TABLE I

BIOLOGICAL ACTIVITIES[a]

Compound	Free steroid: Thymus involution	Free steroid: Liver glycogen	16,17-Acetonide: Thymus involution	16,17-Acetonide: Liver glycogen
16α-Hydroxyhydrocortisone	0.3 (0.2–0.4)	0.4 (0.2–1)	3 (2–3)[b]	3 (1–8)
16α-Hydroxyprednisolone	1 (1–2)	1 (0.5–2)	17 (10–28)	13 (7–22)
16α-Hydroxy-6α-methylhydrocortisone	1 (1–2)	1 (1–2)	14 (10–20)	10 (5–18)
16α-Hydroxy-6α-methylprednisolone	3 (2–4)	2 (1–3)	24 (12–49)	22 (11–43)

[a] Activities are on a weight basis relative to hydrocortisone = 1. Figures in parentheses represent 95% confidence limits. The assay procedure is given: Liver glycogen deposition, thymus involution, fluid diuresis and electrolyte excretion were measured in adrenalectomized immature male rats. Twenty-four hr. after adrenalectomy, the rats were injected subcutaneously with graded doses of the test compound suspended in a modified carboxymethylcellulose vehicle. The rats were injected intraperitoneally with 3 ml. of saline, and three rats placed in each metabolism cage. Urine was collected for 5 hr. and sodium and potassium were determined by flame photometry. Daily injections of the steroids then were continued for the next 4 days. The rats were fasted for 15 hr. prior to the last injection and for an additional 7 hr. afterward. At the end of this time, the animals were anesthetized with sodium pentobarbital, and the livers were quickly excised and hydrolyzed in 30% potassium hydroxide solution. Liver glycogen was measured by the anthrone method of S. Seifter, S. Dayton, B. Noric and E. Muntwyler, *Arch. Biochem.*, **25**, 191 (1950). Also, the thymi were removed and weighed. The assays were done by L. Bortle, E. Heyder, A. Monteforte, J. Perrine and E. Ross. [b] N. R. Stephenson (Department of National Health and Welfare, Ottawa, Canada) has found in his thymus involution assay (subcutaneous, corn oil) that 16α-hydroxyhydrocortisone 16,17-acetonide (V) possessed an activity of 9.26 (8.35–10.28) times that of hydrocortisone on a weight basis. On an equimolar basis its activity was 10.70 (9.64–11.87). We are indebted to Dr. Stephenson for this information.

droxy-6α-methylhydrocortisone (III, 215 mg.)[9] in acetone (10 ml.) was treated with perchloric acid (72%, 25λ) and stirred for 2.5 hr. at room temperature. Then saturated sodium bicarbonate solution (0.4 ml.) and water (15 ml.) were added to the clear solution. The product which separated was collected by filtration and washed with a copious quantity of water, wt. 210 mg., m.p. 244–246°. Recrystallization from acetone–petroleum ether lowered the m.p. to 230–232°; $[\alpha]^{24}D$ +139° (chloroform); λ_{max} 241 mμ (ε 15,400); ν_{max} 3550, 1724, 1680, 1620, 1092 and 1053 cm.$^{-1}$.

(9) The multi-stage syntheses of 16α-hydroxy-6α-methylhydrocortisone (III) and prednisolone (IV) (from the 5α,6α-epoxide of hydrocortisone bis-ethylene ketal *via* the bis ethylene ketal of 6α-methylcortisone acetate) will be described shortly by S. Bernstein and R. Littell, manuscript in preparation.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.31. Found: C, 69.53; H, 8.80.

