The Preparation of Tetrahydropyridines from Enamines and Imines[1]

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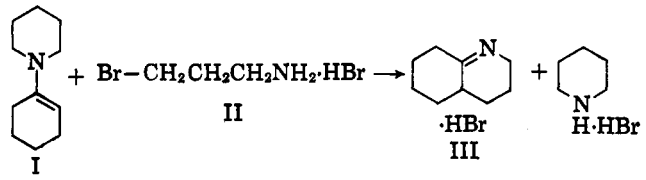
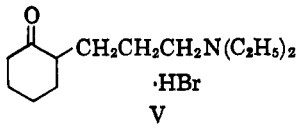
The reaction of 3-bromopropylamine hydrobromide with suitable enamines and imines in dimethylformamide has been shown to be a general route to tetrahydropyridines. These products have been aromatized to pyridines, reduced to piperidines, and, in certain cases, oxidized to unsaturated peroxides which were reduced to amino alcohols.

In a preliminary communication[2] the preparation of $\Delta^{1,9}$-octahydroquinoline (III) in one step in 80–84% yield by the reaction of 3-bromopropylamine hydrobromide (II) with 1-(1-cyclohexen-1-yl)piperidine (I) in dimethylformamide (DMF) was reported. While the C-alkylation of enamines with alkyl halides is well



I + Br−$CH_2CH_2CH_2N(C_2H_5)_2$·HBr ⟶ (no reaction)

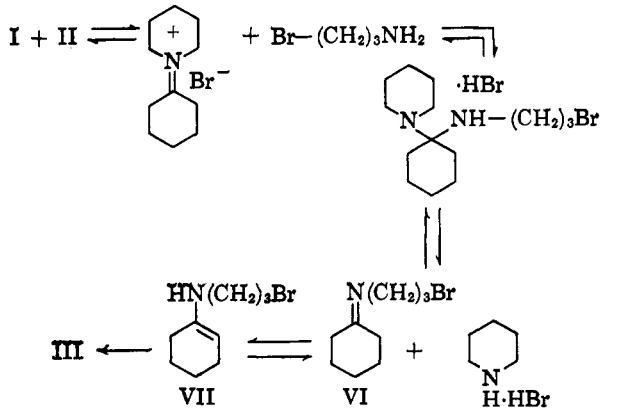
IV



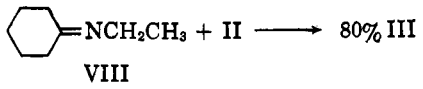
V

known,[3] the present reaction does not appear to be of this simple type, since N,N-diethyl-3-bromopropylamine hydrobromide (IV) does not react with I under the same conditions to yield isolable amounts of 2-(3-diethylaminopropyl)cyclohexanone (V).

We postulate that the reaction involves preliminary donation of a proton from the 3-bromopropylammonium ion to the more basic enamine,[4] addition of 3-bromopropylamine to the resulting enamine salt,[5] elimination of piperidinium ion to form N-cyclohexylidene-3-bromopropylamine (VI), equilibration to its enamine form (VII), and, finally, intramolecular C-alkylation. That the conversion of an enamine to an imine can occur was

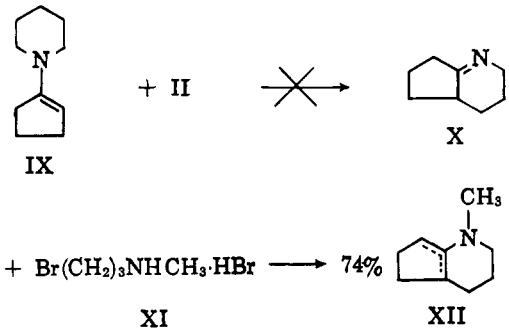


demonstrated by warming equivalent amounts of I and butylamine hydrobromide together in DMF; dilution with ether precipitated an 84% yield of piperidine hydrobromide, and distillation of the filtrate gave an appreciable yield of N-cyclohexylidenebutylamine. The preparation of III in 80% yield using N-cyclohexylideneethylamine (VIII) in place of I shows that imines also undergo this cyclization reaction.

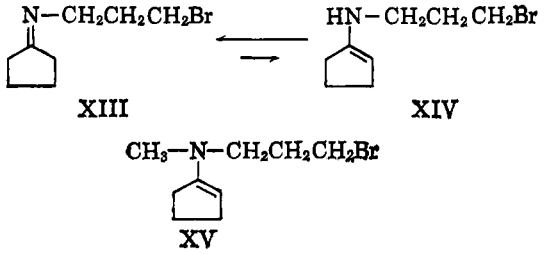


VIII

It is interesting that, while II does not react with 1-(1-cyclopenten-1-yl)piperidine (IX) to produce 2,3,4-4a,6,7-hexahydro-5*H*-1-pyrindine (X), N-methyl-3-bromopropylamine hydrobromide (XI) yielded 74% of the N-methyl derivative XII. Here, apparently,



when the primary aminoalkyl halide is employed, the enamine–imine equilibrium does not favor enamine XIV whereas the desired cyclization does occur with XV, where the enamine form must be present. It also has been found that neither 2-bromoethylamine hydro-



bromide nor N-ethyl-2-bromoethylamine hydrobromide reacts with I to give analogous pyrrolines. This may well be due to rapid, competing side reactions of the bromoethylamines; it has not been studied further.

