[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Syntheses of 1,4-Diazabicyclo[4.4.0]decanes, 1,4-Diazabicyclo[4.3.0]nonanes and 1,8-Diazabicyclo[4.3.0]nonanes

MEIER E. FREED AND ALLAN R. DAY

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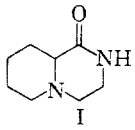
A new synthesis for 1,4-diazabicyclo[4.4.0]decane has been developed. The synthesis of a series of 1,4-diazabicyclo[4.3.0]-nonanes has been accomplished for the first time. The 1,8-diazabicyclo[4.3.0]nonane system has also been synthesized for the first time. A new method for the preparation of 2-aminomethylpiperidines is also reported.

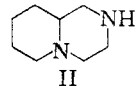
Pipecolic acid (2-piperidinecarboxylic acid) and diethyl 1-carboxymethylpyroglutamate were the starting materials for the diazabicyclodecanes and nonanes reported in this paper.

The first attempt to prepare 1,4-diazabicyclo-[4.4.0]decane was unsuccessful. The commercially available picolinic acid was hydrogenated to 2-piperidinecarboxylic acid and converted to its ethyl ester by the method of McElvain and Adams.[1] The ester was converted to ethyl 1-cyanomethyl-2-piperidinecarboxylate by treatment with chloroacetonitrile. Attempts to hydrogenate the cyanomethyl compound, using platinum oxide or palladium on carbon, failed to yield the corresponding ethyl 1-β-aminoethyl-2-piperidinecarboxylate. Hydrogenolysis occurred and ethyl 2-piperidinecarboxylate was the only product. Although 1-β-aminoethyl-2-piperidinecarboxylate appeared to be an ideal compound for preparing the lactam corresponding to the 1,4-diazabicyclo[4.4.0]decane, attempts to prepare it were dropped in favor of an easier synthesis of the lactam.

When ethyl 2-piperidinecarboxylate, in the presence of a catalytic amount of its hydrochloride, was treated with one equivalent of ethyleneimine the lactam, 5-keto-1,4-diazabicyclo[4.4.0]decane (I) was formed. Reduction of I with lithium aluminum hydride gave 1,4-diazabicyclo[4.4.0]decane (II). During the course of this work compound II

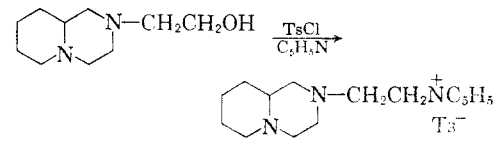


I

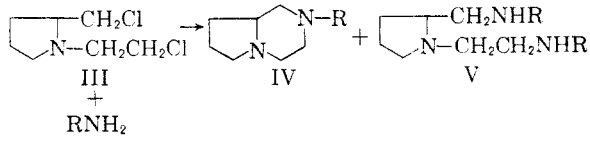


II

was synthesized by a different method.[2] However, the method employed in the present investigation seems to be an improvement in terms of ease and overall yield. When 1,4-diazabicyclo[4.4.0]decane was treated with ethylene oxide it was converted to the 4-β-hydroxyethyl compound. Attempts to prepare the tosyl derivative of the β-hydroxyethyl compound led to the formation of the 4-β-pyridinium derivative.



A number of 1,4-diazabicyclo[4.3.0]nonanes were prepared from 1-β-chloroethyl-2-chloromethylpyrrolidine(III). The preparation of this compound is reported in the preceding paper.[3] In order to introduce a variety of substituents into the 4-position of the 1,4-diazabicyclo[4.3.0]nonane(IV), ring closure of the *N*-mustard(III) was effected by reactions with three classes of amines: *n*-alkylamines, dialkylaminoalkylamines, and β-phenylethylamines. The unsubstituted 1,4-diazabicyclo[4.3.0]nonane (R=H) was prepared by the debenzylation (hydrogenolysis) of the corresponding 4-benzyl derivative. In addition to the diazabicyclononanes smaller amounts of 1-β-alkylaminoethyl-2-alkylaminomethylpyrrolidines(V) were also obtained in some cases. These reactions were carried out



III + RNH_2 IV V

under a variety of conditions but in general the reactions proceeded most satisfactorily when carried out in 50% aqueous acetone. The 1,4-diazabicyclo[4.3.0]nonanes are examples of a new heterocyclic ring system. They are listed in Table I.

The tendency of β-haloamines to undergo rearrangement during reaction with nucleophilic reagents has frequently been noted.[4] Fusion and Zirkle have reported the ring expansion of 1-ethyl-2-chloromethylpyrrolidine to 1-ethyl-3-chloropiperidine.[5] In contrast with the latter observation, the reaction of 3-chloropiperidines with amines to form

(1) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2745 (1923).

(2) K. Winterfield, K. Kullmar, and W. Gobel, *Ber.*, **92**, 1510 (1959).

(3) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2105 (1960).

(4) J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, **69**, 2961 (1947); E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948); S. D. Ross, *J. Am. Chem. Soc.*, **69**, 2982 (1947).

(5) R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760 (1948).

