long needles of *3-fluoro-4-nitrofluorene*, m.p. 147–147.5°; C—F stretching: 8.44 μ.

Anal. Calcd. for $C_{13}H_8FNO_2$: C, 68.12; H, 3.52. Found: C, 67.63; H, 3.46.

3-Fluoro-7-nitrofluorenone. Oxidation of 100 mg. of the fluorene derivative by 200 mg. of chromium trioxide in 5 ml. of acetic acid yielded 48 mg. of yellow needles, m.p. 276–277°, after crystallization from acetic acid. Main peaks in ultraviolet spectrum: λ_{max} 241.5 mμ (ϵ = 18,100), 282 (23,100), 323 (4320), 337.5 (3440); λ_{min} 258 (12,600), 317 (3,940), 332 (3250).

Anal. Calcd. for $C_{13}H_6FNO_3$: C, 64.20; H, 2.49. Found: C, 64.34; H, 2.78.

3-Fluorofluorenamines and acetyl derivatives. The isomeric 3-fluoronitrofluorenes were reduced catalytically (platinum oxide) in ethanol solution in 80–90% yields. The acetyl derivatives were produced in similar yields by the action of acetic anhydride on a benzene solution of the amines. Pertinent data for the compounds are listed below. *3-Fluoro-2-fluorenamine*, m.p. 131–131.5° (from water, cyclohexane). λ_{max} 282 mμ (ϵ = 18,700), 320 (12,600); λ_{min} 243.5 (1,790), 308.5 (11,400). C—F band, 8.66 μ.

Anal. Calcd. for $C_{13}H_{10}FN$: C, 78.37; H, 5.06. Found: C, 78.94; H, 5.26.

N-(3-Fluoro-2-fluorenyl)acetamide, m.p. 194–195° (from ethanol). C—F band, 8.64 μ.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.02. Found: C, 74.24; H, 4.96.

3-Fluoro-4-fluorenamine, m.p. 118–119° (from water, cyclohexane). Ultraviolet spectrum (main peaks of complex curve): λ_{max} 213 mμ (ϵ = 26,100), 250 (11,400), 261 (11,800), 270 (13,100), 299 (6,400), 315 (6,100); λ_{min} 242 (10,000), 279 (4,300). C—F band, 8.48–8.55 μ.

Anal. Found: C, 78.26; H, 5.31.

N-(3-Fluoro-4-fluorenyl)acetamide, m.p. 227–228° (from benzene). C—F band, 8.55 μ.

Anal. Found: C, 74.57; H, 5.20.

6-Fluoro-2-fluorenamine, m.p. 125–126° (from aqueous ethanol, water, cyclohexane) obtained by reduction of 3-fluoro-7-nitrofluorene. λ_{max} 295 mμ (ϵ = 17,900); λ_{min} 245 (2,090). C—F band, 8.58 μ.

Anal. Found: C, 78.29; H, 5.06.

N-(6-Fluoro-2-fluorenyl)acetamide, m.p. 198–199° (from ethanol). C—F band, 8.52 μ.

Anal. Found: C, 74.71; H, 5.24.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Adrenal Hormones and Related Compounds. V.[1] 2-Fluorinated Cortical Hormones

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A preparation of 2-fluoro-Δ^4-3-ketosteroids is described, making use of the reaction of perchloryl fluoride with the enolates of 2-ethoxyoxalyl-Δ^4-3-ketosteroids. By applying this procedure to the cortical hormone precursors 11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia) and the corresponding 6α-methyl derivative (Ib), the 2-fluoro derivatives of hydrocortisone acetate (IIIa) and 6α-methylhydrocortisone acetate (IIIb) have been prepared.

Marked modification of hormonal properties of steroids is brought about by substitution of fluorine at the 6[2a], 9[2b], or 12[2c] positions. We have now prepared some cortical hormone derivatives with fluorine substituted at C-2.[3]

The activation of a ring or side chain α-ketone position of a steroid by ethoxalylation to facilitate and direct electrophilic substitution by alkyl halide[4] or halogen,[5] respectively, has been described. Perchloryl fluoride, which has recently been found capable of fluorinating carbanions under mild conditions,[6] has now been employed with steroid 2-ethoxalylates, and has been found to produce simply and in good yields the correspondingly substituted fluoro steroids.