We have now extended this reaction to a variety of enamines and imines and have found it to be quite general within some steric and stability limits. The enamines and imines prepared are listed in Table I together with their physical properties and methods of preparation. In several cases where imines could be

(1) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

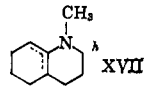
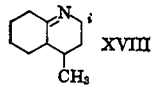
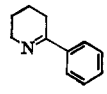
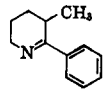
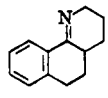
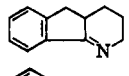
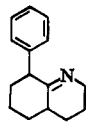
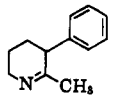
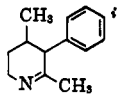
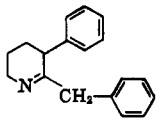
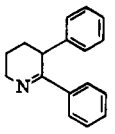
(2) R. F. Parcell, *J. Am. Chem. Soc.*, **81**, 2596 (1959).

(3) *Inter alias* J. N. Collie, *Ann.*, **226**, 316 (1884); R. Robinson, *J. Chem. Soc.*, **109**, 1038 (1916); G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(4) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

(5) The addition of nucleophiles to enamine salts is discussed by N. J. Leonard and A. Hay, *ibid.*, **78**, 1984 (1956).

TABLE I
CYCLIZATIONS

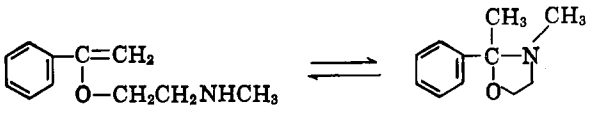
Ketone	Derivative[a]	Solvent	B.p., °C. (mm.)	Yield, %	Cyclization product[b]	B.p., °C. (mm.)	Yield, %
Cyclopentanone	Piperidineenamine	Benzene	85–88 (6)	82	X		0
					XII[h]	65–66 (6)	74
Cyclohexanone	Piperidineenamine	Toluene	109–110 (9)	90	III	76–79 (6)	80–84
	Pyrrolidineenamine	Benzene	115–117 (17)	93	III		77
	N-Methyloxazolidine[c,f]	Benzene	97–98 (25)	79	III		77
	N-Ethylimine[d]				III		82
	Piperidineenamine				 XVII	82–84 (6)	73
	Piperidineenamine				 XVIII	108–110 (19)	65
Acetophenone	α-Methylbenzylimine[e]	Xylene	103–107 (0.15)	80	 XIX	76–80 (0.25)	43–51
	"N-Methyloxazolidine"[f]		62–64 (0.25)	66	XIX	82–85 (0.25)	58
Propiophenone	Piperidineenamine	Toluene	95–97 (1)	40–50	 XX	78–79 (0.25)	77–84
	Pyrrolidineenamine	Benzene	75–78 (0.2)	44	XX		58
	Benzylimine	Xylene	125–128 (0.25)	83	XX		58
1-Tetralone	Piperidineenamine	Toluene	120–125 (0.7)	75	 XXI	110–115 (0.3)	84
	Benzylimine	Xylene	Not isolated		XXI		92
1-Indanone	Piperidineenamine	Toluene	120–126 (0.6)	69	 XXII	100–102 (0.25)	73
2-Phenylcyclohexanone	Piperidineenamine	Toluene	105–110 (0.06)	46	 XXIII	104–107 (0.15)	86
	Pyrrolidineenamine	Benzene	110–112 (0.1)	85–90	XXIII		80–86
Phenylacetone	Pyrrolidineenamine[g]	Ether	105–108 (0.25)	77–78	 XXIV	94–97 (1)	66–72
					 XXV	85–88 (0.3)	44
1,3-Diphenylacetone	Benzylimine	Toluene	Not isolated		 XXVI	150–152 (0.5)	75
Desoxybenzoin	Benzylimine	Toluene	Not isolated		 XXVII	148–152 (0.5)	73

