R′ = $C_6H_5CH_2$—) on the basis of elemental analysis and analogy to the diazomethane reactions.[13] A very small amount of lower boiling material, whose infrared spectra indicated the possible presence of pyrazoline was also obtained but decomposed very rapidly. The spectra of the reaction product before distillation exhibited little difference from the combined spectra of the distillation fractions. Reaction of ethyl α-cyanocinnamate with phenyldiazomethane also gave a compound of type IV as the major product.

EXPERIMENTAL

Reagents. The authors thank Kay-Fries Chemicals, Inc., and Fisher Chemical Co., Inc., for generous gifts of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification. Thanks to Union Carbide Chemicals Co. and Abbott Labs. for samples of some of the aldehydes. We should also like to thank the DuPont Company for a generous gift of EXR-101,[14] which was used to generate the diazomethane, and Dr. W. M. Jones for unpublished directions on the preparation of phenyldiazomethane.

(13) A referee has suggested that this compound may be a cyclopropane. It has been found to decolorize potassium permanganate and to react with bromine in carbon tetrachloride at the same rate as the unsaturated starting material. In comparison, several cyclopropyl compounds reacted with the bromine at a different rate and did not decolorize permanganate. It would seem therefore that this material has the same structure as the diazomethane reaction products.

(14) Contains 70% of *N,N′*,-dinitroso-*N,N′*,-dimethylterephthalamide.

Compounds II. *Method A.* A mixture of 0.6 mole of ethyl cyanoacetate and 0.6 mole of the aldehyde in 80 ml. of glacial acetic acid was treated with a solution of 2 ml. of piperidine in 20 ml. of glacial acetic acid and allowed to stand at ambient temperature. After 24 hr. at room temperature, the mixture was diluted with 200 ml. of water and extracted with three 200-ml. portions of benzene. The combined extracts were washed with water and dried over magnesium sulfate. After removal of the solvent on the steam bath, the residue was distilled.

Compounds II. *Method B.* The reaction in dioxane was carried out as described previously.[1] If the product was not a solid, the solvent was removed *in vacuo* and the residue distilled.

Reaction of II *with diazomethane.* An ethereal solution of compound II was added to an excess of diazomethane in ether in an ice bath[15] and the solution kept for at least 16 hr. at 0 to 5°. This solution was concentrated *in vacuo* without heating and the infrared spectra obtained. Solids were then recrystallized from 95% ethanol and liquids distilled.

Reaction of II (*R′* = $(C_2H_5)_2CH$—) *with phenyldiazomethane.* A solution of II was added to an excess of phenyldiazomethane in petroleum ether (b.p. 35–55°) and kept at about 5° for 24 hr. The solution was concentrated at 250 ml. *in vacuo* and the precipitated azine filtered. The mixture was concentrated further and distilled to give a 20% yield of a liquid, b.p. 168–169° (2.2 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.60; H, 7.92.

Acknowledgment. We acknowledge the assistance of H. Swarz and J. Pattee in the preparation of the diazomethane.

CORAL GABLES, FLA.

(15) Addition of the diazomethane solution to the solution of II gave identical results, as did the use of a methanol–ice bath for cooling.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS INC.]

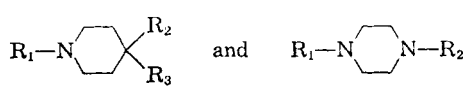
Application of Sodium Borohydride Reduction to Synthesis of Substituted Aminopiperidines, Aminopiperazines, Aminopyridines, and Hydrazines

GORDON N. WALKER, MIRIAM ANN MOORE,[1] AND BARBARA N. WEAVER

Received November 28, 1960

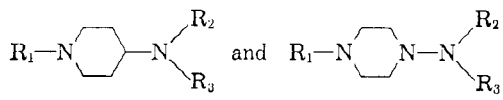
Quaternization of 4-aminopyridine with alkyl and arylalkyl halides gives 4-aminopyridinium salts, which are reduced with sodium borohydride to 1-(alkyl or arylalkyl)-4-aminopiperidines. Both 1-alkyl-4-aminopiperidines and 1-alkyl-4-aminopiperazines may be converted to Schiff bases which in turn are reduced with sodium borohydride to corresponding secondary amines. Similar reduction of appropriate Schiff bases as a means of preparing substituted 3-aminopiperidines, aminopyridines, and aminomethylpyridines, as well as reduction of dialkylhydrazones to corresponding trisubstituted hydrazines, are also described.

Piperidine and piperazine derivatives have occupied a very prominent place in medicinal chemistry and it can hardly be the purpose of this paper to review the great amount of work, much of it recorded in the patent literature, which has been done with these compounds. A host of compounds of general structure:



where R signifies various alkyl, arylalkyl, and oxygen-containing groups, have been prepared in a number of laboratories, and many of these have been demonstrated to have analgetic, neuroleptic, antihistaminic, hypotensive, antibacterial, or antiparasitic activity in various tests. On the other hand, far less work with similarly substituted aminopiperidines and aminopiperazines:

(1) Mrs. Edwin L. Klett.

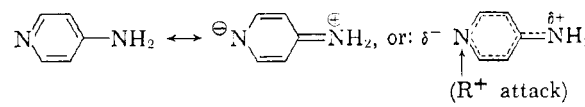


has been recorded. In view of the obvious structural similarity between these types of compounds and the fact that some 4-aminopiperidines have already been described[2a,b] as having spasmolytic activity, it seemed to us that at least some of the many possible aminopiperidines and aminopiperazines substituted with some of the more "interesting" bulkier groups might well have useful pharmacodynamic or microbiological properties. Thus we have been interested in finding techniques for synthesis of new compounds of this type bearing a variety of substituents.