16α-Hydroxy-6α-methylprednisolone 16,17-Acetonide (11β,21-Dihydroxy-16α,17α-isopropylidenedioxy-6α-methyl-1,4-pregnadiene-3,20-dione) (VIII).—16α-Hydroxy-6α-methylprednisolone (IV, 11 g.)[9] was converted into its acetonide VIII essentially by the method above for VII, wt. 10.8 g., m.p. 265–269°. The analytical sample was obtained by recrystallization from acetone–petroleum ether; m.p. 272–275°; $[\alpha]^{25}D$ +100° (chloroform); λ_{max} 241 mμ (ε 15,500); ν_{max} 3430, 1710, 1662, 1625, 1605, 1088 and 1055 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.49; H, 8.22.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT, SCHERING CORP.]

Double Bond Isomerization of Steroidal A-ring α,β-Unsaturated Ketones: 1,5-Dien-3-ones

BY A. L. NUSSBAUM, G. BRABAZON TOPLISS, T. L. POPPER AND E. P. OLIVETO

RECEIVED MARCH 6, 1959

A method was devised for the synthesis of steroidal 1,5-dien-3-ones: introduction of bromine at C-6 of a 1,4-diene-3-one is followed by reductive debromination under neutral conditions. A 6-acetoxy-1,4-dien-3-one also was transformed in this manner. Δ⁴-Cholesten-3-one similarly was converted to the unconjugated ketone.

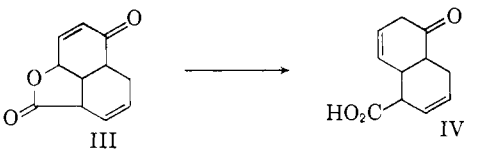
In a recent paper[1] we described the preparation of certain 7α-hydroxysteroids. The final step in that synthesis involved the reductive debromination of 6β-bromo-7α-hydroxy derivatives with metallic zinc. It was observed that, if the reaction were carried out for periods shorter than described, certain spectral changes occurred which indicated that the reaction proceeded by way of a structure not containing the original $\Delta^{1,4}$-dien-3-one. Thus, when 6β-bromo-7α,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,11,20-trione 21-acetate (I) was treated with zinc in aqueous ethanol and the reaction followed spectroscopically, the original λ_{max} at 244 mμ was seen to undergo a hypsochromic shift until it reached 224 mμ. This drift then reversed itself until a final reading at 237 mμ, attributable to 7α,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,11,20-trione 21-acetate,[1] was reached. When the reaction was repeated on a preparative scale and interrupted when the ultraviolet maximum had reached its lowest wave length, it was possible to isolate an isomer of the latter compound. This isomer showed ϵ_{224}^{EtOH} 12,000, a peak which shifted instantaneously to 237 mμ upon the addition of a drop of alkali. This indicated restoration of the original chromophore, and it appeared that the double bond originally at C-4 had not been reduced[2] but isomerized to a position which permitted facile reversion into conjugation. It was concluded that the new isomer was 7α,17α,21-trihydroxy-$\Delta^{1,5}$-pregnadiene-3,11,20-trione 21-acetate (II).[3]

(1) A. L. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, THIS JOURNAL, **80**, 2722 (1958).

(2) Reduction of a conjugated double bond by zinc has been observed by J. Fajkoš, *Coll. Czech. Chem. Comm.*, **8**, 1559 (1958).

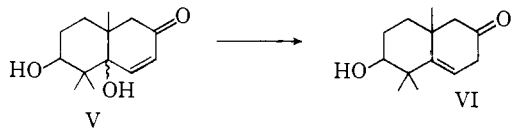
(3) Steroidal compounds possessing the same residual chromophore would be the Δ^1-3-ones. Examples listed by L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), range from 224 to 231 mμ; see also, *inter alia*, E. Caspi and M. M. Pechet, *J. Biol. Chem.*, **230**, 843 (1958).

The utilization of a γ-substituent in isomerizing the double bond of an α,β-unsaturated carbonyl function has been noted previously. Woodward and co-workers[4] observed such a migration in the case of a tricyclic lactone (III–IV). Halsall,



III IV

Rodewald and Willis[5] reported a similar shift of a conjugated double bond of a bicyclic product



V VI

(V–VI). As has been pointed out by Birch,[6] the anion one would expect to be generated in this type of reduction would "add a proton to give a high proportion of the unconjugated ketone, if the addition takes place under conditions where it is irreversible."