Direct ethoxalylation of the cortical hormones was previously found unsatisfactory[7] as a route to the 2 - methyl derivatives. The preferred intermediate was 11β-hydroxy-21-acetoxy-4,17(20)-[*cis*]-pregnadien-3-one (Ia, R′ = Ac),[4] which was

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(4) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

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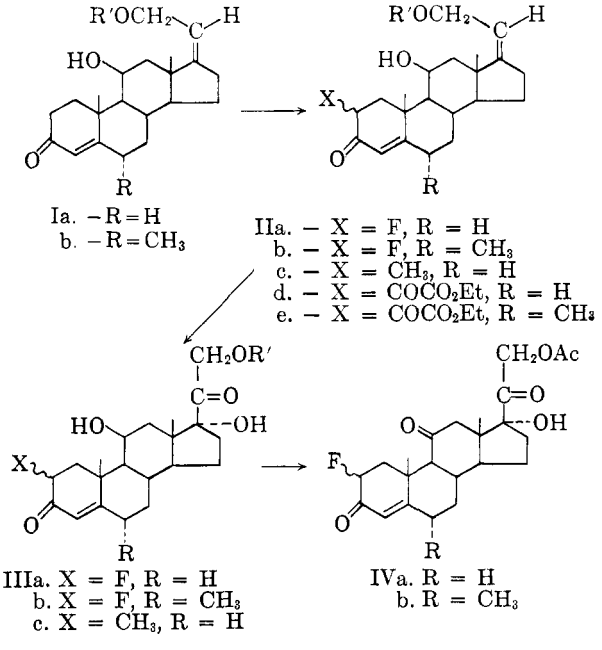
(6) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, Abstracts of Papers, 134th National Meeting, ACS, Chicago, Ill., Sept. 7–12, 1958; C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

(7) Unpublished results obtained in connection with the work reported in ref. (4).

methylated *via* its 2-ethoxyoxalyl derivative (IId), and then converted by oxidative hydroxylation of the side chain to the cortical hormone analog (IIIc).[4] IId proved also to be a suitable intermediate for the present fluorination studies. The major product of the reaction of IId with perchloryl fluoride, obtained in yields up to 59% after removal of the ethoxyoxalyl group and chromatographic purification, was 2-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one (IIa). After reacetylation at C-21, the cortical side chain was introduced by oxidation with *N*-methylmorpholine oxide–hydrogen peroxide in the presence of catalytic amounts of osmium tetroxide,[8] or with phenyliodosoacetate and osmium tetroxide,[4] giving 2-fluorohydrocortisone acetate (IIIa, R′ = Ac) in 72% yield. 2-Fluorocortisone acetate (IVa) was prepared by oxidation of IIIa with sodium dichromate.



An analogous series of reactions carried out on 6α-methyl-11β-hydroxy-21-acetoxy-4,17(20)-[*cis*]-pregnadien-3-one[1] (Ib) afforded the corresponding 2-fluoro-6α-methyl derivatives IIb (R′ = H), IIb, (R′ = Ac) and IIIb (R′ = Ac). The 2-fluoro-6α-methylhydrocortisone acetate so obtained resisted crystallization; although it remained amorphous after chromatographic purification it appeared homogeneous, and afforded a crystalline 11-ketone (IVb) on oxidation with sodium dichromate.

The newly introduced fluorine atom is considered to be in the stable configuration on the basis of the following observation. Attempts to isomerize 2-fluorohydrocortisone acetate (IIIb) with dry hydrogen chloride in chloroform at 0° for 2 hr. did not alter the rotatory dispersion curve of the crude product. Recrystallization afforded pure 2-fluorohydrocortisone acetate identical in all respects to the starting sample. No other material could be isolated.

The stable configurations of α-halocyclohexanones have been related to differences in energy due to (1) electrostatic interaction in the equatorial conformer and (2) steric compression in the axial conformer.[9] Thus the equatorial isomer is more stable in the 2-chloro and 2-bromo-3-keto-Δ^4 steroids. The energetics have not been extended to include fluorine which is both the smallest halogen and the most electro-negative element known. While the stable conformer in the 2-fluoro steroids may well be *equatorial*, rotatory dispersion curves of hydrocortisone acetate and of its 2-fluoro derivative exhibit differences in the characteristic double trough[10] in the 300–360 mμ region which may be attributed to the influence of an axial substituent adjacent to the chromophore.[11] Accordingly, a definitive assignment is not being made at this time.

The infrared absorption maximum for the Δ^4-3-ketone is displaced by fluorine toward higher wave numbers by about 30 cm.$^{-1}$ This shift is in good agreement with that observed by Jensen for 2-fluorocholestan-3-one and appears consistent with that to be expected for equatorial α-fluorocyclohexanones.[12] Studies are presently underway to permit a definitive assignment of configuration. This work, as well as a description of a number of other 2-fluoro-Δ^4-3-ketosteroids which have been prepared in these laboratories, will be reported in future publications.