The methods which have been used heretofore in synthesis of aminopiperidines may be summarized briefly as follows. 4-Aminopiperidine itself is prepared by sodium-alcohol reduction of 4-aminopyridine[3-5] and mention has been made[5] of the fact that 4-aminopyridine salts, in contrast to those of 3-aminopyridine[6] and practically all other simple pyridines, are uniquely resistant to catalytic hydrogenation, a fact which we have confirmed. Similar reductions of 4-aminopyridine derivatives and of 1-substituted 4-pyridone oximes or imines have been described.[7] Other and more flexible methods for synthesis of substituted 4-aminopiperidines include the ring closure of 3-amino-1,5-dihalides with amines[2,8] the reaction of 1-substituted 4-bromopiperidines with amines,[9] and the reductive amination of 4-piperidones[2,10,11] which is perhaps the most useful method described, to date.

The synthesis of 1-substituted 4-aminopiperazines by zinc reduction of nitrosopiperazines has been covered in patents[12] wherein mention is made of interesting pharmacological properties of these compounds and their derivatives.

Until recently there seems to have been very little use made of the fact that 4-aminopyridine can be quaternized directly with alkyl bromides (or iodides) without any prior masking of the amino group, to give 1-alkyl-4-aminopyridinium salts.[7] This fact is a consequence of the inordinately unreactive nature of the 4-amino group which is just as striking in 4-aminopyridine as in the electronically similar *p*-nitroaniline, and which we comprehend at present on the basis of a partly-zwitterionic" (bond-delocalized) formula[13]:



We prepared a number of representative 1-substituted 4-aminopyridinium salts (Ia) listed in Table I, by the simple expedient of heating together in a solvent (indicated) equivalent amounts of 4-aminopyridine and appropriate halogen compound. The reaction was found to be equally adaptable to preparation of α, ω-alkyl bis(4-aminopyridinium)-dibromides (Ib) from α, ω-dibromides, a finding that was corroborated by another group[14] while our work was in progress.

Having experienced unsatisfactory results in attempts to hydrogenate some of the 1-substituted 4-aminopyridinium salts catalytically (platinum), we tried reducing these compounds with sodium borohydride, a reagent with is now well known to bring about efficient reduction of the quaternary —C=N⁺— group in a variety of situations. We thought *a priori* that the best approach might be to effect partial reduction of the pyridinium salts, and at the same time elimination of the halide moiety, with borohydride, and subsequently to complete the process by subjecting (anticipated) piperideine intermediates to catalytic reduction. However, in practice it developed that the second step was unnecessary, for with an excess of sodium borohydride present the 4-aminopyridinium salts were reduced completely to corresponding aminopiperidines (IIa and IIb). Apparently any unsaturated intermediate (aminopiperideine) occurring in the (undoubtedly stepwise) process can and does undergo double bond shift under the alkaline condition of the reaction to an imine or enamine isomer which is readily reduced further by borohydride. Some selected examples of the 4-aminopiperidines (as

(2)(a) E. Cerkovnikov and V. Prelog, *Ber.*, **74**, 1648 (1941). (b) N. Nazarov and E. T. Golovin, *Zhur. Obshchei Khim.*, **26**, 1496 (1956). See *Chem. Abstr.*, **50**, 14, 742 (1956).

(3) B. Emmert and W. Dorn, *Ber.*, **48**, 687 (1915).

(4) E. Koenigs and L. Neumann, *Ber.*, **48**, 956 (1915).

(5) L. Orthner, *Ann.*, **456**, 225 (1927).

(6) H. Nienburg, *Ber.*, **70B**, 635 (1937).

(7) K. Tomita, *J. Pharm. Soc. Japan*, **71**, 1053 (1951). See *Chem. Abstr.*, **46**, 5044 (1952); **48**, 10020 (1954).

(8) V. Hahn, E. Cerkovnikov, and V. Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).

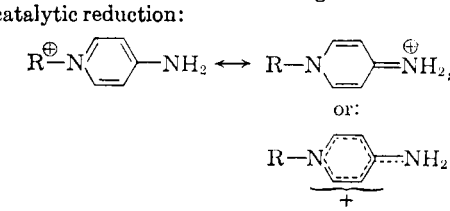
(9) V. Hahn, E. Cerkovnikov, and V. Prelog, *Ber.*, **74**, 1658 (1941).

(10) R. C. Fuson, W. E. Parham, and L. J. Reed, *J. Am. Chem. Soc.*, **68**, 1239 (1946).

(11) R. H. Reitsema and J. H. Hunter, *J. Am. Chem. Soc.*, **70**, 4009 (1948).

(12) E. A. Conroy, U. S. Patents **2,663,706** and **2,663,707** (1953).

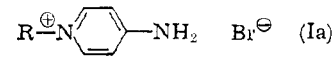
(13) A similar charge-delocalized formula for 4-aminopyridinium salts aids in rationalizing their unusual resistance to catalytic reduction:



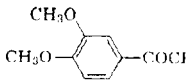
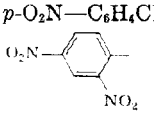
According to this view, the heterocyclic nitrogen loses some of its positively-charged character and becomes less vulnerable to attack by $\overset{+}{H}—\overset{-}{H}$.

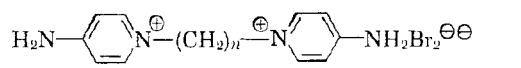
(14) W. C. Austin, L. H. C. Lunts, M. D. Potter, and E. P. Taylor, *J. Pharm. and Pharmacol.*, **11**, 80 (1959).

