2ζ-Fluoro-6α-methylhydrocortisone acetate (IIIb, R′ = Ac). By means of the oxidative hydroxylation procedure described above for preparing 2ζ-fluorohydrocortisone acetate, 1.84 g. of the amorphous 21-acetate described above was converted to 1.30 g. of 2ζ-fluoro-6α-methylhydrocortisone acetate. The latter was eluted by 15% acetone in Skellysolve B from the column of 130 g. of Florisil upon which the total crude reaction product was adsorbed. The chromatographically purified product was amorphous and no solvent was found from which it could be crystallized. A sample eluted from the column was analyzed.

Anal. Calcd. for $C_{24}H_{33}FO_6$: C, 66.03; H, 7.62; F, 4.35. Found: C, 66.69; H, 7.66; F, 3.25. λ_{max} 242 mμ, ε 13,280. The infrared spectrum exhibited the expected absorption bands, including one at 1685 cm.$^{-1}$, attributable to the conjugated carbonyl at C-3, raised by the adjacent fluorine.

2ζ-Fluorocortisone acetate (IVa). A solution of 0.5 g. of 2ζ-fluorohydrocortisone acetate in 15 ml. of methylene chloride was mixed with a solution of 0.35 g. of sodium dichromate dihydrate in 5.0 ml. of water and 0.8 ml. of concentrated sulfuric acid at room temperature. The mixture was stirred for 4 hr. The methylene chloride layer was separated, washed with dilute sodium sulfite solution, saturated aqueous sodium bicarbonate and dried over sodium sulfate. Evaporation to dryness left a white crystalline solid, which, after 2 recrystallizations from ethanol, melted at 229–244° (Kofler block). The infrared spectrum of this substance showed bands at 3565 cm.$^{-1}$ (OH); 1743 cm.$^{-1}$ (acetate); 1730 cm.$^{-1}$ (20-ketone); 1700 cm.$^{-1}$ (11-ketone); 1667 cm.$^{-1}$ (conjugated carbonyl at C-3); and 1617 cm.$^{-1}$ (4:5 double bond). The band at 1667 cm.$^{-1}$ is typical of a Δ^4-3-ketone without α-halo substitution, and would be expected to be raised 10–20 cm.$^{-1}$ by the presence of the adjacent fluorine; analysis also indicated partial loss of fluorine.

Anal. Calcd. for $C_{23}H_{29}FO_6$: C, 65.70; H, 6.95; F, 4.52 Found: C, 66.05; H, 6.93; F, 3.43. λ_{max} 237 mμ, ε 14,175. $[\alpha]_D$ +240° ($CHCl_3$).

Descending chromatography on paper, using formamide as the stationary phase and Skellysolve B as the mobile phase, showed that the compound moved faster than 2-fluorohydrocortisone acetate, but slower than cortisone acetate

2ζ-Fluoro-6α-methylcortisone acetate (IVb). A sample of the chromatographed, amorphous 2-fluoro-6α-methylhydrocortisone acetate was oxidized with a solution of sodium dichromate in acetic acid for 1 hr. at room temperature. The mixture was poured into cold water and extracted with methylene chloride; the latter solution was washed successively with sodium sulfite solution, sodium bicarbonate solution, and water, then dried and evaporated. The residue crystallized from methanol, and melted at 222–225° with sintering at 207°. Evidence that this was 2ζ-fluoro-6α-methylcortisone acetate was given by a positive Tollens test, an infrared absorption spectrum of the expected type, an ultraviolet absorption maximum at 237 mμ (ε 14,250), and the following analysis:

Anal. Calcd. for $C_{24}H_{31}FO_6$: C, 66.34; H, 7.19; F, 4.37. Found: C, 66.94; H, 7.25; F, 3.30. $[\alpha]_D$ +216° ($CHCl_3$).