TABLE I

1,4-DIAZABICYCLO[4.3.0]NONANES

·2HCl

R	Formula Dihydrochlorides	Yield, %	B.P., Base	M.P. Dihydrochloride	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$C_6H_5CH_2$	$C_{14}H_{22}N_2Cl_2$	49	108–115/0.05 mm.	239–240	58.13	58.24	7.67	7.80	9.69	9.76	24.51	24.32
H	$C_7H_{16}N_2Cl_2$	80	74–75/10 mm.	204–205[a]	42.22	42.09	8.10	8.13	14.07	14.04	35.61	35.44
n-C_3H_7	$C_{10}H_{22}N_2Cl_2 \cdot H_2O$	44	130–135/25 mm.	262–263[b]	46.75	46.94	9.35	9.44	10.82	11.02	27.38	27.57
n-C_6H_{11}	$C_{12}H_{26}N_2Cl_2$	36	144–146/0.2 mm.	220–221	53.52	53.33	9.73	9.99	10.41	10.42	26.34	26.10
$(CH_3)_2NCH_2CH_2CH_2$	$C_{12}H_{28}N_3Cl_2 \cdot H_2O$[c]	33	138–140/25 mm.	263–265	42.50	42.42	8.93	8.98	12.38	12.36	31.38	31.33
	$C_{14}H_{30}N_3Cl_3$	33	120–125/0.5 mm.	274–275	48.42	48.25	8.72	8.85	12.12	12.00	30.67	30.39
$C_6H_5CH_2CH_2$	$C_{15}H_{24}N_2Cl_2$	35	122–124/0.5 mm.	225–226	59.90	59.69	7.98	7.93	9.24	9.29	23.40	23.21
$C_6H_5CH_2CH(CH_3)$	$C_{16}H_{26}N_2Cl_2$	46	117–120/0.2 mm.	269–270	60.70	60.55	8.27	8.12	8.85	8.65	22.35	22.24
$C_6H_5CH_2C(CH_3)_2$	$C_{17}H_{28}N_2Cl_2$	48	142–145/0.3 mm.	231–232	61.75	61.55	8.54	8.34	8.47	8.31	21.40	21.27
$4\text{-}CH_3OC_6H_4CH_2CH_2$	$C_{16}H_{22}N_2OCl_2$	26	155–158/0.25 mm.	228–229	57.70	57.60	7.84	7.95	8.43	8.30	21.33	21.21
$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	$C_{17}H_{28}N_2O_2Cl_2$	30	160–168/0.1 mm.	235–236	56.19	56.12	7.77	7.95	7.71	7.68	19.52	19.33

[a] The free base was also isolated: *Anal.* Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.23. Found: C, 66.60; H, 11.11; N, 22.09. [b] As the monohydrate. [c] Monohydrate of trihydrochloride.

2-methylpyrrolidines have been reported.[6] These occurrences suggested that a possibility existed that 1-β-chloroethyl-2-chloromethylpyrrolidine might undergo a similar rearrangement when treated with primary amines.

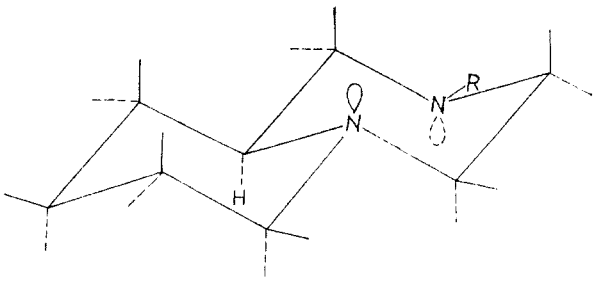
To establish the fact that the products of the cyclization reaction had the expected structure, the synthesis of 1,4-diazabicyclo[4.3.0]nonane was accomplished by way of an unequivocal route from 2-pyrrolidinecarboxylic acid. The products obtained

from the two routes were identical, *i.e.*, the infrared spectra were identical, both formed dihydrochlorides melting at 204–205° and a mixed melting point determination showed no depression. They also formed the same phenylthiourea derivative.

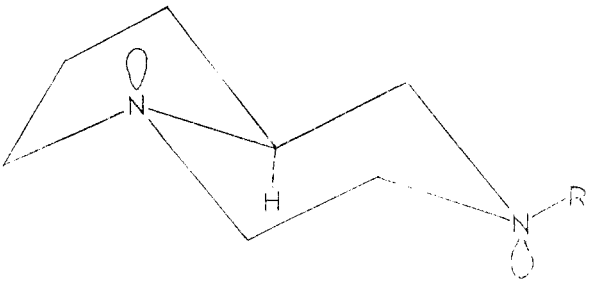
For the synthesis of the unknown 1,8-diazabicyclo[4.3.0]nonane system the procedure which was adopted was suggested by a paper published by Wilk and Close.[7] They had prepared 1-methyl-5-phenylimidazolidine by a lithium aluminum hydride reduction of the corresponding hydantoin. Ethyl 2-piperidinecarboxylate when treated with isocyanic acid and ethyl isocyanate yielded the corresponding hydantoins. The latter were reduced with lithium aluminum hydride to 1,8-diazabicyclo[4.3.0]nonanes. These compounds were distillable liquids. They were rapidly hydrolyzed by cold dilute acids but appear to be stable in basic solution. When a sample of 8-alkyl-1,8-diazabicyclo[4.3.0]nonane was dissolved in cold 1*N* hydrochloric acid, the odor of formaldehyde was immediately apparent upon evaporation of the solution, a quantitative yield of 2-alkylaminomethylpiperidine was obtained. This may prove

(6) R. H. Reitsema, *J. Am. Chem. Soc.*, **71**, 2041 (1949); J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, **81**, 2527 (1959); T. Y. Shen, E. F. Rogers, and L. H. Sarett, American Chemical Society Meeting, Atlantic City, N. J., Sept. 13, 1959, Abstracts, p. 37.