TABLE I



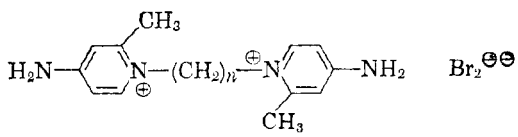
(Ia)

R	Notes	Reflux Time, hr.	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$H_5C_2OOCCH_2$—	c	1.5	92	197	41.4	5.02	10.7	41.4	5.1	10.7
$H_5C_2OOCCH_2CH_2$—	a	5	73	159	43.7	5.5	10.2	43.6	5.37	10.1
$HOCH_2CH_2$—	a	3.5	80	131	38.4	5.06	12.8	38.8	5.03	12.7
$C_6H_5CH_2$—	b	0.5	90	196	54.4	4.94	10.6	54.6	4.88	10.6
$(C_6H_5)_2CH$—	a	3	56	263	63.4	5.02	8.21	63.1	4.99	8.40
$C_6H_5CH_2CH_2$—	a	2	77	260	55.9	5.41	10.0	56.2	5.47	10.2
$C_6H_5CH_2$—$CH(C_6H_5)$—	b, d	9	53	245	64.2	5.39	7.88	63.8	5.30	7.98
$C_6H_5OCH_2CH_2$—	a	4.5	75	184	52.9	5.12	9.49	53.0	5.09	9.34
$C_6H_5COCH_2$—	b	2	96	308	53.3	4.47	9.56	53.1	4.42	9.65
	c, d	0.3	64	271	51.0	4.85	7.93	50.9	4.79	7.89
p-O_2N—$C_6H_4CH_2$—	a	5.5	66	266	54.2	4.55	15.8	54.1	4.51	16.0
	a	1	56	294	38.7	2.66	16.4	38.4	2.51	16.7



(Ib)

n										
4	a	2	87	273	41.6	4.98	13.9	41.3	5.18	14.0
6	a	14	91	303	44.5	5.59	13.0	44.1	5.56	13.0
8	a	5.5	84	300	47.0	6.13	12.2	47.0	6.13	12.0
9	a	5	14	221	48.1	6.37	11.8	48.3	6.34	11.8
10	a	5	88	247	49.2	6.60	11.4	49.2	6.71	11.2
11	a	$7\frac{1}{2}$	48	216	50.21	6.82	11.15	50.23	6.95	10.84
12	a	13	29	209	51.1	7.0	10.9	50.5	7.1	11.3
16	a, e	11	94	185	46.9	6.65	8.41	47.2	6.87	8.46



n										
8	a	8	60	304	49.2	6.60	11.5	49.1	6.84	11.5
9	a	9	17	275	50.2	6.82	11.2	50.5	6.94	11.3

Notes: Prepared by refluxing the components in (a) toluene, (b) benzene, (c) benzene-ethanol, (d) Yield calculated on basis of carbinol from which bromo compound was prepared using hydrobromic acid. (e) Prepared from alkyl iodide.

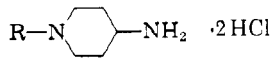
dihydrochlorides) which were prepared by this method are presented in Table II. When a carbonyl group was also present, as in phenacyl salts, it was reduced as well, to the corresponding carbinol. It was not possible to isolate desired products after reduction of 1-(2′,4′-dinitrophenyl)-4-aminopyridinium chloride and 1-benzhydryl-4-aminopyridinium bromide, probably because in these cases the pyridine ring opened under the alkaline conditions of the reaction; also an anomalous product was obtained from reduction of 1-(β-carbethoxyethyl)-4-aminopyridinium bromide, probably due to β-elimination.

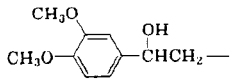
The sodium borohydride reduction of compounds I to piperidines II is sufficient evidence in itself that they are quaternary salts, and subsequent preparation of imines from II, as described below, provides proof for the survival of a primary amino group throughout the preparation and reduction of I.

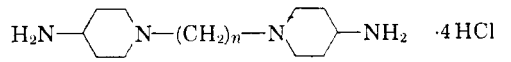
With means available for making 1-substituted 4-aminopiperidines in quantity, we proceeded further and prepared some new 4-aminopiperidines which were substituted at both nitrogen atoms. This was done by reduction of Schiff bases, prepared from primary amino compounds and various aldehydes, again using sodium borohydride. Just as simple anils are reduced expediently by this reagent,[15] so can more complex and more strongly

(15) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, 22, 1068 (1957).

TABLE II



R	Notes	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$H_5C_2OOCCH_2$—	a, c, f	17	169	39.0	8.0	10.1	38.4	8.18	10.1
$C_6H_5CH_2$—	a	41	255	54.8	7.66	10.65	54.4	7.76	10.49
$C_6H_5CH_2CH_2$—	a	88	321	56.3	8.00	10.11	56.7	7.89	9.72
$C_6H_5CH_2CH(C_6H_5)$—	b, f	40	237 dec.	61.5	7.60	7.93	61.8	7.60	8.2
$C_6H_5OCH_2CH_2$—	b	44	220	53.2	7.56	9.56	53.0	7.83	9.0
$C_6H_5CH(OH)CH_2$—	a, c	90	248 dec.	53.2	7.56	9.56	53.7	7.2	9.38
	a, c, e	56	220 dec.	51.0	7.42	7.93	50.6	7.36	7.94
p-O_2N—C_6H_4—CH_2—	b, d	10	265 dec.	46.76	6.21	13.63	46.44	6.43	13.33



n									
6	a	22	204	44.9	8.94	13.07	45.2	8.94	13.00
10	a	16	295	49.6	9.57	11.57	50.1	10.1	11.2
12	a	34	311	51.6	9.84	10.93	51.3	9.78	10.3
16	a	20	315	54.9	10.28	9.85	54.2	10.39	9.76

Notes: Base salted out, during work-up, with (a) potassium carbonate, (b) sodium chloride. Hydrochloride is (c) hygroscopic, (d) unstable, (e) sensitive to light, (f) monohydrate.