Acknowledgment. We wish to express our appreciation to Messrs. R. A. Houtman, W. A. Struck, R. C. Anderson, and S. R. Shaw for analyses and rotatory dispersion curves, to Dr. J. L. Johnson, M. F. Grostic, and J. E. Stafford for infrared and ultraviolet spectroscopy, and to J. D. Highstrete for technical assistance.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH]

Hypotensive Agents. XI. 3-Azabicyclohexane and 3-Azabicycloheptane Derivatives

LEONARD M. RICE

Received April 27, 1959

Dialkylaminoalkyl substituted bases containing the 3-azabicyclo[3:1:0]hexane[1] and 3-azabicyclo[3:1:1]heptane ring systems have been prepared and quaternized to asymmetric bis-quaternary salts. The 3-azabicyclo[3:1:0]hexane derivatives were synthesized from 1,2-cyclopropane dicarboxylic acid anhydride and caronic anhydride respectively. The 3-azabicyclo-[3:1:1]heptane derivatives were prepared by employing norpinic anhydride. Reaction of the anhydrides with appropriate dialkylaminoalkylamines yielded the corresponding imides, by way of the amic acids, which were subjected to lithium aluminum hydride reduction to give the bicyclic bases. Quaternization yielded the bis-ammonium salts which were screened for hypotensive activity.

The high biological activity which we have previously encountered in many series of unsymmetrical bis-ammonium salts containing bi- and tricyclic nitrogen heterocycles has led us to extend this work and synthesize derivatives of 3-azabicyclo[3:1:0]hexane, VII and VIII, and 3-azabicyclo-[3:1:1]heptane, IX. Prior studies of related bicyclic ring systems have been concerned with quaternary derivatives containing the 3-azabicyclo-[3:2:0]heptane nucleus I,[2] the 3-azabicyclo[3:2:1]-octane nucleus II[3] and III,[4] the 3-azabicyclo-[3:3:0]octane nucleus IV,[5] the 3-azabicyclo[3:3:1]-

(1) Other compounds containing this ring system have recently been prepared wherein the substitution was 6,6-diaryl. Private communication, Dr. P. B. Russell, Abstracts, 135th National Meeting, ACS, Boston, Mass., April 1959. Organic division 59.

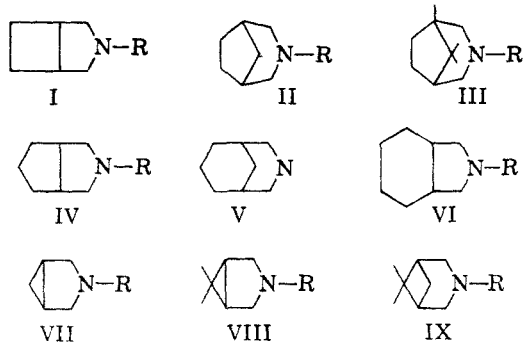
(2) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 1100 (1957).

(3) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 185 (1957).

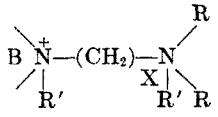
(4) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

(5) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **24**, 7 (1959).

nonane nucleus V,[6] and many derivatives of the 3-azabicyclo[4:3:0]nonane nucleus, VI.[7]



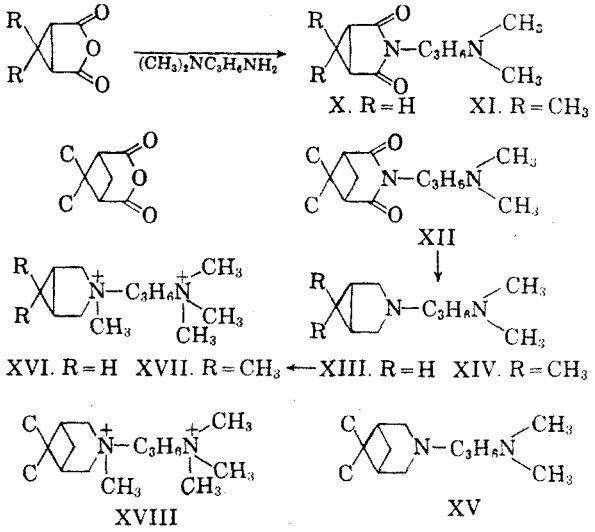
Early in our work it was noted that the most favorable arrangement of atoms for good hypotensive response was contained in the structure as shown below[7] where R′ is methyl or ethyl or a part of a small heterocycle, R′ is methyl or ethyl, X is 2 or 3 and B is a bi- or tricyclic ring.



This has since been confirmed by Cavallito and his co-workers.[8–10] Because in all these series of unsymmetrical bis-ammonium salts the most effective combination was found to be either the dimethylaminoethyl or dimethylaminopropyl side chain in which the quaternizing group was also methyl, we have used this grouping in the present investigation.