In the steroid field, β,γ-unsaturated ketones have commanded some interest in the last few years. Fieser, in a stimulating review,[7] suggested a possible connection between Δ^5-cholesten-3-one and carcinogenesis. Methods for the preparation of the Δ^5-3-ketones conveniently proceed from the Δ^5-3β-alcohols and have been discussed by Djerassi.[8] In view of the fact that the Δ^5-3β-alcohols of the more highly oxygenated corticosteroids are not as readily available as the corresponding Δ^4-3-ketones,[9] it appeared interesting to explore the general applicability of the method here described.

A cholesterol derivative was chosen as a suitable model compound. Cholesterol itself has been converted to Δ^5-cholesten-3-one,[10] thus making the necessary reference compound available. When 6β-bromo-Δ^4-cholesten-3-one[11] (VII) was exposed to reductive debromination with zinc in aqueous ethanol at room temperature, it was observed that the original ultraviolet maximum at 246 mμ decreased to a minimum intensity over a period of seven hours; after that, the absorption maximum, now shifting slightly toward shorter wave lengths, intensified until a value corresponding to a full chromophore was reached. It appeared that the starting material was indeed converted to the desired Δ^5-cholesten-3-one (VIII), but that some isomerization to the conjugated ketone was occurring almost simultaneously. This was confirmed by an examination of the infrared spectra of the reaction aliquots: The original carbonyl band at 6.02 μ decreased in intensity, while a new band was formed at 5.85 μ, corresponding to the formation of an unconjugated carbonyl group. After seven hours, however, the latter had begun to recede at the expense of the former, now at 5.97 μ, until it disappeared entirely.[12] Nevertheless, an appreciable amount of the desired unconjugated ketone had been formed, and when the reaction was repeated on a preparative scale, some 25% of Δ^5-cholesten-3-one (VIII) could be isolated after silica gel chromatography. Since Δ^5-cholesten-3-one has already been converted to cholesterol,[13] the reaction here described is an alternative to the enol acetate–metal hydride procedure discussed earlier (see ref. 9).

Because of our interest in steroidal 3-keto-1,4-dienes, we decided to apply the reaction to members of this class of compounds. When 6-bromo-$\Delta^{1,5}$-androstadiene-3,17-dione[14] (IX) was treated with zinc in aqueous ethanol, the desired 3,17-diketo-$\Delta^{1,5}$-androstadiene (X), ϵ_{224}^{EtOH} 11,800, was isolated in 43% yield. This encouraged us to proceed to the more interesting $\Delta^{1,4}$-corticosteroids. 6β-Bromoprednisone acetate[15] (XIa), when subjected to reductive debromination, gave the 1,5-isomer XII. The same compound was obtained by treating 6β-acetoxyprednisone acetate[16] (XIb) in like manner, though under rather more severe reaction conditions. 1,5-Diene XII was preparatively reconverted to prednisone, with concomitant saponification at C-21, by the action of methanolic alkali.

Prednisolone acetate was converted to the 1,5-dienone XIII *via* a 6-bromide[17] as outlined above. The yield was considerably lower, however.

For the physiologically prominent 9α-fluoro-11β-hydroxy compounds,[18] the direct approach had to be somewhat modified. Bromination of the corresponding 1,4-dienes was not satisfactory, and introduction of the desired γ-substituent was performed on a precursor, the 9β,11β-epoxide. For instance, 21-acetoxy-17α-hydroxy-16α-methyl-9β,-

(4) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kiersteadt *Tetrahedron*, **2**, 1 (1958).

(5) T. G. Halsall, W. J. Rodewald and D. Willis, *Proc. Chem. Soc.*, 231 (1958).

(6) A. J. Birch, *J. Chem. Soc.*, 2325 (1950).