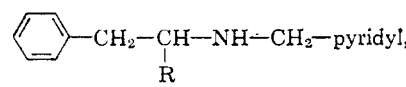
basic compounds such as III be converted to corresponding secondary amines (IV) without the difficulty of accompanying hydrogenolysis which prevails when catalytic methods are employed. Although the yields of some of the compounds obtained by this method (see Experimental part) are rather low, this usually reflects difficulty experienced either in preparation of the imines (III) or in isolation of the frequently water-soluble, and occasionally unstable, products IV, rather than any deficiency in the reduction method *per se*. The approach to synthesis of compounds IV described here may be considered as a possibly more widely applicable adjunct to the piperidone-reductive amination method used previously.[11]

The problem of synthesizing 3-aminopiperidine derivatives similar to the 4-amino compounds presented some different aspects. Unlike 4-aminopyridine, 2- and 3-aminopyridine cannot be converted readily to quaternary salts, and the amino-group preferably is protected in some manner. However, substituted 3-aminopyridines (V), again prepared by sodium borohydride reduction of appropriate Schiff bases, *could* be quaternized, at least with simple halides, without appreciable interfering reaction at the secondary amino group, and again, presumably by way of labile di- and tetrahydro intermediates, quaternary salts of V are reduced completely with excess sodium borohydride to disubstituted 3-aminopiperidines, VI. An expedient route was also found leading to the somewhat less stable monosubstituted 3-aminopiperidines, VII, consisting of borohydride reduction of imines derived from 3-aminopiperidine[6] itself.

Some attempts were made to extend the foregoing techniques to derivatives of aminomethylpyridines. It was possible to synthesize monosubstituted aminomethylpyridines, VIII by the usual borohydride reduction of imines derived from 3- and 4-aminomethylpyridines,[16] although this procedure was not applicable to the unstable imines obtained from 2-aminomethylpyridine. Quaternization of compounds such as VIII, however, proved to be out of the question because of the higher order of reactivity of the secondary amino group, which in these cases is comparable with that of dibenzylamine.

The recently acquired prominence of simple hydrazines[17] in pharmaceutical chemistry, together with earlier reports concerning hydrazine-like aminopiperazines,[12] prompted us to extend our work to some new derivatives of these parent bases. We found that hydrazones IX derived from 1-methyl-4-aminopiperazine could be reduced to compounds X with sodium borohydride, a reaction which parallels III → IV and provides a similar opportunity for variation of substituent groups in-

(16) An alternative, and more widely applicable, method for preparation of compounds of this type:



to be described elsewhere, consists of borohydride reduction of imines prepared from phenylalkylamines and pyridine aldehydes.

(17) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959).