[a] Method of F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953), except as noted, and, in most cases, catalyzed by *p*-toluenesulfonic acid. [b] 3-Bromopropylamine hydrobromide used except as noted. [c] Sample by courtesy of Dr. D. E. Butler. [d] R. F. Parcell, U. S. Patent 2,921,076 (January 12, 1960). [e] C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961). [f] E. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 237 (1952). [g] C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936). [h] N-Methyl-3-bromopropylamine hydrobromide used. [i] 3-Bromobutylamine hydrobromide used.

prepared in markedly shorter heating periods than the corresponding enamines, the imines were used with no adverse effect on over-all yield. Furthermore, the N-methylethanolamine derivatives of cyclohexanone and acetophenone have been substituted successfully for enamines as starting materials. While the cyclohexanone derivative actually was the expected N-methyloxazolidine,[6] acetophenone gave a product which appeared to be about a 50–50 mixture of open chain enol

(6) E. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 237 (1952).

ether and N-methyloxazolidine (XVI) on the basis of its infrared and ultraviolet spectra (see Experimental). The only other derivative of acetophenone which



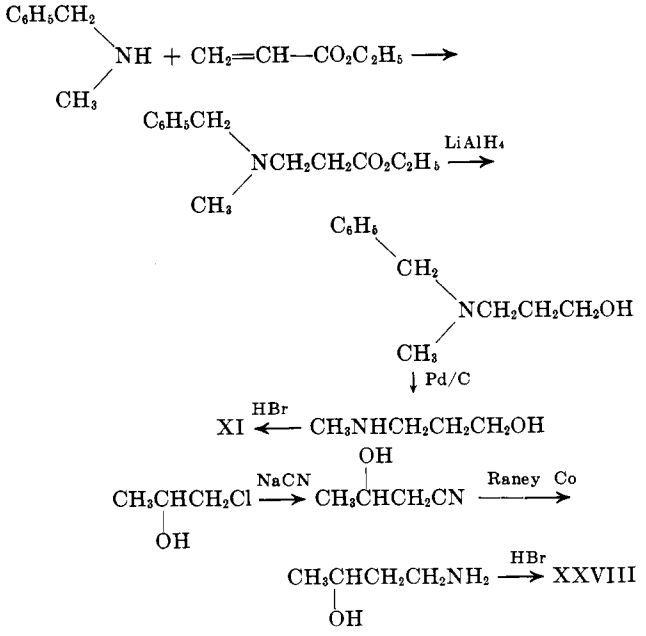
XVI

proved useful was the α-methylbenzylimine,[7] since stable enamines could not be prepared.

These carbonyl derivatives were treated with slightly less than an equivalent of 3-bromopropylamine hydrobromide in DMF (300 ml./mole) under a protective blanket of nitrogen. The mixture also was protected from air during reaction and work-up when the sensitivity of the products required it. After the reaction had been started on the steam bath, cooling was usually necessary to keep the temperature below 110°. Reaction was then completed on the steam bath. Table I lists the cyclizations with 3-bromopropylamine hydrobromide. The products were not analyzed directly because of their air sensitivity, but were characterized by boiling points and infrared spectra, then converted to aromatized, reduced, and, in some cases, air-oxidized derivatives (*vide infra*). Several other aminoalkyl bromide hydrobromides were tried to test further the scope of the cyclization (Table I).

It will be seen from Table I that the cyclization is generally successful with aminopropyl bromide hydrobromides and gives moderate to excellent yields with a variety of ketones. A relatively simple method is thus at hand for converting a ketone to the corresponding tetrahydropyridine.

While most of the aminohalides used in this study were available commercially, two required preparation. N-Methyl-3-bromopropylamine hydrobromide[8] (XI) and 3-bromobutylamine hydrobromide[9] (XXVIII) were prepared as shown.

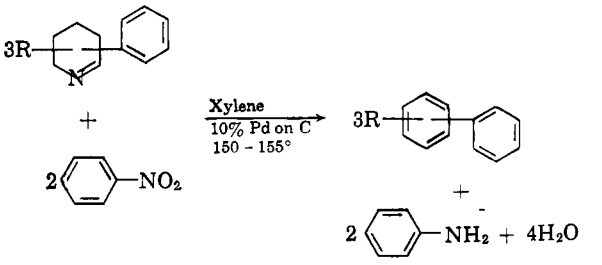


(7) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.* **83**, 1374 (1961).

(8) J. Cowan and C. S. Marvel, *ibid.*, **58**, 2277 (1936).

(9) M. de Montmollin and E. Zolliker, *Helv. Chim. Acta*, **12**, 613 (1929).