It is to be noted that all of the compounds prepared are either 3,4-polymethylene bridged pyrrolidines or 3,5-polymethylene bridged piperidines with or without additional bridging or substitution. To date the most favorable ring systems for good hypotensive response have been found in those compounds containing the dimethylene, trimethylene, and tetramethylene bridged pyrrolidine rings or the dimethylene bridged piperidine types. To further study and clarify the structure activity relationship in these series, it was desirable to prepare compounds wherein the bridging consisted of a lone methylene carbon atom. This report is concerned with the synthesis of bases containing such ring systems, which have not been previously reported in the literature in their completely reduced states.

The synthesis of the *N*-substituted ring system, 3-azabicyclo[3:1:0]hexane and its 6,6-dimethyl substituted analogue, was achieved by employing cyclopropane dicarboxylic anhydride and caronic anhydride respectively as the key intermediates. Cyclopropane dicarboxylic anhydride was prepared by both the methods of Guthzeit[11,12] and of Wiberg.[13] Caronic anhydride was synthesized by the elegant method of Perkin.[14] The corresponding *N*-substituted 3-azabicyclo[3:1:1]heptane was obtained employing norpinic anhydride as the starting material. Norpinic anhydride was obtained by the method of Kerr[15] as modified by Guha.[16] In general, the appropriate anhydride was reacted with a slight excess of dimethylaminopropylamine.



The resultant mixture of imide and amic acid was heated and maintained at 180–190° for two hours in order to complete the cyclization. The dione bases were obtained in good yields as distillable colorless oils. These imide bases and their corresponding hydrochloride and methonium salts are listed in Table I together with pertinent data.

Reduction of the imides was carried out by the addition of an ethereal solution of the dione to an ethereal solution of lithium aluminum hydride at such a rate as to just maintain reflux of the reaction solvent. The reduction products were isolated by distillation in excellent yields as colorless oils. The relevant data are shown in Table II.

A related dione, caronimide, containing the azabicyclohexane structure has been previously reported but attempted electrolytic reduction re-

(6) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 844 (1958).
(7) L. M. Rice and C. H. Grogan, *J. Am. Chem. Soc.*, **75**, 4911 (1953).
(8) C. J. Cavallito, A. P. Gray, and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).
(9) C. J. Cavallito, A. P. Gray, and T. B. O'Dell, *Arch. intern. pharmacodynamie*, **101**, 38 (1955).
(10) A. P. Gray, D. E. Heitmeier, and C. J. Cavallito, *J. Am. Chem. Soc.*, **81**, 728 (1959).
(11) M. Conrad and M. Guthzeit, *Ber.*, **1185** (1884).
(12) A. Wasserman, *Helv. Chim. Acta*, **13**, 213, 229 (1930).
(13) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4997 (1957).
(14) W. H. Perkin, Jr., and J. F. Thorpe, *J. Chem. Soc.*, **75**, 57–60 (1899).
(15) C. A. Kerr, *J. Am. Chem. Soc.*, **51**, 614 (1929).
(16) P. C. Guha and K. Ganapathi, *Ber.*, **69**, 1189 (1936).

TABLE I

N-DIMETHYLAMINOPROPYL-3-AZABICYCLOALKANEDIONES AND DERIVATIVES

Compound	Formula	B.P., °C.	Mm.	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Ionic Halogen Calcd.	Ionic Halogen Found
X	$C_{10}H_{16}N_2O_2$	106–107	0.4	61.20	60.97	8.22	8.13	14.28	14.29		
XI	$C_{12}H_{20}N_2O_2$	101–111	0.3	64.25	64.34	8.99	8.87	12.49	12.41		
XII	$C_{13}H_{22}N_2O_2$	90–92	0.1	65.51	65.12	9.31	9.42	11.75	11.50		
				HYDROCHLORIDES							
X	$C_{10}H_{17}N_2O_2Cl$	215–216[a]		51.61	51.63	7.36	7.47	12.04	11.76	15.23	14.95
XI	$C_{12}H_{21}N_2O_2Cl$	162–163[a]		55.27	55.28	8.12	8.04	10.74	10.53	13.60	13.50
XII	$C_{13}H_{23}N_2O_2Cl$	214–215[a]		56.82	56.89	8.44	8.72	10.20	10.27	12.90	13.02
				METHIODIDES							
X	$C_{11}H_{19}N_2O_2I$	200–201[a]		39.06	39.27	5.66	5.92	8.28	8.15	37.53	37.40
XI	$C_{13}H_{23}N_2O_2I$	237–238[a]		42.63	42.36	6.33	6.33	7.65	7.43	34.65	34.40
XII	$C_{14}H_{25}N_2O_2I$	215–216[a]		44.22	44.39	6.63	6.35	7.37	7.41	33.38	33.34

[a] M.p., °C.