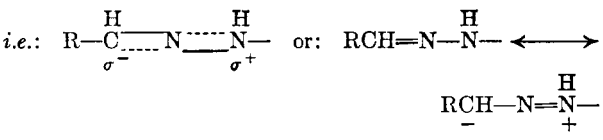
TABLE III

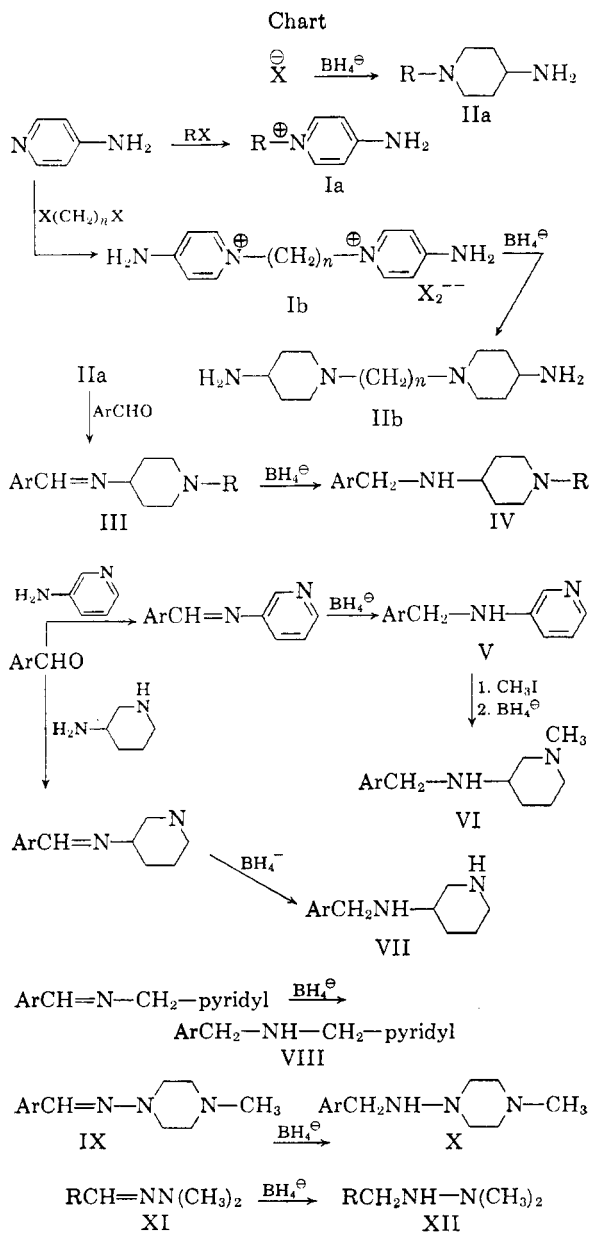
R_1—NH—R_2

R_1	R_2	Yield, %	M.P.	Empirical Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Notes
3,4-Dimethoxybenzyl	1-Methyl-4-piperidyl	60	254–256° dec.	$C_{15}H_{26}O_2N_2Cl_2$	53.41	7.77	8.31	53.12	7.98	8.16	b, f
3,4,5-Trimethoxybenzyl	1-Methyl-4-piperidyl	37	264–265° dec.	$C_{16}H_{28}O_3N_2Cl_2$	52.32	7.68	7.63	52.59	7.81	7.73	b
3,4-Dimethoxybenzyl	1-(β-Hydroxyethyl)-4-piperidyl	12	255–256° dec.	$C_{16}H_{28}O_3N_2Cl_2$	52.32	7.68	7.63	51.90	7.65	7.65	b
4-Methoxybenzyl	1-(3,4-Dimethoxybenzyl)-4-piperidyl	46	274–275° dec.	$C_{22}H_{32}O_3N_2Cl_2 \cdot H_2O$	57.26	7.43	6.07	57.56	7.32	6.16	b
3,4,5-Trimethoxybenzyl	1-Methyl-4-piperazyl	56	135–137°	$C_{15}H_{25}O_3N_3$	61.0	8.53	14.2	60.7	7.99	13.9	a
p-Dimethylaminobenzyl	1-Methyl-4-piperazyl	40	125–127° 157–160°	$C_{14}H_{24}N_4$	67.7	9.74	22.56	68.0	9.8	22.38	a, g
3-Pyridylmethyl	1-Methyl-4-piperazyl	95	201–202° 220–226°	$C_{11}H_{18}N_4 \cdot H_2O$ $C_{11}H_{20}N_4Cl_2 \cdot {}^1/_2\,H_2O$	45.84	7.35	25.0 19.44	45.84	7.58	25.2 19.47	a
1-Hydroxy-1-phenyl-2-propyl	1-Methyl-4-piperazyl	25	219–221° dec.	$C_{14}H_{25}ON_3Cl_2$	52.17	7.76	13.04	51.74	8.00	13.18	b
3,4-Dimethoxybenzyl	2-Pyridyl	65	102–103°	$C_{14}H_{16}O_2N_2$	68.8	6.60	11.47	68.7	6.70	11.52	a
3,4,5-Trimethoxybenzyl	2-Pyridyl	45	167–168°	$C_{16}H_{19}O_3N_2Cl$	58.0	6.16	9.01	57.3	5.90	8.92	b
p-Dimethylaminobenzyl	2-Pyridyl	52	125–126°	$C_{14}H_{17}N_3$	73.97	7.54	18.5	73.98	7.56	18.6	c
3,4,5-Trimethoxybenzyl	3-Pyridyl	63	109–110°	$C_{15}H_{18}O_3N_2$	65.67	6.61	10.2	66.0	6.51	10.2	a
3,4,5-Trimethoxybenzyl	3-Pyridylmethyl	90	205–207°	$C_{16}H_{22}O_3N_2Cl_2$	53.2	6.13	7.75	53.3	6.29	7.60	b
p-Dimethylaminobenzyl	3-Pyridylmethyl	96	185–186° dec.	$C_{15}H_{22}N_3Cl_3$	51.36	6.32	11.98	50.95	6.31	12.09	b
3,4-Dimethoxybenzyl	4-Pyridylmethyl	22	200° dec.	$C_{15}H_{20}O_2N_2Cl_2$	54.4	6.08	8.46	54.9	6.51	7.80	b, e, f
3,4,5-Trimethoxybenzyl	4-Pyridylmethyl	43	214–216°	$C_{16}H_{22}O_3N_2Cl_2$	53.19	6.13	7.75	53.11	6.4	7.79	b
p-Dimethylaminobenzyl	4-Pyridylmethyl	45	195–196°	$C_{15}H_{22}N_3Cl_3 \cdot {}^1/_2\,H_2O$	50.1	6.44	11.7	50.05	6.72	11.3	b
1-Phenyl-2-propyl	3-Pyridylmethyl	55	205–207°	$C_{15}H_{20}N_2Cl_2$	60.2	6.73	9.36	59.80	6.83	9.41	d
1-Phenyl-2-propyl	4-Pyridylmethyl	80	181–183°	$C_{15}H_{20}N_2Cl_2$	60.2	6.73	9.36	59.99	6.81	9.50	b
3,4,5-Trimethoxybenzyl	—$N(CH_3)_2$	45	81–83°	$C_{12}H_{20}O_3N_2$	60.0	8.39	11.66	60.4	7.7	11.83	a
p-Dimethylaminobenzyl	—$N(CH_3)_2$	7	158–161° dec.	$C_{11}H_{21}N_3Cl_2$	49.6	7.9	15.8	49.8	8.2	15.8	b, e
1-Phenyl-2-propyl	—$N(CH_3)_2$	70	123–125°	$C_{11}H_{19}N_2Cl$	61.5	8.92	13.05	61.1	8.80	13.39	b, h
1,2-Diphenylethyl	—$N(CH_3)_2$	23	183–185°	$C_{16}H_{21}N_2Cl$	69.42	7.65	10.12	69.17	7.49	10.27	d
C_6H_5—CH=CH—CH(CH_3)—	—$N(CH_3)_2$	5	117–120° dec.	$C_{12}H_{19}N_2Cl$	63.5	8.4	12.37	63.0	8.0	12.22	d

Notes: Recrystallized from: (a) methanol, (b) ethanol, (c) aqueous methanol, (d) ethanol-ether. Other characteristics: (e) unstable, (f) hygroscopic, (g) polymorphic, (h) Reported,[17] m.p. 128°.

troduced. The analogous reduction of some simple hydrazones was also explored. While good results were forthcoming in preparation of various examples of structure XII, it soon became apparent that the method was limited to just such fully *N,N*-substituted hydrazones as IX and XI, because all compounds of the type RCH=NNHR′ and RCH=NNH$_2$ which were tried resisted borohydride attack completely. The increased stability of hydrazones containing an NH moiety is understandable on the basis of a delocalized or partial-zwitterionic, structure,





EXPERIMENTAL[18]

1-(3′,4′-Dimethoxybenzyl)-4-aminopyridinium bromide (A). *Veratryl bromide.*[19] Anhydrous hydrogen bromide was passed through an ice-cold solution of 33.6(0.20 mole) of veratryl alcohol in 500 ml. of benzene, for 10 min. The lower layer which formed was separated, and the benzene solution was treated with anhydrous sodium carbonate and stirred until moisture and excess hydrogen bromide were absorbed. The solution of veratryl bromide was filtered, and without further purification was used in the next step.