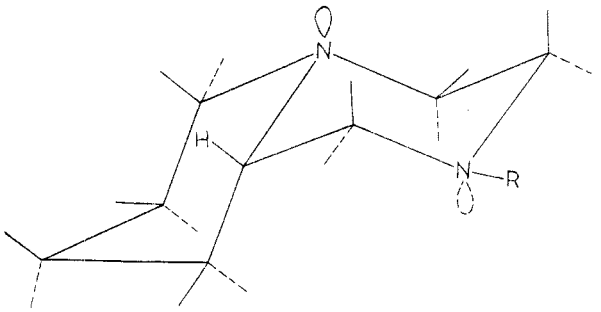
(7) I. J. Wilk and W. J. Close, *J. Org. Chem.*, **15**, 1020 (1950).



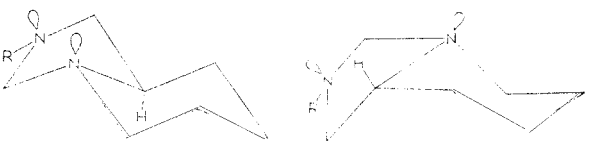
trans-1,4-Diazabicyclo[4.4.0]decane



trans-1,4-Diazabicyclo[4.3.0]nonane



cis-1,4-Diazabicyclo[4.4.0]decane



trans *cis*

1,8-Diazabicyclo[4.3.0]nonane

to be a useful synthesis of substituted 2-aminomethylpiperidines.

Conformations of the diazabicyclo ring systems. X-ray analysis has shown that *N*-substituted heterocyclic structures such as *N,N'*-dichloropiperazine[8] and the tetracyclic α-isosparteine exist in chair conformations. Thus it appeared reasonable to consider only the chair-chair form of the 1,4-diazabicyclo[4.4.0]decanes. Two such forms possible are the *trans* and the *cis*. They differ in that the unshared electron pair of the bridgehead nitrogen and the hydrogen of the bridgehead carbon may be situated *trans* or *cis* to each other.

The investigations of Bohlmann on the conformations of many alkaloids possessing the quinolizidine structure provides a means of distinguishing between such conformational isomers.[9] This work reported the correlation of a group of bands appearing in the infrared spectra of quinolizidines, between 2700–2800 cm.$^{-1}$, with a *trans* ring fusion, the absence of such bands being evidence for a *cis* ring fusion. Those bands are also present in simple amines but not in amine derivatives such as amides.

Since 1,4-diazabicyclo[4.4.0]decane contains both bridgehead and nonbridgehead nitrogen, the electron pair of the latter were immobilized by formation of the 4-phenylthiourea. The infrared spectrum of this compound showed the *trans* bands at 2760–2785 cm.$^{-1}$. From this it would appear probable that the more stable conformation is that of *trans* 1,4-diazabicyclo[4.4.0]decane.

Similarly, when the infrared spectrum of the 4-phenylthiourea derivative of 1,4-diazabicyclo-[4.3.0]nonane was examined, the *trans* bands were again present, appearing at 2775 cm.$^{-1}$. Here again the *trans* conformation appears to be more stable.

In view of the foregoing results, it was expected that in the 1,8-diazabicyclo[4.3.0]nonanes the *trans* form would also be the more stable. However, when the infrared spectra of the phenylurea derivative of 1,8-diazabicyclo[4.3.0]nonane was examined, there were no bands in the 2700–2800 cm.$^{-1}$ region. This evidence suggests that the *cis* form is the more stable. Examination of simple ball-spring models of the *cis* and *trans* forms of this molecule reveals a possible explanation for this observation. When the models are constructed in accordance with accepted principles, *i.e.*, with large substituents in the equatorial position, the free electron pairs belonging to the two nitrogen atoms are found in axial positions, in close proximity for the *trans* form. The spacial requirement of the nitrogen electron pair is greater than that for hydrogen[10] and on steric grounds alone this could destabilize the *trans* form. In addition it must be considered that the repelling effect due to the proximity of two electron pairs would be a destablizing force. Thus the greater stability of the *cis* form is probably due to the unfavorable 1,3-diaxial interaction of the electron pairs of the nitrogen atoms in the *trans* form.

EXPERIMENTAL

Melting points were determined by the capillary tube method in a Hoover-Thomas apparatus. The melting point values are uncorrected.

Ethyl 1-cyanomethyl-2-piperidinecarboxylate. Chloroacetonitrile (15 g., 0.2 mole) was added to a well stirred slurry of ethyl 2-piperidinecarboxylate (31 g., 0.2 mole) and anhy-

(8) P. Anderson and O. Hassel, *Acta. Chem. Scand.*, **3**, 1180 (1949).

(9) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); F. Bohlmann and C. Arndt, *Ber.*, **91**, 2167 (1958); F. Bohlmann, *Ber.*, **92**, 1798 (1959).

(10) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

drous potassium carbonate (28 g., 0.2 mole). A fairly vigorous reaction occurred. After stirring for 2 hr., sufficient water was added to dissolve the inorganic salts and the solution was then extracted with benzene. The extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the benzene by distillation, the remaining oil was distilled *in vacuo*. There was obtained 27 g. (69%) of ethyl 1-cyanomethyl-2-piperidinecarboxylate, b.p. 110–115°/0.2 mm., n_D^{25} 1.4700. The base was converted to the hydrochloride by the addition of hydrogen chloride to an acetone solution of the base. The hydrochloride was recrystallized from ethanol-acetone, m.p. 138–139°.