TABLE II

N-DIMETHYLAMINOPROPYL-3-AZABICYCLOALKANES

Compound	Formula	B.P., °C.	Mm.	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Ionic Halogen Calcd.	Ionic Halogen Found
XIII	$C_{10}H_{20}N_2$	84–85	10	71.37	70.19[a]	11.98	11.91	16.65	16.38		
XIV	$C_{12}H_{24}N_2$	104–106	14	73.41	72.62[a]	12.32	12.17	14.27	14.00		
XV	$C_{13}H_{26}N_2$	118–120	12	74.22	74.35	12.46	12.20	13.32	12.95		
				DIHYDROCHLORIDES							
XIII	$C_{10}H_{22}N_2Cl_2$	237–238[b]		49.79	49.65	9.19	9.27	11.62	11.61	29.40	29.50
XIV	$C_{12}H_{26}N_2Cl_2$	230–231[b]		53.52	53.28	9.73	9.43	10.41	10.27	26.34	26.30
XV	$C_{13}H_{28}N_2Cl_2$	248–249[b]		55.12	55.21	9.96	10.01	9.89	9.68	25.03	25.48
				DIMETHIODIDES							
XVI	$C_{12}H_{26}N_2I_2$	277–278[b]		31.89	32.17	5.80	5.85	6.19	6.02	56.14	56.10
XVII	$C_{14}H_{30}N_2I_2$	227–228[b]		35.01	34.95	6.36	6.02	5.83	5.59	52.86	52.53
XVIII	$C_{15}H_{32}N_2I_2$	230–231[b]		36.45	36.51	6.53	6.49	5.69	5.44	51.36	51.40

[a] Analysis of the free base invariably gave a low carbon due to difficulty of complete combustion. [b] M.p., °C.

sulted in ring cleavage.[17] In view of this and other work by Simonsen *et al.*,[18,19] it was thought possible in the case of 3-azabicyclo(3:1:0)hexane that the reduction might open the cyclopropane ring yielding a monocyclic compound. We therefore prepared the corresponding *N*-substituted dimethylaminopropyl piperidine for direct comparison. The infrared spectra of the two compounds was different as well as the melting points of their respective hydrochloride salts. The refractive indexes of the two bases were also different, *N*-dimethylaminopropyl-3-azabicyclo[3:1:0]hexane n_D^{26} 1.463, *N*-dimethylaminopropyl piperidine n_D^{26} 1.458.

Quaternization by methyl iodide of the 3-azabicyclo[3:1:0]-hexane bases proceeded readily to yield the bis-ammonium salts. In the case of 3-azabicyclo[3:1:1]heptane, however, the quaternization was more difficult and had to be performed in a bomb tube. This is in keeping with most other 3,5-polymethylene bridged piperidines which we have worked with previously.

Pharmacology. The hypotensive activity of these compounds was evaluated on dogs by means of the cannulation technique under nembutal anesthesia. As expected from previous studies, diones, when tested as either their hydrochloride or methonium salts, were inactive. The dihydrochlorides of the reduced bases were also inactive. The bis-quaternary methonium salts of the base were of graded activity. Dimethylaminopropyl-3-azabicyclo[3:1:0]-hexane dimethiodide had a low order of activity whereas its dimethyl analogue had increased activity. The introduction of another carbon in the bridging, as in XVIII, resulted in increased biological potency. This compound was approxi-

(17) K. N. Menon and J. L. Simonsen, *J. Chem. Soc.*, 303 (1929).

(18) S. N. Iyer and J. L. Simonsen, *J. Chem. Soc.*, 2049 (1926).

(19) K. V. Hariharan, K. N. Menon, and J. L. Simonsen, *J. Chem. Soc.*, 431 (1928).

mately $^1/_2$ the potency of the ring system III bearing the same side chain.[20,21]

EXPERIMENTAL

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane-2,4-dione. A total of 16.8 g. (0.15 mole + 10% excess) of dimethylaminopropylamine was added to 21 g. (0.15 mole) of caronic anhydride contained in a 50-ml. round bottom flask. After the immediate exothermic reaction subsided, the reaction mixture was stirred and heated gently until a homogeneous melt was obtained. The temperature was slowly raised to 180–190° and maintained for 2 hr. The imide was isolated by distillation *in vacuo* to yield 28 g., 83%, of product, b.p. 101–111° at 0.3 mm.