The physiological properties of these 2-fluorocorticoids are under investigation in the Endocrinology Department of these laboratories. Preliminary biological assay[13] of 2-fluorohydrocortisone acetate and of 2-fluoro-6α-methylhydrocortisone acetate in general corroborated the conclusions reported by Kissman, *et al.*,[3] that the 2-fluoro substituent apparently lacked the remarkable potentiating action shown by the 9α-fluoro-, 2α-methyl- and 6α-fluoro groups.

(8) U. S. Patent 2,769,823; B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, 80, 2326 (1958).

(9) E. J. Corey, *J. Am. Chem. Soc.*, 75, 2301 (1953); *J. Am. Chem. Soc.*, 76, 175 (1954).

(10) C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(11) Unpublished studies by W. A. Struck and R. A. Houtman of these laboratories.

(12) Reported shifts for α-halocyclohexanones are:
equatorial: bromine, 17–23 cm.$^{-1}$; chlorine, 26–31 cm.$^{-1}$
axial: bromine, −2–8 cm.$^{-1}$; chlorine, 10–18 cm.$^{-1}$
For axial fluorine, the 9α-fluoro-11-ketosteroids exhibit a shift of 20 cm.$^{-1}$ while the corresponding chloro and bromo compounds exhibit shifts of 8 and 2 cm.$^{-1}$, respectively.

(13) Private communication from Drs. R. O. Stafford, W. E. Dulin, and F. L. Schmidt, to whom we are grateful for the biological studies.

EXPERIMENTAL

General procedure for preparing 2-fluoro-Δ^4-3-ketosteroids. A solution of 0.02 mole of the steroid in 100 ml. of commercial tertiary butyl alcohol was prepared by heating to 55–80°, while stirring and flushing the atmosphere above the solution with a gentle stream of nitrogen. The source of heat was removed and 5.45 ml. (0.04 mole) of ethyl oxalate was added all at once to the warm solution, followed immediately by sufficient methanolic sodium methoxide solution[14] to contain 1.62 g. (0.03 mole) of sodium methoxide. Generally the yellow sodium enolates of the 2-ethoxalylates began to precipitate within a few minutes. The mixture was stirred under nitrogen, without further heating, for about 1.5 hr.; then 300 ml. of absolute ether was added to the suspension of the sodium enolate, and the latter was collected by filtration on a Büchner funnel. These sodium salts were all hygroscopic in varying degrees, so that care had to be taken not to condense atmospheric moisture on them by virtue of the large cooling effect of evaporating ether. In highly humid atmospheres, therefore, the precipitate was covered by a rubber dam while applying vacuum in order to express all possible solvent. By the time nearly all the ether had evaporated and the precipitate had warmed up to ambient temperature again, handling difficulties usually became negligible. The precipitate could be stored conveniently in a desiccator over Drierite.

The dry sodium enolate was dissolved in 170 ml. of methanol and the solution cooled to −10 to −15° in an ice salt bath, with protection from atmospheric moisture. A nitrogen atmosphere was again maintained. Perchloryl fluoride gas from a cylinder was passed into 100 ml. of methanol at 0 to +5°, until the weight gain was 2.9 to 3.4 g. The cold solution of perchloryl fluoride was added to the solution of sodium enolate with stirring, at a rate such as to keep the temperature below −5°. Five to 10 min. were generally required for the addition. The solution was stirred for 0.5 hr. longer in the ice salt bath, and then an amount of methanolic sodium methoxide solution calculated to neutralize all the perchloryl fluoride originally weighed was added. The solution was stirred an additional 0.5 hr., concentrated to about 1/3 its volume under reduced pressure, and then poured into about 750 ml. of cold water. The precipitate of crude product was collected, washed with water, and dried in a vacuum desiccator over Drierite. It was purified by chromatography on Florisil, using about 40 g. of Florisil per gram of crude steroid, and developing the column with increasing concentrations of acetone in hexanes (Skellysolve B), starting with 5% and increasing to 20% acetone, by volume. The steroidal products were generally eluted by 10% or 20% acetone, and were isolated from the appropriate column fractions in fairly pure condition. A single recrystallization usually sufficed to give a sample pure enough for analysis.

2ζ-Fluoro-11β,21-dihydroxy-4,17(20)-[cis]-pregnadien-3-one (IIa, R′ = H). Application of the general procedure to 7.45 g. of 11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one-21-acetate[5] (Ia, R′ = Ac) furnished 3.43 g.[15] (49.2%) of 2ζ-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one, m.p. 155–162°, as isolated in crystalline state from the 20% acetone–Skellysolve B eluates of the chromatographic column. After two recrystallizations from a mixture of ethyl acetate and Skellysolve B, a sample of the compound melted at 176.5–178.5°; however the m.p. was not reproducible even under controlled rates of heating, and samples that were indistinguishable analytically melted at various ranges between 170–186°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39; F, 5.45. Found: C, 72.49; H, 8.21; F, 5.35. $[\alpha]_D$ +195° ($CHCl_3$). λ_{max} 241.5 mμ, ε 13,850.