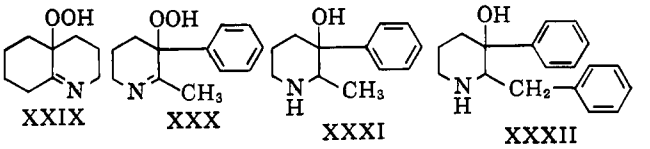
Aromatization of the tetrahydropyridines was carried out by a method similar to that of Schmidle and Mansfield.[10] A mixture of the tetrahydropyridine, nitrobenzene, xylene, and 10% palladium on charcoal was



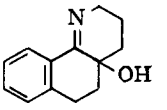
heated at reflux under a water trap until the volume of water produced indicated that the reaction was essentially complete. The basic products were isolated by acid extraction of the reaction mixture and were separated by distillation. In some cases more than two double bonds were introduced to achieve complete aromatization. This procedure works well even on a several mole scale and represents a marked improvement in many cases over previous routes. Table II lists these reactions together with analytical data for some derivatives used to characterize further the products.

Reduction of the tetrahydropyridines was carried out either catalytically or chemically with a metal hydride. These reactions are summarized in Table III together with some derivatives of the piperidines obtained. In some cases, mixtures of stereoisomers were obtained, and this fact is reflected in the wide melting points of their analytically pure salts.

Several tetrahydropyridines were further characterized by their reaction with oxygen or peroxide. Cohen and Witkop[11] studied the air oxidation of III, which yielded the hydroperoxide XXIX. When air was bubbled through a hexane solution of XXIV, a 98% crude yield of hydroperoxide XXX precipitated. This was reduced over palladium on charcoal to XXXI.



In like manner XXVI was converted to XXXII. Compound XXI behaved somewhat differently, however, yielding the unsaturated alcohol XXXIII directly on being air-oxidized or treated with *t*-butyl hydroperoxide. In this case, apparently, the intermediate



XXXIII

peroxide is able to oxidize another molecule of imine. Each of the three piperidine alcohols was converted to its N-methyl derivative.

Experimental

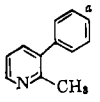
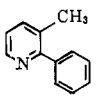
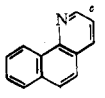
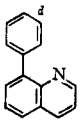
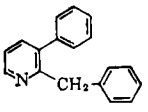
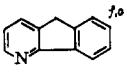
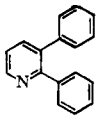
All of the ketones and all but two of the amino halides used in this study are available commercially. The preparations of the enamines and imines are listed in Table I.

(10) C. Schmidle and R. Mansfield, *J. Am. Chem. Soc.*, **78**, 1702 (1956).

(11) L. A. Cohen and B. Witkop, *ibid.*, **77**, 6595 (1955).

TABLE II

AROMATIZATIONS

Imine	Time	Product	B.p., °C. (mm.)	Yield, %	Ultraviolet data[g] λ_{max}	mμ	$\epsilon \times 10^{-3}$	Derivative	M.p., °C.	Formula	Calcd. (found) C	H
XXIV	18–24 hr.	 [a]	90–95 (0.1)	93	CH_3OH	267	4.52	Perchlorate	135–137	$C_{12}H_{11}N \cdot HClO_4$	53.44 (53.75)	4.49) (4.50)
						234	8.79					
					$+H^+$	278	5.34					
						232	10.70	N-Oxide	75–76	$C_{12}H_{11}NO$	77.81 (78.04)	5.99 (6.07)
XX	18 hr.	 [b,m]	95–100 (0.2)	76	CH_3OH[h]	273	6.60	Perchlorate	137–138	$C_{12}H_{11}N \cdot HClO_4$	53.44 (53.35)	4.49 (4.40)
						233	8.70					
					$+H^+$	286	9.27					
						228	Sh	N-Oxide	167–168	$C_{12}H_{11}NO$	77.81 (77.89)	5.99 (6.01)
XXI	2.5 hr.	 [c]	135–141 (0.2)	92	CH_3OH[i]	345	2.70	Perchlorate	189–190	$C_{13}H_9N \cdot HClO_4$	55.82 (55.69)	3.61 (3.52)
						330	2.24					
						315	1.47					
						265	20.90					
						232	37.50					
XXIII	4 days	 [d]	128–133 (0.15)	85	CH_3OH[j,k]	302	5.41	Perchlorate	215–216	$C_{15}H_{11}N \cdot HClO_4$	58.93 (58.93)	3.95 (3.87)
						296	5.43					
						232	2.62					
XXVI	4 hr.		160–165 (0.75)	89	CH_3OH	266	5.07	Perchlorate	138–140	$C_{18}H_{15}N \cdot HClO_4$	62.52 (62.62)	4.66 (4.33)
						261	5.15					
					$+H^+$	278	6.25					
						232	10.26					
XIX	3 hr.	 [e]	90–93 (1.0)	92	CH_3OH[l]	276	10.66	Perchlorate	137–138	$C_{11}H_9N \cdot HClO_4$	51.67 (51.69)	3.94 (3.81)
						243	13.25					
					$+H^+$	297	15.22					
						243	8.40	N-Oxide	158–159	$C_{11}H_9NO$	77.17 (77.42)	5.30 (5.37)
XXII	3 hr.	 [f,o]	110–112 (0.8)	85	CH_3OH[f]	307	16.54	Hydrochloride	263–264	$C_{12}H_9N \cdot HCl$	70.77 (70.88)	4.95 (4.96)
						282.5	8.95					
						250	10.26					
					$+H^+$	323	20.80	N-Oxide	163–164	$C_{12}H_9NO$	78.67 (78.73)	4.95 (4.74)
						250	5.48					
XXVII	4 hr.		137–138 (0.3)	94	CH_3OH	279	8.58	Hydrochloride	211–213	$C_{17}H_{13}N \cdot HCl$	76.25 (76.14)	5.28 (5.39)
						252	10.07					
					$+H^+$	303	7.16					
						259	9.22					