(B) To the benzene solution from (A) was added 19 g. of 4-aminopyridine. The mixture was boiled for 1.5 hr. The aminopyridine was consumed and in its place there appeared a thick suspension of crystals of the product. The cooled suspension was filtered and the crystals were washed with benzene. The yield of air-dried, slightly-discolored product was 54 g. (83%). Recrystallization from ethanol gave a pure sample, m.p. 248–250° dec.

Anal. Calcd. for $C_{14}H_{17}O_2N_2Br$: C, 51.7; H, 5.27; N, 8.62. Found: C, 51.5; H, 5.18; N, 8.68.

A similar two-step procedure, involving preparation of crude 1,2-diphenylethyl bromide and 3,4-dimethoxyphenacyl bromide,[20] was employed in the synthesis of the 1,2-diphenylethyl- and 3,4-dimethoxyphenacyl-substituted compounds, respectively, in Table I. The remaining compounds of Table I were prepared from commercially available bromo- (in one case, iodo-) compounds by essentially the same procedure, with necessary modifications, as noted, in solvents used and reaction times. In reactions involving α,ω-dibromoalkanes, a mixture of the dibromoalkane, two equivalents of 4-aminopyridine, and a suitable amount (*ca.* 10 parts, by weight) of toluene in each case was refluxed for the time indicated, during which interval the product often separated as a heavy oil. When this happened, the supernatnant solution, while still warm, was decanted away from the oil, which was then allowed to crystallize in the presence of a small amount of alcohol. This manipulation served to remove any starting materials which might still have been present.

2-Methyl-4-aminopyridine[21] (from which a few quaternary compounds were synthesized) was most conveniently prepared by a two-step reduction[22] of 4-nitro-2-piccoline-N-oxide[21,23] as follows: (A). A solution of 45 g. of 4-nitro-2-picoline N-oxide in 200 ml. of ethanol, containing 4 g. of 10% palladium-charcoal was shaken under hydrogen (45 lb. initially). Rapid exothermic uptake of approximately 3.3 moles of hydrogen occurred (0.5 hr.). Filtration of the catalyst and evaporation of the solvent gave a dark red oil from which crystals (33 g., 91%) of *2-methyl-4-aminopyridine N-oxide* were obtained. Recrystallization of a sample from ethanol afforded pale yellow crystals, m.p. 181–183° dec.

Anal. Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.21; H, 6.51; N, 22.36.

(B) The material from (A) (30 g.) was dissolved in 300 ml. of a 1:1 solution of glacial acetic acid–water, and was treated with excess zinc dust in portions, while stirring and warming the mixture on a steam bath (1 hr.). The ice-chilled mixture was then covered with ether and treated gradually with a large excess (500 g.) of sodium hydroxide in the form of a cold, 40% solution. The ether extract was dried over po-

(18) Melting points are corrected.

(19) R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).

(20) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

(21) H. J. den Hertog, C. R. Kolder, and W. P. Combé, *Rec. trav. chim.*, **70**, 591 (1951).

(22) *Cf.* E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953), and K. Thomas and D. Jerchel, *Angew. Chem.*, **70**, 719 (1958).

(23) This material was very kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

tassium carbonate, and the ether was evaporated. There was obtained 16.8 g. (64%) of crude product, m.p. 82–88°. Recrystallization from cyclohexane raised the m.p. to 95° (reported[21]: m.p. 95.5–96°).

1-(3',4'-Dimethoxybenzyl)-4-aminopiperidine. A solution of 30 g. of 1-(3',4'-dimethoxybenzyl)-4-aminopyridinium bromide in 700 ml. of methanol was stirred and treated with excess sodium borohydride (*ca.* 250 g.) gradually over a period of about an hour. It was found advisable to carry out this operation in a large (3 l.) beaker because of the vigorous frothing action brought about by addition of the reagent, especially in the early stages. The mixture was then heated on a steam bath and stirred occasionally, for another hour, until a concentrated, thick suspension was obtained. The mixture was cooled and treated with 500 ml. of water. The resulting solution was covered with 2 l. of ether and the two phases were stirred while there was added (in portions) enough anhydrous potassium carbonate to convert the lower layer into a heavy paste. The ether solution was separated, dried over potassium carbonate, and filtered. Evaporation of the ether and finally the residual methanol gave an oil which separated into two phases upon standing. The lower phase, consisting mostly of a potassium carbonate solution, was drawn off; the remaining oil was allowed to stand several days until more inorganic material had settled out, and again was separated, by decantation. The oil (20 g.) was dissolved in *ca.* 30 ml. of ethanol; this solution was filtered to remove remaining traces of inorganic impurities, and, while chilling in an ice bath, was treated with excess anhydrous hydrogen chloride. The crystals of hydrochloride (16.5 g.) were collected, washed with cold ethanol, and recrystallized once from the same solvent. The yield of colorless salt was 12.2 g. (40%). Further recrystallization from methanol-ether gave a pure sample, m.p. 223–225° dec.

Anal. Calcd. for $C_{14}H_{24}O_2N_2Cl_2$: C, 52.0; H, 7.48; N, 8.67. Found: C, 51.6; H, 7.54; N, 8.34.