(7) L. F. Fieser, *Bull. soc. chim., France*, 541 (1954).

(8) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(9) A method to convert Δ^4-3-ketones to the corresponding Δ^5-3β-ols *via* the enol acetate has been described by W. G. Dauben and J. F. Eastham, THIS JOURNAL, **72**, 2305 (1950). In a very recent paper, J. Iriarte, C. Djerassi and H. J. Ringold, *ibid.*, **81**, 436 (1959), utilized this "reversed Oppenauer" and combined it with the Jones oxidation (ref. 8) to synthesize a number of $\Delta^{5(6)}$-19-nor steroids.

(10) L. F. Fieser, *Org. Syntheses*, **35**, 43 (1955), and references cited there.

(11) L. Ruzicka, *Helv. Chim. Acta*, **19**, 1147 (1936).

(12) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, THIS JOURNAL, **78**, 430 (1956), observed the transient formation of a non-conjugated ketone with ν_{max}^{Nujol} at 1710 during the mild hydrolysis of a steroidal enamine derived from a Δ^4-3-ketone.

(13) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(14) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, THIS JOURNAL, **72**, 4531 (1950).

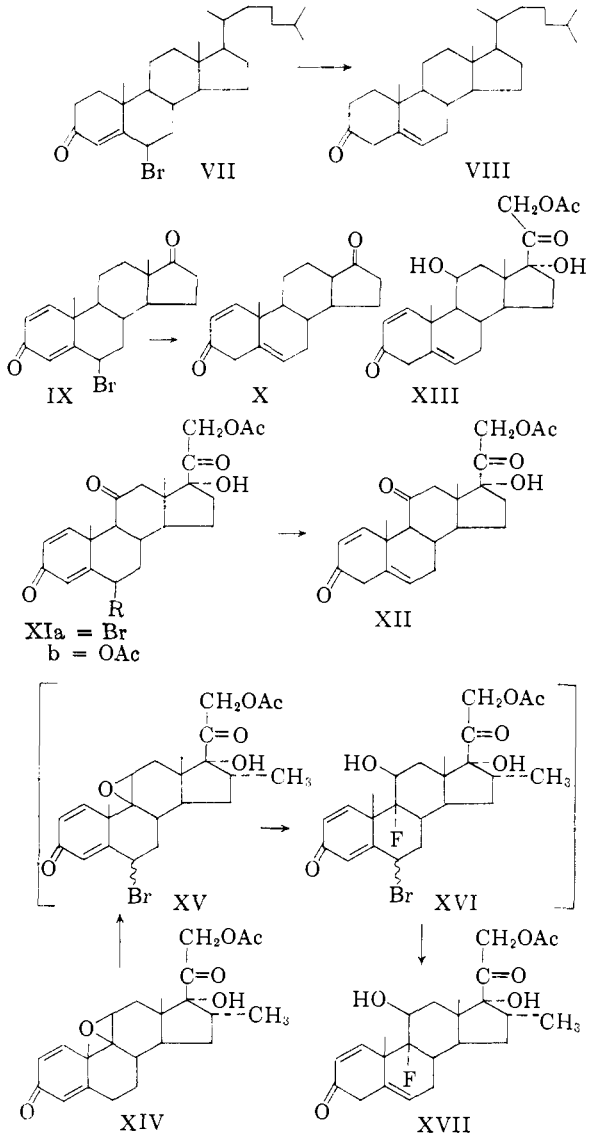
(15) D. Gould, E. L. Shapiro, H. L. Herzog, M. J. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **79**, 502 (1957).

(16) Obtained by microbiological hydroxylation of prednisone with *Chaetomium funicolum* and subsequent acetylation; *cf.* Belgium Patent 548,450.