[a] Takeo Ishiguro, Japanese Patent 6382 (1960). [b] R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960). [c] Skraup, *Monatsh.*, **2**, 162 (1881). [d] C. E. Kaslow and M. Hayek, *J. Am. Chem. Soc.*, **73**, 4986 (1951). [e] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 349 (1940). [f] J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.*, **32**, 371 (1955). [g] Ultraviolet data obtained on a Cary recording spectrophotometer Model 11 and the $+H^+$ data, by addition of a drop of 1 *N* H_2SO_4 to the methanolic solution used for the CH_3OH data. [h] Identical with that of a sample prepared by the method of *b*. [i] $+H^+$, 365 (3.33); 351 (3.29); 307 (4.97); 280 (2.44); 223 (40.10). [j] $+H^+$, 328 (infl.); 316 (4.72); 240 (52.66). [k] Identical with that of a sample prepared by the method of *d*. [l] P. Krumholz, *J. Am. Chem. Soc.*, **73**, 3487 (1951). [m] Also converted to 2-phenylnicotinic acid,[n] m.p. 168–169°. [n] R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Tetrahedron Letters*, 1 (1959). [o] Also converted to 4-azafluorenone,[b] m.p. 139.5–140°.

N-Methyloxazolidine Derivative of Acetophenone.[6]—A mixture of 240 g. (2.0 moles) of acetophenone, 180 g. (2.4 moles) of N-methylethanolamine, and 2 g. of *p*-toluenesulfonic acid in 250 ml. of xylene was heated at reflux under a water trap until *ca.* 50 ml. of aqueous phase was collected. Two 30-g. portions of N-methylethanolamine were added to the pot, and 50 ml. of aqueous phase was collected after each addition. Total heating time was 4 hr. The mixture was then distilled to yield 270 g. of desired product, collected at 67–87° (0.3 mm.). Redistilled, it had b.p. 62–64° (0.25 mm.) and amounted to 236 g. It exhibited an infrared maximum at 5.94 μ (C=C), and ultraviolet maxima at 279 (ε 239) and 241 mμ (3045). α-Methoxystyrene also exhibited ultraviolet maxima at 279 (ε 492) and 241 mμ (6000).[12]

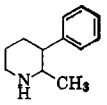
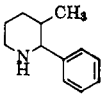
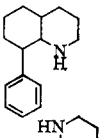
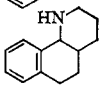
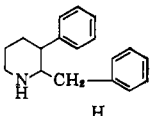
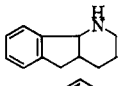
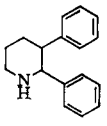
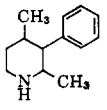
Preparation of N-Methyl-3-bromopropylamine Hydrobromide (XI). **A. 3-(N-Benzyl-N-methylamino)propanol.**—A solution of 620 g. (5.12 moles) of benzylmethylamine in 1 l. of absolute alcohol was chilled to 10° in an ice bath. This was treated with 550 g. (6.4 moles) of methyl acrylate all at once and the resulting solution left in the ice bath for 24 hr. (ice allowed to melt). Solvent was removed on a rotary evaporator, the mixture diluted to 2.5 l. with benzene, and solvent was again removed. The residual liquid was diluted with ether and added dropwise to a stirred slurry of 160 g. (4.3 moles) of lithium aluminum hydride in 7 l. of ether over 3 hr. The mixture was stirred 1 hr. longer and allowed to stand overnight. It was then decomposed with 168 ml. of water, 125 ml. of 50% sodium hydroxide, and 590 ml. of water added dropwise in succession. The resulting precipitate was filtered off and washed with ether. The combined filtrates were evaporated and the residue distilled. There was obtained 841 g. (92%), b.p. 98–100° (0.25 mm.).