Anal. Calcd. for $C_{10}H_{17}N_2O_2Cl$: C, 51.61; H, 7.36; N, 12.04; Cl, 15.24. Found: C, 51.48; H, 7.48; N, 11.96; Cl, 15.25.

Attempts to reduce the cyanomethyl compound to the corresponding β-aminoethyl derivative were unsuccessful. Hydrogenolysis occurred with both platinum and palladium as catalysts and only ethyl 2-piperidinecarboxylate was isolated.

5-Keto-1,4-diazabicyclo[4.4.0]decane. Ethyl 2-piperidinecarboxylate (15 g., 0.1 mole) and 0.15 g. of the corresponding hydrochloride were added to 100 ml. of ethanol and the solution heated to boiling. To the refluxing solution was added dropwise 4.3 g. (0.1 mole) of ethyleneimine in 50 ml. of dry ethanol. Refluxing was continued for 24 hr. The solvent was removed *in vacuo*. The residue was recrystallized from ethyl acetate, yield 52%, m.p. 133–135°. It was recrystallized again from acetone, m.p. 134–134.5°.

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.25; H, 9.14; N, 18.15. Found: C, 62.21; H, 9.15; N, 17.98.

1,4-Diazabicyclo[4.4.0]decane. 5-Keto-1,4-diazabicyclo[4.4.0]decane (20 g., 0.13 mole) in 200 ml. of dry tetrahydrofuran was added dropwise to a stirred suspension of 8 g. (0.21 mole) of lithium aluminum hydride in 300 ml. of tetrahydrofuran. The reaction mixture was refluxed for 12 hr., cooled, and 32 ml. of water added gradually to decompose the lithium aluminum compounds. The mixture was stirred for 2 hr. and filtered. The precipitate was extracted with 250 ml. of hot 2-propanol and the extract added to the filtrate. The combined solutions were dried over anhydrous sodium sulfate and then concentrated to about 25 ml. at 100°. The residual oil was distilled *in vacuo*. The yield of 1,4-diazabicyclo[4.4.0]decane was 63%, b.p. 98–99°/25 mm.

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.55; H, 11.52; N, 19.96. Found: C, 68.39; H, 11.73; N, 20.17.

The dihydrochloride was prepared in dry ether solution and recrystallized from 2-propanol, m.p. 213–214°.

Anal. Calcd. for $C_8H_{18}N_2Cl_2$: C, 45.10; H, 8.52; N, 13.14; Cl, 33.27. Found: C, 44.95; H, 8.64; N, 13.16; Cl, 33.09.

The phenylthiourea derivative was prepared by treating a cyclohexane solution of the base with phenylisothiocyanate. It was recrystallized from ethanol, m.p. 118–119°.

Anal. Calcd. for $C_{15}H_{21}N_3S$: C, 65.60; H, 7.71; N, 15.27. Found: C, 65.75; H, 7.59; N, 15.27.

4-(2-Hydroxyethyl)-1,4-diazabicyclo[4.4.0]decane. To 5 g. (0.036 mole) of 1,4-diazabicyclo[4.4.0]decane in 20 ml. of methanol was added a solution of 2 g. of ethylene oxide in 10 ml. of methanol. After standing for 16 hr., the methanol was removed and the residue distilled *in vacuo*. The yield was 4.7 g. (72%), b.p. 98–100°/0.3 mm., n_D^{26} 1.5920.

Anal. Calcd. for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.21. Found: C, 65.33; H, 11.03; N, 15.30.

Treatment of the base in ether solution with methyl iodide gave a dimethiodide which was recrystallized from ethanol, m.p. 195–196°.

Anal. Calcd. for $C_{12}H_{26}N_2OI_2$: C, 30.78; H, 5.60; N, 5.98; I, 54.22. Found: C, 30.59; H, 5.84; N, 6.13; I, 54.21.

4-(2-Hydroxyethyl)-1,4-diazabicyclo[4.4.0]decane (2.5 g., 0.014 mole) was dissolved in 30 ml. of dry pyridine. The solution was cooled to 5° and 2.7 g. of *p*-toluenesulfonyl chloride added in small portions, while keeping the temperature below 10°. The mixture was allowed to stand at 0–5° for 3 days. The pyridine was removed under reduced pressure at room temperature. The residue was stirred with 5 ml. of ice water, then with 20 ml. of cold 2*N* potassium carbonate solution. The residual oil was dissolved in benzene and the solution dried over anhydrous sodium sulfate. The benzene solution was refluxed for 4 hr. and then concentrated to a small volume. When the oily residue was triturated with acetone, it solidified. It was recrystallized from methanol-acetone, yield 17%, m.p. 134–135°.

Anal. Calcd. for $C_{22}H_{31}N_3SO_3$: C, 63.50; H, 7.26; N, 10.08; S, 7.70. Found: C, 63.25; H, 7.19; N, 9.98; S, 7.64. The analysis indicates the compound to be 4-(2-pyridiniumethyl)-1,4-diazabicyclo[4.4.0]decane tosylate

4-Benzyl-1,4-diazabicyclo[4.3.0]nonane. To a solution of 9 g. (0.04 mole) of 1-(β-chloroethyl)-2-chloromethylpyrrolidine hydrochloride in 100 ml. of 50% aqueous acetone was added 17 g. (0.16 mole) of benzylamine. After 16 hr. of refluxing most of the acetone was removed by distillation. The aqueous solution was cooled, made strongly basic with solid sodium hydroxide and extracted with benzene. The benzene solution was dried over sodium hydroxide pellets. The benzene and benzylamine were removed by distillation and the residue distilled *in vacuo*. The yield of the free base was 49%, b.p. 130–135°/2 mm. The dihydrochloride was prepared from an ethereal solution of the base and dry hydrogen chloride. It was recrystallized from ethanol-acetone, m.p. 239–240, $[\alpha]_D^{22}$ −13.34° (1% in 95% ethanol).