(17) Bromination of an 11β-ol at C-6 is rather more difficult than of the corresponding 11-one. This is not surprising in view of the fact that the 11β-hydroxy group may undergo oxidation or elimination; *cf.* J. Ellis, G. H. Phillips and W. F. Wall, *J. Chem. Soc.*, 4001 (1958). The reaction was actually carried out in dioxane (*cf.* R. Joly, G. Nominé and C. Bertin, *Bull. soc. chim. (France)*, 1459 (1956)).

(18) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).

11β-epoxy-1,4-pregnadiene-3,20-dione (XIV)[19,20] was treated with bromine in dioxane.[17] The resulting 6-bromo compound XV was converted to the fluorohydrin XVI and the isomerization to the $\Delta^{1,5}$-derivative carried out as usual to give XVII. The intermediates XV and XVI were used without purification.



We are presently investigating the limits of applicability of the method here described and the chemistry of the novel compounds obtained.

Acknowledgment.—We wish to thank Prof. D. H. R. Barton for his enlightening discussions, and Dr. E. B. Hershberg for his help in preparing this manuscript.

Experimental[21]

7α,17α,21-Trihydroxy-1,5-pregnadiene-3,11,20-trione 21-Acetate (II).—6β-Bromo-7α,17α,21-trihydroxy-1,4-pregnadiene-3,11,20-trione 21-acetate (I) (200 mg.) was dissolved in 60 ml. of ethanol and 10 ml. of water. Powdered zinc (2 g.) was added, and the resulting suspension was stirred with efficient agitation for 20 hours at room temperature. The mixture was filtered and the filtrate concentrated *in vacuo* to incipient crystallization. Filtration gave 90 mg., m.p. 270–275° dec., ϵ_{224}^{EtOH} 11,000. Several recrystallizations from methylene chloride–ether gave an analytical sample, m.p. 273–280° dec., ϵ_{224}^{EtOH} 12,000; λ^{Nujol} at 2.89, 2.99, 5.71, 5.81(sh), 5.85, 5.95, 5.97(sh), 6.07(sh), 6.17(weak), 8.06 μ.

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.39; H, 6.73. Found: C, 66.06; H, 6.94.

Δ⁵-Cholesten-3-one (VIII).—6β-Bromo-Δ⁴-cholesten-3-one (1 g.) (VII), dissolved in 300 ml. of ethanol and 50 ml. of water, was stirred at 50° for one hour with 10 g. of zinc powder. The suspension was filtered and concentrated to dryness *in vacuo*. The residue was dissolved in petroleum ether and chromatographed over 25 g. of silica gel. The first crystalline fraction was eluted with petroleum ether–benzene. Crystallization from methanol gave 210 mg. of Δ⁵-cholesten-3-one, m.p. 118–125°, essentially no ultraviolet maximum at 240 mμ, infrared spectrum identical with genuine material. One recrystallization raised the melting point to 124–126°. More polar eluate from the column gave the Δ⁴-isomer.

3,17-Diketo-1,5-androstadiene (X).—6β-Bromo-1,4-androstadiene-3,17-dione (IX) (12.05 g.) was dissolved in 3.6 l. of ethanol and 600 ml. of water. Zinc powder (120 g.) was added, and the mixture was stirred vigorously for 72 hours. The reaction was worked up as indicated in the preceding example, and 4.1 g. of the product, m.p. 164–168°, ϵ_{224}^{EtOH} 11,500, isolated. Several recrystallizations from methylene chloride–ether gave an analytical sample, m.p. 169–173°; ϵ_{224}^{EtOH} 11,800; λ^{Nujol} at 5.78, 5.93, 6.23 (weak) μ; $[\alpha]^{24}D$ +146.4° (dioxane).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.93; H, 8.30.