B. 3-Methylaminopropanol.—The preceding product was reduced in methanol over 20% palladium on charcoal at 3–4 atm. of hydrogen. There was obtained 372 g. (89%), b.p. 74–76° (10 mm.).

C. XI.—The preceding product was mixed carefully with 1500 ml. of 48% hydrobromic acid and the resulting solution heated at reflux under an efficient Vigreux column with a partial take-off head. Water was removed as formed below 105°. A total of 840 ml. was removed in 7 hr. (theory, 810 ml.). The residual liquid was evaporated under water pump pressure as far as possible without allowing the residue to be heated over 120° or until fuming began. The residue was cooled and triturated with

(12) D. E. Butler, private communication.

TABLE III
REDUCTIONS

Compound reduced	Method	Product	B.p., °C. (mm.)	Yield, %	Derivative	B.p., (mm.) or M.p., °C.	Formula	Calcd. (found) C	Calcd. (found) H
XXIV	Pd/C		[a]	82[b]	·HCl	208–209	$C_{12}H_{17}N \cdot HCl$	68.07 (68.06)	8.57 (8.73)
					N-CH_3·HCl	225–227	$C_{13}H_{19}N \cdot HCl$	69.16 (69.09)	8.93 (9.23)
XX	Pd/C		86–88 (1.0)	88	·HCl	214–215	$C_{12}H_{17}N \cdot HCl$	68.07 (68.23)	8.57 (8.51)
					N-CH_3·HCl	177–178	$C_{13}H_{19}N \cdot HCl$	69.16 (69.03)	8.93 (8.94)
XVII	Pd/C		70–71 (6)	68	Picrate[c]	199–201	$C_{10}H_{19}N \cdot C_6H_3N_3O_7$	50.25 (50.35)	5.80 (5.71)
XXIII	Pd/C		118–120 (0.7)	74	Picrate	203–206	$C_{15}H_{21}N \cdot C_6H_3N_3O_7$	56.75 (56.67)	5.44 (5.42)
XXI	$NaBH_4$ or PtO_2		96–97 (0.2)	94	·HCl	212–239	$C_{13}H_{17}N \cdot HCl$	69.78 (69.77)	8.11 (8.23)
					N-CH_3	84 (0.15)	$C_{14}H_{19}N$	83.53 (83.56)	9.51 (9.61)
XXVI	$NaBH_4$		137–138 (0.3)	94	·HCl	200–220	$C_{18}H_{21}N \cdot HCl$	75.11 (75.29)	7.71 (7.84)
					N-CH_3	136 (0.3)	$C_{19}H_{23}N$	85.99 (85.98)	8.73 (8.96)
XXII	$LiAlH_4$		77 (0.2)	75	·HCl	223–224	$C_{12}H_{15}N \cdot HCl$	68.72 (68.68)	7.69 (7.58)
XXVII	$NaBH_4$	 [d]	129–130 (0.3) M. p. 85–87	88	·HCl	242–245	$C_{17}H_{19}N \cdot HCl$	74.57 (74.73)	7.36 (7.48)
					N-CH_3·HCl	184–189	$C_{18}H_{21}N \cdot HCl$	75.11 (74.84)	7.71 (7.61)
XXV	$NaBH_4$		137–137.5 (19)	82			$C_{13}H_{19}N$	82.48 (82.26)	10.12 (10.28)

[a] E. Schultz, U. S. Patent 2,636,881 (April 28, 1953), gives b.p. 75–79° (0.5). [b] Isolated as the hydrochloride. [c] M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1715 (1934). [d] S. Sugasawa and S. Ushioda, *Tetrahedron*, **5**, 48 (1959), report m.p. 86.5–87.5°.

an acetone–ether mixture. There was obtained 885 g. (91%), m.p. 64–68°.[8]

Preparation of 3-Bromobutylamine Hydrobromide (XXVIII). **A. β-Hydroxybutyronitrile.**—A solution of 202 g. (4.12 moles) of sodium cyanide in 300 ml. of water was added all at once to a solution of 344 g. (3.62 moles) of 1-chloro-2-propanol in about 600 ml. of acetone. When the resulting solution was heated to 50°, an exothermic reaction started. After this stopped, the solution was heated under reflux for 0.5 hr., then stirred for 5 hr. longer, and let stand overnight. After filtration, the solution was evaporated *in vacuo* up to 55–60°. The residue was diluted with 1.5 l. of ether and dried over magnesium sulfate. Distillation yielded 288 g. (93%), b.p. 98–100° (10 mm.).[13]

B. 3-Hydroxybutylamine.—A solution of 255 g. (3.0 moles) of the preceding compound in toluene was reduced over Raney cobalt in the presence of a large excess of ammonia at 2000 p.s.i. Twice distilled, the product had b.p. 75–76° (8.5 mm.) and amounted to 234 g. (88%).