Other 4-aminopiperidines (Table II) were obtained from respective quaternary salts by essentially this same procedure. The free bases were found to be hygroscopic, water-soluble oils, as expected, and in working up their solutions, after reduction, it was always necessary to salt out the amines with sodium chloride or potassium carbonate (see Table II) in order to extract them with ether. As indicated above, when potassium carbonate was used for this purpose some of the inorganic salt was usually carried over, with remaining methanol, into the ether extract. Care had to be exercised finally to eliminate this inorganic residue as completely as possible, or otherwise the hydrochlorides, subsequently prepared from crude bases, were contaminated with potassium chloride, which was usually difficult or impossible to remove by recrystallization. In this regard the bis(4-aminopiperidyl)alkanes were especially troublesome. Although it is possible to distill the simpler substituted aminopiperidines *in vacuo*[2,7] this procedure is in general inadvisable with the more complex compounds described here, being accompanied or overwhelmed by decomposition, especially in the case of oxy-substituted and bis(4-aminopiperidyl)compounds. When 4-aminopiperidines, as free bases, were needed for further work, they were used directly in crude state after separation of as much inorganic residue as possible, by the technique described above or by drying the crude base *in vacuo* while allowing inorganic residue to settle out. *1-Methyl-4-aminopiperidine* and *1-(β-hydroxyethyl)-4-aminopiperidine*, both of which form hygroscopic hydrochlorides, were obtained in a condition suitable for further reaction by applying the latter method.

1,10-Bis-(4-amino-1-piperidyl)decane was additionally characterized by preparation of the *bisdichloroacetate dichloride:* Reaction of the crude base with excess dichloroacetyl chloride took place with strong heat evolution; subsequent treatment of the mixture with ethanol and recrystallization of the material from the same solvent gave somewhat hygroscopic, colorless crystals, m.p. 227–230° dec.

Anal. Calcd. for $C_{24}H_{44}O_2N_4Cl_6$: C, 45.51; H, 7.00; N, 8.85. Found: C, 45.45; H, 7.4; N, 9.14.

1-Methyl-4-(3',4'-dimethoxybenzylamino)piperazine. A solution of 8.1 g. of 1-methyl-4-aminopiperazine[12] and 11.2 g. of veratraldehyde in 200 ml. of toluene was refluxed under a water trap for 1.5 hr. The solution was evaporated. The residual yellow oil was dissolved in 150 ml. of methanol and reduced by treating with sodium borohydride (ca. 40 g.) in portions. When effervescent reaction was complete, the mixture was heated on a steam bath for 0.5 hr. The cooled residue was treated with 150 ml. of cold water, and enough sodium chloride was added to saturate the aqueous solution. The product was extracted with ether, and the dried (potassium carbonate) ether solution was evaporated. The remaining pale yellow oil (20.5 g.) was treated with excess cold alcoholic hydrogen chloride. The yield of crude, hygroscopic *dihydrochloride* was 10 g. (41%). Recrystallization from ethanol gave very pale yellow, hygroscopic crystals, m.p. 199–202° dec.

Anal. Calcd. for $C_{14}H_{26}O_2N_2Cl_2 \cdot H_2O$: C, 47.2; H, 7.64; N, 11.8. Found: C, 47.6; H, 7.8; N, 12.0.

Other secondary aminopiperidines and aminopiperazines listed in Table III were prepared by essentially the same procedure.

Attempts to reduce imines, derived from 1-phenyl-2-propanone and 1-substituted 4-aminopiperidines, with sodium borohydride did not lead to desired products, evidently because of cleavage of the unstable imines.

3-(3',4'-Dimethoxybenzylamino)pyridine. A solution of 16.8 g. of 3-aminopyridine and 30 g. of veratraldehyde in 500 ml. of xylene was refluxed under a water separator for 24 hr. The solvent was evaporated, and the residual, oily imine (45.5 g.) was dissolved in methanol (*ca.* 200 ml.) and reduced with sodium borohydride by the usual technique of adding the reagent in portions. The mixture was heated on the steam cone 0.3 hr. prior to dilution with water. This resulted in formation of an oil which crystallized when the mixture was chilled. The crude product, upon being collected, washed with water, and air-dried, had m.p. 115–117° and the yield was 33 g. (72%). Recrystallization from methanol afforded colorless crystals, m.p. 123–125°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.76; H, 6.80; N, 11.7.

The other pyridines listed in Table III were prepared by the same procedure, using appropriate aldehydes and various aminopyridines and aminomethylpyridines, except that for condensation of aldehydes with aminomethylpyridines toluene was used in place of xylene, and the required reaction time was shorter (1–3 hr.).

1-Methyl-3-(3',4'-dimethoxybenzylamino)piperidine. With excess methyl iodide, 14.1 g. of 3-(3',4'-dimethoxybenzylamino)pyridine was converted rapidly and exothermically to the corresponding methiodide. After evaporation of the excess reagent, the crystals were suspended in methanol (200 ml.) and reduced with sodium borohydride (*ca.* 125 g.) in portions, following the same procedure as has already been described for 4-aminopyridinium salts. Subsequent dilution of the cooled, concentrated reaction mixture with *ca.* an equal volume of water gave a solution, from which the product was isolated by salting with potassium carbonate into ether solution, as described above. The potassium carbonate-dried ether solution, upon evaporation, settling, dissolution in ether-alcohol, filtration, and reevaporation, gave an oil, which was converted to the *dihydrochloride:* Yield, 14.6 g. (75%) of colorless crystals. Recrystallization from ethanol-methanol afforded material having m.p. 233–235° dec.

Anal. Calcd. for $C_{15}H_{26}O_2N_2Cl_2$: C, 53.41; H, 7.77; N, 8.31. Found: C, 53.12; H, 7.97; N, 8.10.

3-(3',4'-Dimethoxybenzylamino)piperidine. A mixture of 7.6 g. of 3-aminopiperidine,[6] 12.7 g. of veratraldehyde and 250 ml. of toluene was refluxed under a water separator for 3.5 hr. The crude imine, after evaporation of the solvent, was reduced with sodium borohydride in methanol as usual.