The dipicrate was prepared from the free base and picric acid in hot ethanol solution. It was recrystallized from ethanol, m.p. 249–250°.

Anal. Calcd. for $C_{26}H_{26}N_8O_{14}$: C, 46.30; H, 3.89; N, 16.63. Found: C, 46.23; H, 3.90; N, 16.50.

A second product was obtained from the above preparation which distilled at 185–195°/2 mm. The presence of N—H absorption in the infrared indicated the product was the triamine, 1-(β-benzylaminoethyl)-2-benzylaminomethylpyrrolidine. The base (1.5 g., 11.6%) was converted to a trihydrochloride in ether solution. After recrystallization from 2-propanol, the hydrochloride melted at 245–246°.

Anal. Calcd. for $C_{21}H_{32}N_3Cl_3$: C, 58.23; H, 7.45; Cl, 24.57; N, 9.71. Found: C, 58.03; H, 7.59; Cl, 24.34; N, 9.52.

The tripicrate of this second product, made from the trihydrochloride and aqueous lithium picrate, melted at 112–113°.

Anal. Calcd. for $C_{39}H_{33}N_{12}O_{21}$: C, 46.75; H, 3.78; N, 16.25. Found: C, 46.55; H, 3.56; N, 16.37.

5-Keto-1,4-diazabicyclo[4.3.0]nonane hydrochloride. Ethyl 2-pyrrolidinecarboxylate (20 g., 0.14 mole), prepared by the esterification (Fischer) of proline, was dissolved in 100 ml. of dry ethanol and a trace of dry hydrogen chloride was introduced. To this was added 6 g. of ethyleneimine in 50 ml. of ethanol. The mixture was refluxed for 20 hr. and the solvent removed under reduced pressure. The residue could not be crystallized and could not be distilled without extensive decomposition. A chloroform solution of the residue was adsorbed on a column of alumina. Elution with chloroform separated the product from a dark band of more strongly adsorbed material. The chloroform solution was treated with dry hydrogen chloride and a hydrochloride was obtained. It was recrystallized from ethanol; yield 30%, m.p. 242–243°.

Anal. Calcd. for $C_7H_{13}N_2OCl$: Cl, 20.20; N, 15.90. Found: Cl, 20.40; N, 15.92.

1,4-Diazabicyclo[4.3.0]nonane. (a) *From 5-keto-1,4-diazabicyclo[4.3.0]nonane.* 5-Keto-1,4-diazabicyclo[4.3.0]nonane (7.5 g., 0.053 mole) in 75 ml. of dry tetrahydrofuran was added to a stirred suspension of lithium aluminum hydride (3.3 g., 0.09 mole) in 100 ml. of tetrahydrofuran. After 15 hr. of refluxing, 15 ml. of water was carefully added. The precipitate was removed and washed with ethanol. The washings were added to the filtrate and the resulting solution was dried over anhydrous sodium sulfate. The solvent was removed and the residual oil distilled *in vacuo*, yield 30%, b.p. 74–75°/10 mm., n_D^{25} 1.4950. The hydrochloride was prepared in the usual manner and recrystallized from etha-

nol, $[\alpha]_D^{22}$ −2.84 (1% in 95% ethanol). Treatment of the free base with phenyl isothiocyanate in petroleum ether (b.p. 30–60°) gave the corresponding *N*-phenylthiourea derivative which was recrystallized from petroleum ether–acetone, m.p. 122–123°.

Anal. Calcd. for $C_{14}H_{19}N_3S$: N, 16.10; S, 12.25. Found: N, 15.97; S, 12.05.

(b) *From 4-benzyl-1,4-diazabicyclo[4.3.0]nonane.* Two grams (0.09 mole) of 4-benzyl-1,4-diazabicyclo[4.3.0]nonane in 10 ml. of glacial acetic acid was hydrogenated over 200 mg. of platinum oxide at 40 lb. p.s.i. and 60°. After removing the catalyst, 2 ml. of concd. hydrochloric acid was added and the solution concentrated on a steam bath to a syrup. On cooling, the product solidified and was recrystallized from ethanol. The product melted at 204–205° and a mixed melting point determination with the dihydrochloride obtained from the reduction of 5-keto-1,4-diazabicyclo[4.3.0]-nonane gave no depression.

4-Propyl-1,4-diazabicyclo[4.3.0]nonane. Nine grams (0.04 mole) of 1-β-chloroethyl-2-chloromethylpyrrolidine hydrochloride was placed in a 100 ml. flask fitted with a dropping funnel and a Dry Ice condenser. The flask was cooled in an ice bath and 9.6 g. (0.16 mole) of *n*-propylamine was added over a period of 10 min. The ice bath was then removed. After a few minutes, refluxing began spontaneously and all of the material dissolved. After standing overnight, the mixture was taken up in 100 ml. of water. The solution was made strongly basic with 40% sodium hydroxide solution, extracted with ether, and the ether extract dried over anhydrous sodium sulfate. After removing the ether, the residual oil was distilled *in vacuo;* yield 44%, b.p. 130–135°/25 mm. The free base darkens on standing. It was converted to the dihydrochloride in the usual manner. It was recrystallized from ethanol-acetone. The dihydrochloride had an analysis corresponding to a monohydrate which suggests that the free base had picked up a molecule of water before the hydrochloride was prepared.