C. XXVIII.—By the preceding procedure used for XI, 424 g. (4.75 moles) of 3-hydroxybutylamine and 2 l. of 48% hydrobromic acid yielded, with a 48-hr. heating period, 346 g. of desired product, m.p. 168–180°.[9]

Cyclization Reaction.—To a solution of 1.0 mole of bromoalkylamine hydrobromide in 300 ml. of dimethylformamide in a 1 l. flask was added all at once with swirling 1.1 moles of enamine or imine. The flask was stoppered with a thermometer-bearing plug and warmed on the steam bath to initiate reaction. When an exothermic reaction began, the reaction temperature was maintained at 100–110° by cooling at the tap when necessary. After the exothermic reaction subsided, the mixture was again heated on the steam bath to complete the reaction—several hours for only slightly exothermic reactions, 0.5–1 hr. for very exothermic ones. The product was isolated by pouring the mixture into 1 l. of water containing 25–100 ml. of concentrated hydrochloric acid, washing with ether to remove nonbasic materials, adding excess 50% sodium hydroxide (carefully, under a layer of ether), and extracting with ether. The ether extracts were dried over magnesium sulfate and distilled. In many cases, a nitrogen blanket was used during the reaction and work-up because of the air sensitivity of the starting material or product.

Aromatizations.—A mixture of 0.5 mole of tetrahydropyridine compound, 250 ml. of xylene, 250 ml. of nitrobenzene, and 10 g. of 10% palladium on charcoal was heated at reflux under a water trap until no more water collected. After cooling, the mixture was filtered to remove catalyst, then extracted several times with dilute hydrochloric acid. The combined extracts were washed with ether, then rendered basic with solid potassium carbonate, and extracted three times with ether. The combined ether extracts were dried over magnesium sulfate and distilled. After aniline was removed at water pump pressure, the desired product was distilled under mechanical pump pressure.

Reduction of the Tetrahydropyridines.—Only one example of each type will be recorded.

A. Catalytic. 3-Methyl-2-phenylpiperidine.—A solution of 70 g. (0.40 mole) of 3-methyl-2-phenyl-3,4,5,6-tetrahydropyridine (XX) in absolute ethanol was reduced over 5% palladium on charcoal at 3–4 atm. of hydrogen. The mixture was filtered to remove catalyst and distilled. The product had b.p. 86–88° (1.0 mm.) and amounted to 62 g. (88%).

B. Metal Hydride. 2,3-Diphenylpiperidine.—A solution of 70.5 g. (0.30 mole) of imine XXVII in 300 ml. of absolute ethanol

(13) A. Dewael, *Bull. soc. chim. Belges*, **33**, 504 (1924), reports 60% yield' b.p. 214-215°.

was treated portionwise with 12 g. (0.32 mole) of sodium borohydride without cooling. After standing for 1.5 hr., the mixture was evaporated on the steam bath. The residue was treated cautiously with 100 ml. of acetone and, when the exothermic reaction stopped, was diluted with 750 ml. of water and 50 ml. of 40% sodium hydroxide. The product was extracted into ether, washed with water, dried over caustic pellets, and distilled to provide 62.5 g. (88%), b.p. 129–130° (0.3 mm.).

2-Methyl-3-phenyl-3,4,5,6-tetrahydropyridine Hydroperoxide (XXX).—Air was bubbled rapidly through a solution of 100 g. (0.58 mole) of imine XXIV in 1 l. of cyclohexane with occasional swirling for 20 hr. All solvent had evaporated in this time. The residue weighed 116 g. (98%), m.p. 118–119° dec.

3-Hydroxy-2-methyl-3-phenylpiperidine (XXXI).—The preceding hydroperoxide XXX in 1 l. of dioxane was hydrogenated over 20% palladium on charcoal at 3–4 atm. of hydrogen. The residue obtained on evaporation of the solvent was triturated with petroleum ether (b.p. 35–60°), chilled, and filtered to provide 94 g., m.p. 86–98°, cloudy to 118°. The product was purified by solution in dilute acetic acid, washing with ether, reprecipitation with sodium hydroxide, ether extraction, drying, evaporation of the solvent, and trituration with petroleum ether, m.p. 95–101°. This was used as is for derivatives.

N-Formyl-3-hydroxy-2-methyl-3-phenylpiperidine.—A solution of 43 g. (0.22 mole) of XXXI in 100 ml. of benzene and 150 ml. of ethyl formate was heated under reflux for 30 hr., then chilled, and filtered to give 44 g., m.p. 153–156°. After recrystallization from toluene, it had m.p. 155–157° and amounted to 42 g. (86%).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 70.98; H, 7.80.