The crude product, isolated by salting out with potassium carbonate into ether solution, was converted to the *dihydrochloride:* yield, 20.6 g. (84%) of colorless crystals. Recrystallization from ethanol gave a pure sample, m.p. 229–231°.

Anal. Calcd. for $C_{14}H_{24}O_2N_2Cl_2$: C, 52.01; H, 7.48; N, 8.67. Found: C, 51.87; H, 7.43. N, 8.75.

By the same procedure, two additional compounds were prepared from 3-aminopiperidine.[6]

3-(4'-Dimethylaminobenzylamino)piperidine was obtained by reduction of the *p*-dimethylaminobenzylidene derivative and isolated in 76% yield as the *trihydrochloride:* hygroscopic, light-sensitive crystals from ethanol, having no definite melting point (gradual decomposition when heated).

Anal. Calcd. for $C_{14}H_{26}N_3Cl_3$: C, 49.06; H, 7.65; N, 12.26. Found: C, 48.5; H, 7.50; N, 11.9.

3-(3-Pyridylmethylamino)piperidine was obtained by reduction of the 3-pyridylidene derivative, and isolated in 79% yield as the *trihydrochloride:* very hygroscopic crystals which, like the preceding compound, did not have a definite melting point.

Anal. Calcd. for $C_{11}H_{20}N_3Cl_3$: C, 43.94; H, 6.71; N, 13.98. Found: C, 44.02; H, 6.98; N, 13.96.

N,N-Dimethyl-N'-(3,4-dimethoxybenzyl)hydrazine. When 16.3 g. of veratraldehyde and 6.5 g. of *N,N*-dimethylhydrazine were mixed there was heat evolution. The oil was taken up in 200 ml. of benzene, and the solution was refluxed under a water separator for 4 hr., which resulted in slow, steady collection of water. After evaporation of the benzene, the oily hydrazone was dissolved in methanol and reduced with sodium borohydride by the usual procedure. The product, isolated by extraction with ether after dilution of the reaction mixture, was an oil. The *hydrochloride* separated in 13.9 g. (56%) yield, m.p. 172–174.5°, when this oil was treated with alcoholic hydrogen chloride. Recrystallization from ethanol-ether did not raise this melting point.

Anal. Calcd. for $C_{11}H_{19}O_2N_2Cl$: C, 53.54; H, 7.76; N, 11.36; Cl, 14.37. Found: C, 53.62; H, 7.2; N, 11.6; Cl, 14.46.

The other hydrazine derivatives listed in Table III were prepared by essentially the same procedure, except that toluene was used in place of benzene in condensation of *p*-dimethylaminobenzaldehyde with 1,1-dimethylhydrazine. Hydrazones which were obtained by condensation of various pyridine aldehydes with 1,1-dimethylhydrazine were not affected by treatment with sodium borohydride.

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SUMMIT, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, LEPETIT S.P.A.]

Bicyclic Homologs of Piperazine. II. Synthesis of 3,8-Diazabicyclo[3.2.1]octane. New Synthesis of 8-Methyl-3,8-diazabicyclo[3.2.1]octane

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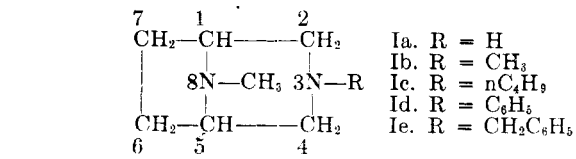
3,8-Diazabicyclooctane[3.2.1] (I) was obtained by a four step synthesis from 2,5-dicarbethoxypyrrolidine (II). This compound was converted into 2-benzylcarbamyl-5-carbethoxypyrrolidine (III) which, when heated, gave 3-benzyl-3,8-diazabicyclooctane[3.2.1]-2,4-dione (IV). The latter by reduction with lithium aluminum hydride to 3-benzyl-3,8-diazabicyclooctane[3.2.1] (V) and reductive debenzylation gave I. An alternate synthesis of I from the already known 8-carbobenzoxy-3,8-diazabicyclooctane[3.2.1]-2,4-dione (VIII) is also described. The known 8-methyl-3,8-diazabicyclooctane[3.2.1] has now been obtained by a new improved synthesis in five steps starting from II through V.

In the preceding paper of this series[1] we described the synthesis of several 3-substituted 8-methyl-3,8-diazabicyclooctanes[3.2.1] of general formula



Ia. R = H
Ib. R = CH_3
Ic. R = nC_4H_9
Id. R = C_6H_5
Ie. R = $CH_2C_6H_5$

obtained starting from 2,5-dicarbethoxypyrrolidine (II),[2] which was converted in three steps into *N*-carbobenz-oxy-2,5-pyrrolidine dicarboxylic acid anhydride. The latter reacted with appropriate amines to give 3-substituted 8-carbobenz-oxy-3,8-diazabicyclooctane[3.2.1]-2,4-diones from which the corresponding bicyclic bases were obtained by direct reduction with lithium aluminum hydride in ether.

We now describe the synthesis of the unsubstituted bicyclic ring, 3,8-diazabicyclooctane[3.2.1] (I). The key intermediate for the synthesis is 3-benzyl-3,8-diazabicyclooctane[3.2.1]2,4-dione (IV). This compound was initially prepared in a 52% yield by hydrogenolysis in methanol[3] of 3-benzyl-8-carbobenz-oxy-3,8-diazabicyclooctane[3.2.1]-2,4-dione[1] (VI). In the course of this reduction 2-benzylcarbamyl-5-carbomethoxypyrrolidine (VII) was also identified as by-product.

A more efficient method was subsequently found for obtaining the intermediate IV from 2,5-dicarbethoxypyrrolidine (II). 2-Benzylcarbamyl-5-carbethoxypyrrolidine (III) was obtained in 87%

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