In addition to the free alcohol, the *21-acetate* (IIa, R′ = Ac) was isolated in 2–5% yields from the 7% acetone in Skellysolve B eluates of the column, as crystals melting at 163–169°. The melting point of this compound was elevated to a fairly reproducible value of 201–210°. by recrystallization from 95% alcohol.

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00; F, 4.87. Found: C, 70.95; H, 8.00; F, 4.61. $[\alpha]_D$ +185°. λ_{max} 251 mμ, ε 14,775.

The *21-acetate* (IIa, R′ = Ac) was also prepared by acetylation of the 21-alcohol with acetic anhydride in pyridine at room temperature. A solution of 2.97 g. of the alcohol in 20 ml. of pyridine and 25 ml. of acetic anhydride was kept at room temperature in a nitrogen atmosphere for 20 hr. The crystalline acetate, m.p. 178–200°, was isolated in practically quantitative yield by pouring the mixture into ice water. Its identity with the 21-acetate described above was confirmed after recrystallizing a sample, by finding the melting points, mixed m.p., and infrared spectra identical.

2ζ-Fluorohydrocortisone acetate (IIIa, R′ = Ac). A solution of 3.24 g. of 2ζ-fluoro-11β,21-dihydroxy-4,17(20)-[*cis*]-pregnadien-3-one 21-acetate in a mixture of 110 ml. of tertiary butyl alcohol, 30 ml. of methylene chloride, and 4.1 ml. of pyridine was treated with 10.9 ml. of a solution of *N*-methylmorpholine oxide–hydrogen peroxide complex in tertiary butyl alcohol[8] and 5.0 mg. of osmium tetroxide in 1.7 ml. of tertiary butyl alcohol. The solution was stirred at room temperature overnight, then 30 ml. of 0.5% aqueous sodium hydrosulfite and 2 g. of Magnesol were added, and stirring was continued for 0.5 hr. more. The solution was filtered and the solids were washed with 40 ml. of 75% tertiary butyl alcohol in water. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in methylene chloride, which was then washed with 10% aqueous sodium dihydrogen phosphate and with water, dried over sodium sulfate, and passed through a column of 220 g. of Florisil. The column was developed with 2.4 l. of 10% acetone in Skellysolve B, 2.8 l. of 15% acetone in Skellysolve B, and 2.0 l. of 25% acetone in Skellysolve B, collecting 400-ml. fractions. The 15% acetone contained 2.55 g. (72.5%) of 2-fluorohydrocortisone acetate, which after one recrystallization from a mixture of ethyl acetate and Skellysolve B, melted at 194–199°. Further recrystallizations raised the m.p. to 208–210.5°, and a sample of this quality gave the following analysis.

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.40; F, 4.50. Found: C, 65.74; H, 7.03; F, 4.6. $[\alpha]_D$ +198° ($CHCl_3$). λ_{max} 243 mμ, ε 14,100.

2ζ-Fluoro-11β,21-dihydroxy-6α-methyl-4,17(20)-[cis]-pregnadien-3-one. Starting with 7.73 g. of 11β,21-dihydroxy-6α-methyl-4,17(20)-[*cis*]-pregnadien-3-one 21-acetate (Ib, R′ = Ac) the 2ζ-fluoro derivative was obtained as the free 21-alcohol (IIb, R′ = H) by the general procedure described above in yields of 62.5%. The compound crystallized well from ethyl acetate, but its m.p. was not precisely reproducible. Samples of apparently equal purity melted over short ranges that varied from 170–194°. A sample melting at 188–189° was analyzed.

Anal. Calcd. for $C_{22}H_{31}FO_3$: C, 72.89; H, 8.62; F, 5.24. Found: C, 72.73; H, 8.61; F, 5.14. λ_{max} 243 mμ.

The corresponding *21-acetate* (IIb, R′ = Ac), prepared by acetylation with acetic anhydride in pyridine at room temperature overnight, as described for the lower homolog, could be crystallized from tertiary butyl alcohol as a solvate which lost its appearance of crystallinity at 80° (on a Kofler block, viewed in polarized light), and melted at about 147–156°.

(14) Commercial 25% sodium methoxide in methanol, obtained from Olin Mathieson Chemical Corp. was assayed titrimetrically for total alkali, calculated as grams of sodium methoxide per 100 grams of solution. The required amounts were weighed in a syringe whose tare weight was obtained with the walls wetted by the solution; the weighed amounts were then injected rapidly into the reaction vessels.

(15) This figure is an average of eight runs, in which the yields varied from 2.91 g. (41.6%) to 4.10 g. (58.9%).

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

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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.

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