1,2-Dimethyl-3-hydroxy-3-phenylpiperidine.—A solution of 39 g. (0.18 mole) of the previous compound in 500 ml. of dioxane was added dropwise to a stirred slurry of 19 g. of lithium aluminum hydride in 1 l. of ether. After 20 hr. of stirring, the mixture was decomposed in the usual manner and filtered. The filtrate was distilled to give 28.5 g. of product collected at 103–105° (0.6 mm.). Redistilled, the material had b.p. 97–98° (0.3 mm.) and amounted to 23 g. (63%).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 75.94; H, 8.98.

2-Benzyl-3-phenyl-3,4,5,6-tetrahydropyridine Hydroperoxide.—Air was bubbled rapidly through a solution of 100 g. (0.40 mole) of the imine XXVI in 1 l. of cyclohexane for 20 hr. The mixture was diluted with petroleum ether and filtered.

2-Benzyl-3-hydroxy-3-phenylpiperidine (XXXII).—The crude damp product obtained before was reduced in dioxane over 20% palladium on charcoal under 3–4 atm. of hydrogen. The residue from evaporation of the filtered solution was taken up in ether and shaken with 150 ml. of 6 *N* hydrochloric acid. The precipitated hydrochloride was filtered off, washed with 1:1 isopropyl alcohol–ether, and dried. It amounted to 72 g. (60% for two steps) and had m.p. 195–203°. An analytical sample recrystallized from isopropyl alcohol–ether had m.p. 210–211°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$: C, 71.15; H, 7.30. Found C, 71.37; H, 7.47.

2-Benzyl-3-hydroxy-1-methyl-3-phenylpiperidine.—A mixture of 12 g. (0.045 mole) of the preceding amine (liberated from the hydrochloride), 8 ml. of 37% formalin, and 15 ml. of 98% formic acid was heated on the steam bath for 4 hr., then diluted to 200 ml. with water, rendered basic, and extracted with ether. The combined extracts were washed with water, dried over caustic pellets, filtered and evaporated. The residue was converted to the hydrochloride. There was obtained 11 g. (77%), m.p. 147–155°. After two recrystallizations from isopropyl alcohol–ether, 10 g. remained, m.p. 220° dec.

Anal. Calcd. for $C_{19}H_{23}NO \cdot HCl$: C, 71.79; H, 7.61. Found: C, 71.52; H, 7.59.

Preparation of 2,3,4,4a,5,6-Hexahydro-4a-hydroxybenzo[*h*]-quinoline (XXXIII). A. *Via* Air Oxidation of XXI.—A solution of 50 g. (0.27 mole) of the imine XXI in 1 l. of cyclohexane was treated with a vigorous stream of air through a pipet. When all solvent had evaporated, a solid residue remained which melted at 113–130°, and weighed 48 g. (89%). After several recrystallizations from benzene–petroleum ether, there was recovered 31.5 g., m.p. 131–134°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.54; H, 7.51; N, 6.96. Found: C, 77.64; H, 7.53; N, 6.90.

B. *Via* Oxidation of XXI with *t*-Butyl Hydroperoxide.—A solution of 37 g. (0.20 mole) of XXI in 100 ml. of benzene was warmed to 70° and treated all at once with 25 g. of *t*-butyl hydroperoxide. The resulting solution was evaporated to dryness on the steam bath during 1 hr. The residue was triturated with petroleum ether and filtered. There was obtained 34 g. (85%), m.p. 129–134°.

1,2,3,4,4a,5,6,10b-Octahydro-4a-hydroxybenzo[*h*]quinoline.—A solution of 90 g. of XXXIII in methanol was reduced over platinum dioxide under 3–4 atm. of hydrogen. The filtered solution was evaporated, the residue taken up in 300 ml. of hot benzene, and petroleum ether added to turbidity at the boiling point. The mixture was chilled and filtered. There was obtained 41 g. of product, m.p. 125–131°. After recrystallization from benzene–petroleum ether, there was recovered 36.5 g. of material, m.p. 132–133.5°. (The combined mother liquors yielded 46 g. of material contaminated with the other isomer which did not crystallize.)

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 77.06; H, 8.55.

N-Methyl-1,2,3,4,4a,5,6,10b-octahydro-4a-hydroxybenzo[*h*]-quinoline.—A mixture of 26 g. (0.128 mole) of the preceding crystalline material, 12 ml. of 37% formalin, and 30 ml. of 98% formic acid was heated under reflux for 4.5 hr., then diluted with 500 ml. of water, rendered basic, and extracted with ether. The extracts were washed with water, dried over caustic pellets, and evaporated. The residue had m.p. 126–131° and amounted to 26.5 g. (95%). A sample recrystallized from benzene–petroleum ether had m.p. 129–131°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.26; H., 8.97.

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