sulfuric acid in 35 ml. of benzene was refluxed for 3 hr., then cooled and extracted with dilute hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide, and extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, and concentrated. The residual oil was taken up in a small volume of *n*-hexane and allowed to evaporate slowly, when XIII crystallized in colorless needles, m.p. 83–85°.

The picrate, m.p. 182–183°, formed in methanol–ether.

Anal. Calcd. for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.05; H, 5.13; N, 11.55.

The methiodide, m.p. 241–242°, formed in acetone–ether.

Acknowledgment.—We are indebted to Mr. Carl Gochman for excellent technical assistance and to Dr. G. H. Ellis and associates for analytical and optical data. We are grateful for the opportunity of acknowledging in this special issue many years of friendly and helpful connection with Professor Louis Frederick Fieser.

Organic Mass Spectrometry. I. Mass Spectra of Pteridine, Methylpteridines, and Hydroxypteridines*

TOSHIO GOTO,[1a] AKIRA TATEMATSU,[1b] AND SADAO MATSUURA[1c]

Chemical Institute and Department of General Education, Nagoya University, Chikusa, Nagoya, Japan, and Faculty of Pharmacy, Meijo University, Showa, Nagoya, Japan

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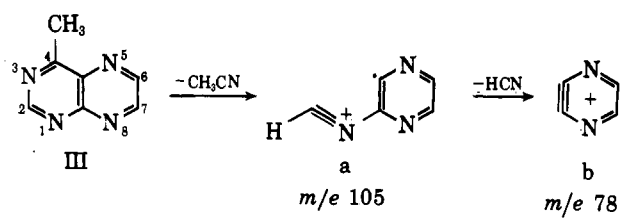
Mass spectra of pteridine, methylpteridines, and hydroxypteridines have been measured and the assignments have been made to the principal fragments by comparison with the spectra of some deuterium-labeled compounds.

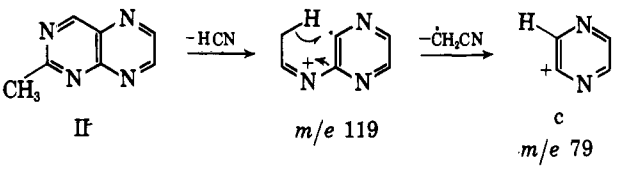
Compounds containing the pteridine nucleus are frequently found in nature.[2] However, structure determination of naturally occurring pteridines is usually limited by the small quantities of material available. Application of mass spectrometry to the structural problems of pteridine derivatives would, therefore, be highly desirable. In order to determine the principal fragmentation modes of the pteridine nucleus, the mass spectra of basic pteridine derivatives such as methyl- and hydroxypteridines as well as pteridine itself have been recorded.

Pteridine and Methylpteridines.—Mass spectra of pteridine, three methylpteridines, and a dimethylpteridine are given in Figure 1. These pteridines give a very intense molecular peak which is always the base peak. Their fragmentation patterns are not very complicated; the parent compound, pteridine (I), loses molecules of hydrogen cyanide successively, whereas an acetonitrile molecule is eliminated at some stage from the methyl derivatives II–V. However, since the pteridine molecule has four nitrogen atoms, each of which could be eliminated as hydrogen cyanide, the precise fragmentation processes cannot be determined without more extensive studies.

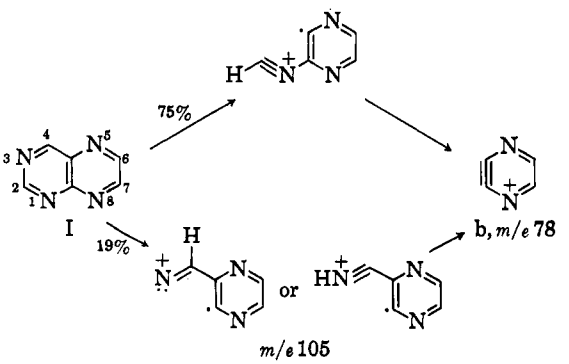
4-Methylpteridine (III) decomposes with the consecutive loss of molecules of acetonitrile and hydrogen cyanide and gives peaks at *m/e* 105 and 78. In this case the structure for the *m/e* 105 ion is limited to a and the fragment at *m/e* 78 must be the dehydropyrazine cation b, since no hydrogen cyanide is eliminated before an acetonitrile molecule is lost from the molecular ion (no peak at *m/e* 119).



2-Methylpteridine (II), however, eliminates hydrogen cyanide first to give an ion of *m/e* 119 which fragments in two ways: by the loss of acetonitrile (*m/e* 78) or by the elimination of a CH_2CN radical (*m/e* 79). The latter process can be explained by postulating a cyclic mechanism leading to the ion c.



That the C-4–N-3 part of the pteridine nucleus is eliminated most easily holds also in the fragmentation of pteridine itself. Thus, deuterium-labeling experiments show that 75% of the hydrogen cyanide which is first eliminated from pteridine comes from the C-4–N-3 part in the molecule and 19% from the C-2–N-1 part (Table I). The second molecule of hydrogen cyanide is abstracted mainly from the C-2–N-1 part and, thus, the peak at *m/e* 78 consists of mostly the dehydropyrazine cation b, but alternative pathways are also operating to a minor extent.



In the case of 7-methylpteridine (IV) the first step of the fragmentation is mainly loss of hydrogen cyanide. There are three CN groups, namely C-2–N-1, C-4–N-3, and C-6–N-5, each of which can give a molecule of hydrogen cyanide; the C-2–N-1 group, however, is not expected to be eliminated first by analogy with the behavior of pteridine. In order to determine which of the remaining CN groups is lost, the mass

* To Prosessor Louis F. Fieser.

(1) (a) Chemical Institute, Nagoya University; (b) Faculty of Pharmacy, Meijo University; (c) Department of General Education, Nagoya University.

(2) For a recent review on pteridines, see W. Pfleiderer, *Angew. Chem., Intern. Ed. Engl.*, **3**, 114 (1964).