17α,21-Dihydroxy-1,5-pregnadiene-3,11,20-trione 21-Acetate XII. A. From 6β-Hydroxyprednisone Acetate (XIa).—6β-Bromo-17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione 21-acetate (4.5 g.) was dissolved in 1.3 l. of ethanol and 225 ml. of water. Zinc powder (45 g.) was added, and the mixture stirred efficiently for 14 hours at room temperature. Workup as usual followed by recrystallization from acetone–hexane gave 2.88 g. of product VI, m.p. 213–220°. An analytical sample was obtained by several recrystallizations from acetone, m.p. 213–216°, ϵ_{224}^{EtOH} 13,000 (calculated for an acetone solvate): λ^{Nujol} at 3.00(broad), 5.70, 5.75, 5.86, 6.00, 6.18(sh), 8.14 μ; $[\alpha]^{25}D$ +138.4° (dioxane).

Anal. Calcd. for $C_{23}H_{28}O_5 \cdot C_3H_6O$: C, 68.10; H, 7.47. Found: C, 67.87; H, 7.39.

After drying for three hours in high vacuum at 130°, 193.3 mg. of the solvate lost 22.2 mg. (This represents 11.4% against a calculated 12.6%).

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 69.00; H, 7.00. Found: C, 69.01; H, 7.31.

B. From 6β-Acetoxyprednisone Acetate (XIb).[16]—Diacetate XIb (175 mg.) was dissolved in 50 ml. of ethanol and 9 ml. of water and 1.7 g. of zinc powder was added. The mixture was stirred and refluxed for 2.5 hours, filtered, evaporated to a small volume under a stream of nitrogen and the resulting crystals filtered off to give 78 mg. of XII, identical with the product obtained from bromide XIa by melting and mixture melting point, ultraviolet and infrared spectrum.[22]

Conversion of 17α,21-Dihydroxy-1,5-pregnadiene-3,11,20-trione 21-Acetate (XII) to Prednisone.—The foregoing 1,5-diene (250 mg.) was dissolved in 6.6 ml. of methanol, the solution was flushed with nitrogen, and 0.66 ml. of 1 *N* sodium hydroxide solution was added. The reaction was allowed to proceed for half an hour at room temperature; the *p*H then was adjusted to neutral with acetic acid and the solution poured into an excess of water. Filtration of the resulting solid gave 207 mg. of essentially pure prednisone, as evidenced by the infrared spectrum and ϵ_{238}^{EtOH} 15,000.

(19) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, THIS JOURNAL, **80**, 3161 (1958).

(20) E. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. Pechet, *ibid.*, **80**, 4431 (1958).

(21) All melting points were taken on a Kofler block. Rotations were taken in a 1-dm. tube at a concentration of *ca.* 1% in dioxane, unless otherwise specified. Ultraviolet spectra were taken in methanol. Analysis and spectral data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(22) We thank Miss F. E. Carlon for her help in carrying out this experiment.

11β,17α,21-Trihydroxy-1,5-pregnadiene-3,20-dione 21-Acetate (XIII).—11β,17α,21-Trihydroxy-1,4-pregnadiene-3,-20-dione 21-acetate (10 g.) was suspended in 100 ml. of dioxane and 80 ml. of acetic acid. A solution of 2.3 g. of bromine in 10 ml. of acetic acid was added, and the mixture allowed to stand at room temperature for 50 minutes. At that time, another 0.4 g. of bromine in 2 ml. of acetic acid was added. After an additional 15 minutes, all of the steroid had dissolved, and the solution had become decolorized to a light yellow. It was poured into 1.5 l. of ice-water; the resulting solid was filtered, washed to neutral and air-dried. This crude material had a positive Beilstein test and showed ϵ_{244}^{EtOH} 12,600. Since purification of this solid proved difficult, it was used as such.