The dimethiodide was prepared from the free base and methyl iodide, in ether solution, and recrystallized from ethanol, m.p. 215–216°.

Anal. Calcd. for $C_{12}H_{26}N_2I$: N, 6.19; I, 56.14. Found: N, 5.98; I, 56.15.

4-Amyl-1,4-diazabicyclo[4.3.0]nonane. To 4.5 g. (0.02 mole) of 1-β-chloroethyl-2-chloromethylpyrrolidine hydrochloride was added 7 g. (0.08 mole) of *n*-amylamine. Xylene (25 ml.) was added and the solution refluxed for 1 hr. The xylene was removed under reduced pressure. The residue was worked up as in the preparation of 4-propyl-1,4-diazabicyclo[4.3.0]nonane. The yield was 36%, b.p. 82–85°/0.2 mm.

The dihydrochloride was prepared from an acetone solution of the base and was recrystallized from acetone-alcohol.

A dipicrolonate was prepared from the base and two equivalents of picrolonic acid in methanol solution. The yellow product was recrystallized from ethanol, m.p. 223–224°.

Anal. Calcd. for $C_{32}H_{42}N_{10}O_{10}$: C, 52.88; H, 5.83; N, 19.26. Found: C, 53.02; H, 5.93; N, 19.31.

A second fraction was obtained, from the original distillation, which boiled at 144–148°/0.2 mm., yield 18%. This material was found to be the unclosed triamine, 1-β-amylaminoethyl-2-amylaminomethylpyrrolidine. It was not possible to prepare a pure salt from this base. A trimethiodide was made from the base and excess methyl iodide in acetone solution. It was recrystallized from acetone, m.p. 221–222°.

Anal. Calcd. for $C_{20}H_{46}N_3I_3$: C, 34.30; H, 6.30; N, 5.98; I, 53.70. Found: C, 34.12; H, 6.10; N, 6.12; I, 54.00.

4-γ-Dimethylaminopropyl-1,4-diazabicyclo[4.3.0]nonane. To 4.5 g. (0.025 mole) of freshly distilled 1-β-chloroethyl-2-chloromethylpyrrolidine was added, slowly with stirring, 9 g. (0.075 mole) of *N,N*-dimethyl-1,3-propanediamine. The solution was heated carefully to 80° at which point a vigorous reaction took place and some cooling was necessary. Finally the mixture was heated at 100° for 3 hr. After cooling, the solid mass was dissolved in a minimum amount of water. The solution was made strongly basic with sodium hydroxide pellets. The oily layer was taken up in 1-butanol and the aqueous layer extracted with more 1-butanol. The 1-butanol extracts were dried over anhydrous sodium sulfate and the butanol removed under reduced pressure. The residue was fractionally distilled at 25 mm. The yield was 33%, b.p. 138–140°/25 mm., n_D^{25} 1.4815. The trihydrochloride was prepared from an acetone solution of the base and recrystallized from methanol-acetone, $[\alpha]_D^{22}$ −9.16° (1% in 95% ethanol).

4-β-Piperidinoethyl-1,4-diazabicyclo[4.3.0]nonane. To 6.8 g. (0.03 mole) of 1-β-chloroethyl-2-chloromethylpyrrolidine hydrochloride was added gradually 15 g. (0.12 mole) of 1-(2-aminoethyl) piperidine with stirring and warming. The reaction was less exothermic than when *N,N*-dimethyl-1,3-propanediamine was used. The mixture was then heated at 150° for 20 min. The mixture was worked up as in the case of 4-γ-dimethylaminopropyl-1,4-diazabicyclo [4.3.0]nonane except that chloroform was used as the extracting solvent. Fractional distillation *in vacuo* gave a 33% yield of product, b.p. 120–125°/0.5 mm. The trihydrochloride was prepared in 2-propanol solution and recrystallized from 2-propanol-methanol, $[\alpha]_D^{22}$ −12.44 (1% in 95% ethanol).

4-β-Phenylethyl-1,4-diazabicyclo[4.3.0]nonane. β-Phenylethylamine (7.2 g., 0.06 mole) was added slowly with stirring to 4.5 g. (0.02 mole) of 1-β-chloroethyl-2-chloromethylpyrrolidine hydrochloride. The reaction was quite exothermic. Finally the mixture was heated at 160–170° for 20 min. The mixture was worked up as in the case of the dimethylaminopropyl derivative except that ether was used as the extracting solvent. Fractional distillation gave a 35% yield of product, b.p. 122–124°/0.5 mm., n_D^{28} 1.5375. The dihydrochloride was made in ether solution and recrystallized from acetone-ether. The dimethiodide was made in boiling acetone and recrystallized from dry ethanol, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{28}N_2I_2$: C, 39.78; H, 5.48; N, 5.47; I, 49.35. Found: C, 39.88; H, 5.28; N, 5.44; I, 49.52.

From the original fractional distillation, a higher boiling fraction (200–210°/0.5 mm.) was obtained which proved to be 1-β-(β-phenylethyl)aminoethyl 2-β-phenylethylaminomethylpyrrolidine, yield 31%. It was converted to a trihydrochloride which was recrystallized from methanol-acetone, m.p. 256–257°.

Anal. Calcd. for $C_{23}H_{38}N_3Cl_3$: C, 59.93; H, 7.87; N, 9.12; Cl, 23.08. Found: C, 59.72; H, 7.67; N, 9.20; Cl, 22.88. A tripicrate, made in dry ethanol solution, melted at 225–226°.