The *hydrochloride* was prepared in isopropyl alcohol with excess alcoholic HCl and precipitated with ether. On recrystallization from isopropyl alcohol–ether it melted at 162–163°.

The *methiodide* was prepared in ethyl acetate with a slight excess of methyl iodide and recrystallized from isopropanol-ether, m.p. 237–238°.

N-Dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]-hexane. A solution of 12 g. (excess) of lithium aluminum hydride in 800 ml. of anhydrous ether was prepared in a 2-liter, 3-necked reaction flask fitted with a stirrer, dropping funnel, and condenser, and protected from atmospheric moisture. A solution of 22.4 g. (0.1 mole) of 3-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:0]hexane-2,4-dione in 400 ml. of anhydrous ether was added dropwise with stirring at such a rate as to just maintain reflux of the ether. The reaction mixture was stirred an additional 2 hr. and then decomposed by dropwise addition of water. After an hour of additional stirring the inorganic precipitate was filtered and washed with 3 portions of ether, which were combined with the filtrate and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled under reduced pressure to yield the base, 18 g., 91%, b.p. 104–106° at 14 mm.

The *hydrochloride* was prepared in the usual manner, m.p. 230–231°.

The *dimethiodide* was prepared by refluxing the base dissolved in absolute alcohol with a 10% excess of methyl iodide for several hours, m.p. 227–228°.

All of the compounds were prepared as outlined in the above examples except the *dimethiodide of N-dimethylaminopropyl-6,6-dimethyl-3-azabicyclo[3:1:1]heptane.* In this case, the base dissolved in methanol was heated in a bomb tube for 4 hr. with a 10% excess of methyl iodide. The product was washed out of the bomb tube, precipitated with ether and recrystallized several times from alcohol ether, m.p. 231°.

RADNOR, PA.

(20) W. E. O'Malley, G. W. Haemmerli, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **47**, 263 (1958).

(21) This compound is known as Wy-1395, Trimethidinium, and OSTENSIN.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, DIAMOND ALKALI COMPANY]

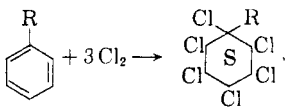
The Addition-Chlorination of Phenol[1]

IRVING ROSEN AND JOHN P. STALLINGS

Received April 28, 1959

Benzene derivatives with strong electron releasing groups such as phenol have not been addition-chlorinated in the past because of the ease with which they undergo substitution. The modification of the electron releasing properties of the hydroxy group in phenol by the use of electron withdrawing groups attached to the oxygen atom permits addition-chlorination to take place readily. Phenyl haloacetates were addition-chlorinated in good yields. Hydrolysis of the addition products suggests that the major stable product from the addition-chlorination of phenol is 2,4,6-trichlorophenol.

The literature contains descriptions of the addition-chlorination of several substituted benzenes. The most comprehensive study of these reactions was made by T. van der Linden.[2] The reactions he studied are summarized below. The most recent work reported on this reaction with substituted benzenes dwelled upon the effect of reaction conditions on the product yields.[3,4]



where R = F, CN, COCl, COOH, NO_2, CCl_3, $CHCl_2$, CH_2Cl, CH_3

A common property of these substituted benzenes is that they do not readily undergo chlorine substitution without the presence of an acid catalyst. Under conditions favorable for addition-chlorination, the addition reaction can take place instead of the substitution reaction. In some cases both reactions have occurred. Some of the major products isolated from reactions of this sort have been substituted by chlorine and then addition-chlorinated.

Among the compounds missing from the above are those which contain strong electron releasing groups and which readily undergo substitution-chlorination, even in the absence of an acid catalyst, *i.e.*, compounds such as phenol and aniline.

(1) Presented before the Organic Division at the 135th Meeting of the American Chemical Society, Boston, Mass., April 10, 1959.

(2) T. van der Linden, *Rec. trav. chim.*, **53**, 45 (1934); **53**, 703 (1934); **55**, 282 (1936); **57**, 342 (1938); **57**, 1075 (1938).

(3) D. E. Harmer, *AECU-3077* (1955).

(4) I. Rosen and J. P. Stallings, *Ind. & Eng. Chem.*, **50**, 1511 (1958).