Anal. Calcd. for $C_{41}H_{42}N_{12}O_{21}$: C, 47.40; H, 4.07; N, 16.18. Found: C, 47.21; H, 4.20; N, 16.30.

4-(α-Methyl-β-phenylethyl)-1,4-diazabicyclo[4.3.0]nonane. 1-(β-Chloroethyl)-2-chloromethylpyrrolidine hydrochloride (4.5 g., 0.02 mole) and 11 g. (0.08 mole) of α-methyl-β-phenylethylamine were refluxed for 18 hr. in 100 ml. of 50% aqueous acetone. The acetone was removed by distillation and the aqueous solution made strongly basic with sodium hydroxide. The solution was extracted with benzene and the extract dried over sodium sulfate and fractionally distilled *in vacuo.* The product distilled at 117–120°/0.2 mm., yield 46%. The dihydrochloride was prepared in 2-propanol solution and recrystallized from the same solvent, $[\alpha]_D^{22}$ −4.81 (1% in 95% ethanol).

The monomethiodide made in boiling acetonitrile was recrystallized from ethyl acetate, m.p. 134–135°.

Anal. Calcd. for $C_{17}H_{27}N_2I$: C, 52.80; H, 7.05; N, 7.27; I, 32.84. Found: C, 52.73; H, 6.89; N, 6.29; I, 32.90. The value for nitrogen was consistently about 1% low and could not be improved by recrystallizations.

4-(α,α-Dimethyl-β-phenylethyl)-1,4-diazabicyclo[4.3.0]nonane. This compound was prepared from α,α-dimethyl-β-phenylethylamine by the procedure used for making 4-(α-methyl-β-phenylethyl)-1,4-diazabicyclo[4.3.0]nonane.

The dipicrate melted at 202–203°.

Anal. Calcd. for $C_{29}H_{32}N_8O_{14}$: C, 48.65; H, 4.5; N, 15.63. Found: C, 48.72; H, 4.63; N, 15.54.

4-β-(4-Methoxyphenyl)ethyl-1,4-diazabicyclo[4.3.0]nonane. This compound was also prepared by the method used for making 4-(α-methyl-β-phenylethyl)-1,4-diazabicyclo[4.3.0]-nonane using β-4-methoxyphenylethylamine as the starting amine.

The dipicrate melted at 214–215°.

Anal. Calcd. for $C_{23}H_{30}N_8O_5$: C, 46.80; H, 4.22; N, 15.62. Found: C, 46.95; H, 4.45; N, 15.57.

4-β-(3,4-Dimethoxyphenyl)ethyl-1,4-diazabicyclo[4.3.0]nonane. To a stirred suspension of 9 g. (0.04 mole) of 1-β-chloroethyl-2-chloromethylpyrrolidine and 30 g. of powdered potassium carbonate in 100 ml. of refluxing xylene was slowly added a solution of 7.2 g. (0.04 mole) of β-3,4-dimethoxyphenylethylamine in 50 ml. of xylene. Refluxing was continued for 12 hr. and water was then added to dissolve the solids. The aqueous layer was separated and the xylene layer extracted with dilute hydrochloric acid. The acid extract was added to the aqueous layer and the solution made strongly basic with potassium hydroxide pellets. The oily layer was extracted with chloroform and the chloroform solution was dried over anhydrous sodium sulfate. Fractional distillation *in vacuo* gave a 30% yield of product, b.p 160–168°/0.1 mm. The dihydrochloride was made in ether solution and recrystallized from 2-propanol.

A dipicrate was prepared by adding an aqueous solution of lithium picrate to an aqueous solution of the dihydrochloride. It was recrystallized from water and then from acetone, m.p. 248–249°.

Anal. Calcd. for $C_{29}H_{32}N_8O_{16}$: C, 46.52; H, 4.31; N, 14.97. Found: C, 46.72; H, 4.50; N, 15.15.

7,9-Dikeio-1,8-diazabicyclo[4.3.0]nonane. Potassium isocyanate (2.7 g.) was added to a solution of 6.25 g. of ethyl pipecolate hydrochloride in 20 ml. of water. After standing overnight, 4 drops of concd. hydrochloric acid was added and the solution evaporated to dryness at 100°. The residue was extracted with hot acetone. The acetone solution was evaporated to dryness and the residual oil triturated with dry ether until it solidified. It was recrystallized from ether, m.p. 123–123.5°.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.50; H, 6.54; N, 18.30. Found: C, 54.70; H, 6.64; N, 18.51.

1,8-Diazabicyclo[4.3.0]nonane. To 11.4 g. (0.3 mole) of lithium aluminum hydride suspended in 300 ml. of dry tetrahydrofuran was added slowly 14 g. (0.09 mole) of 7,9-diketo-1,8-diazabicyclo[4.3.0]nonane in 50 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 8 hr. After cooling, 48 ml. of water was carefully added with stirring and the inorganic material removed by filtration. The precipitate was washed with 2-propanol and the washings were added to the tetrahydrofuran solution. The solution was concentrated under reduced pressure to an oil. The latter was taken up in ether and the solution dried over anhydrous sodium sulfate. Fractional distillation gave a 26% yield of 1,8-diazabicyclo[4.3.0]nonane, b.p. 155–156°, n_D^{23} 1.4740. The dihydrochloride was prepared in ethanol-ether solution and recrystallized from ethanol, m.p. 178–179°.

Anal. Calcd. for $C_7H_{16}N_2Cl_2$: C, 42.22; H, 8.10; N, 14.08; Cl, 35.60. Found: C, 42.05; H, 8.23; N, 14.20; Cl, 35.41.

A phenylurea derivative was prepared by treating the base with phenylisocyanate in dry ether solution. It was recrystallized from ethanol, m.p. 210–210.5°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.80; N, 17.13. Found: C, 68.74; H, 7.60; N, 16.95.

8-Ethyl-7,9-diketo-1,8-diazabicyclo[4.3.0]nonane. Ethyl pipecolate (3.2 g., 0.02 mole) was added to 1.4 g. of ethyl isocyanate in 25 ml. of cyclohexane. After standing for 2 hr., the solution was concentrated to a syrup on a steam bath. Several drops of concd. hydrochloric acid were added with stirring and a semisolid mass formed. This was extracted with ether and the ether solution dried over anhydrous sodium sulfate. After removing the ether, the residual oil was distilled *in vacuo*. The yield of 8-ethyl-7,9-diketo-1,8-diazabicyclo[4.3.0]nonane was 64%, b.p. 106–108°/0.1 mm., n_D^{26} 1.5004.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.7; N, 15.37. Found: C, 59.33; H, 7.9; N, 15.44.

8-Ethyl-1,8-diazabicyclo[4.3.0]nonane. A solution of 11 g. (0.06 mole) of 7,9-diketo-1,8-diazabicyclo[4.3.0]nonane in 25 ml. of dry ether was added solwly to a stirred suspension of 7.6 g. (0.2 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. The mixture was then refluxed for 24 hr. Thirty milliliters of water was carefully added and the mixture was stirred for 2 hr. 2-Propanol (100 ml.) was then added and the mixture filtered. After drying the filtrate over sodium sulfate, the solvent was removed and the residual oil distilled *in vacuo*. The yield was 67%, b.p. 98–100°/25 mm., n_D^{24} 1.4730.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.10; H, 11.76; N, 18.15. Found: C, 70.24; H, 11.58; N, 18.22.

When a sample of the base was treated with methyl *p*-toluenesulfonate in ether solution, a dimetho-*p*-toluenesulfonate was obtained. It was recrystallized from acetone, m.p. 210–210.5°.

Anal. Calcd. for $C_{25}H_{38}N_2S_2O_6$: C, 56.90; H, 7.27; N, 5.32. Found: C, 56.82; H, 7.36; N, 5.41.

8-Butyl-7,9-diketo-1,8-diazabicyclo[4.3.0]nonane. This compound was prepared by the procedure used for 8-ethyl-7,9-diketo-1,8-diazabicyclo[4.3.0]nonane. The yield was 69%, b.p. 155–158°/2 mm., n_D^{28} 1.4928.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.80; H, 8.69; N, 13.32.

8-Butyl-1,8-diazabicyclo[4.3.0]nonane. The corresponding keto compound was reduced with lithium aluminum hydride as described for the preparation of 8-ethyl-1,8-diazabicyclo-[4.3.0]nonane. The yield was 65%, b.p. 115–117°/10 mm., n_D^{25} 1.4718.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.47; H, 12.17; N, 15.36. Found: C, 72.63; H, 12.31; N, 15.22.

A dimetho-*p*-toluenesulfonate was prepared by treating the base in ether solution with methyl *p*-toluenesulfonate. It was recrystallized from methanol-acetone, m.p. 176–177°.

Anal. Calcd. for $C_{27}H_{42}N_2S_2O_6$: C, 58.48; H, 7.63; N, 5.05; S, 11.54. Found: C, 58.62; H, 7.81; N, 4.90; S, 11.70.

Preparation of 2-alkylaminomethylpiperidines from 8-alkyl-1,8-diazabicyclo[4.3.0]nonanes. When any of the 1,8-diazabicyclo[4.3.0]nonanes were treated with 2*N* hydrochloric acid, the odor of formaldehyde was immediately discernible. A stream of nitrogen passed through the solution and then into a solution of 2,4-dinitrophenylhydrazine producing a precipitate of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 165–166°. Evaporation of the hydrochloric acid solutions gave the corresponding aminomethylpiperidine hydrochlorides. The latter were recrystallized from methanol-acetone or ethanol-ether. The yields were nearly quantitative.

1,8-Diazabicyclo[4.3.0]nonane → 2-Aminomethylpiperidine dihydrochloride, m.p. 177–178°.

Anal. Calcd. for $C_6H_{16}N_2Cl_2$: C, 38.50; H, 8.62; N, 14.98; Cl, 37.90. Found: C, 38.31; H, 8.72; N, 14.78; Cl, 37.68.

8-Ethyl-1,8-diazabicyclo[4.3.0]nonane → 2-Ethylaminomethylpiperidine dihydrochloride, m.p. 201–202°.

Anal. Calcd. for $C_8H_{20}N_2Cl_2$: C, 44.70; H, 9.37; N, 13.03; Cl, 32.92. Found: C, 44.68; H, 9.21; N, 12.95; Cl, 32.82.

8-*n*-Butyl-1,8-diazabicyclo[4.3.0]nonane → 2-Butylaminomethylpiperidine dihydrochloride, 192.5–193°.

Anal. Calcd. for $C_{10}H_{22}N_2$: C, 49.45; H, 9.97; N, 11.53; Cl, 29.15. Found: C, 49.65; H, 9.80; N, 11.61; Cl, 29.32.

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