A solution of 2.5 l. of ethanol and 500 ml. of water was heated to boiling, 10 g. of zinc powder was added, and then the entire bromination product. Further 10-g. portions of zinc were added, at 15-minute intervals, up to a total of 120 g. Aliquots were taken out at intervals, and their ultraviolet spectrum determined. The high-intensity maximum migrated to lower wave lengths, until, after three hours, it reached a terminal 227.5 mμ. The reaction was interrupted, the solution filtered, and the zinc washed thoroughly with hot ethanol. Concentration to dryness gave a yellow amorphous material, which was chromatographed on 300 g. of Florisil. The first eluates with benzene–ether (3:1) gave 1.4 g. of crystals of m.p. 195–205°, having the same spectroscopic properties as the analytical sample. Later eluates were progressively more contaminated with the 1,4-isomer VII, and set aside for recycling.

An analytical sample was prepared by recrystallization from wet isopropyl ether. It had m.p. 200–207°, ϵ_{224}^{EtOH} 11,800; $[\alpha]^{25}D$ +187.9° (dioxane); λ^{Nujol} at 2.98, 5.72, 5.82, 6.04, 6.20(sh) and 8.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_6 \cdot 1/2\ H_2O$: C, 67.15; H, 7.54. Found: C, 67.00; H, 7.52.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-Δ1,5-pregnadiene-3,20-dione 21-Acetate (XVII).—21-Acetoxy-17α-hydroxy-16α-methyl-9β,11β-epoxy-Δ1,4-pregnadiene-3,20-dione (XIV) (3.61 g.) was dissolved in 490 ml. of carbon tetrachloride and 430 ml. of chlorobenzene. The vessel was swept with argon, 10.8 ml. of 10% pyridine–methylene chloride and 910 mg. of N-bromosuccinimide were added and the resulting solution was refluxed with strong concomitant illumination for 45 minutes. It then was cooled, partitioned between methylene chloride and water, and the organic layer was dried and concentrated *in vacuo*. Crystallization from acetone–hexane gave 3.5 of crude XV, m.p. 165–175° dec., which was converted directly to fluorohydrin XVI as follows. It was dissolved in 5 ml. of chloroform, cooled to −25° and added to 240 ml. of a hydrofluoric acid solution[23] (containing 312 mg./ml. of hydrogen fluoride in a 2:1 tetrahydrofuran–chloroform mixture) previously cooled to −70°. The solution was stirred at 0° for five hours, poured into excess sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed to neutrality and concentrated to incipient crystallization. Filtration gave 1.96 g., m.p. 165–167°, of XVI. The latter was dissolved in 600 ml. of ethanol and 100 ml. of water, 20 g. of zinc powder was added, and the mixture was stirred at room temperature for three hours. It was filtered and allowed to concentrate to dryness under a draft. The residual oil was chromatographed on silica gel. Eluates with benzene–ether (3:1) furnished 357 mg. of the desired XVII. An analytical sample, from ethyl acetate, had m.p. 191–193° dec., ϵ_{220} 14,800.

Anal. Calcd. for $C_{24}H_{31}O_6F \cdot EtOAc$: C, 64.35; H, 7.52. Found: C, 64.81; H, 7.26.

(23) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, THIS JOURNAL, **78**, 4956 (1956).

BLOOMFIELD, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Preparation and Reactions of Quaternary Ammonium Salts Derived from *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate

BY ARTHUR C. COPE AND EDWARD E. SCHWEIZER

RECEIVED AUGUST 29, 1958

The isolation of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) (50%) from the product obtained from dimethylamine and *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) demonstrates the existence of the corresponding quaternary tosylate (II, R = CH_3) in the initial reaction mixture. The reaction also yields a significant amount of trimethylamine, formed by alkylation of dimethylamine by the quaternary tosylate. The reaction of the ditosylate I with other secondary amines followed by successive treatment with a basic ion exchange resin and hydrobromic acid yields quaternary ammonium bromides containing the 8-oxa-3-azabicyclo[3.2.1]octane ring system (IX and XI), and 2,5-bis-(N-aminomethyl)-tetrahydrofuran derivatives (VIII and X). The Hofmann degradations of the quaternary hydroxides prepared from IX and XI were studied.

The reaction of secondary amines with *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) has been shown[1] to result in closure of a six-membered heterocyclic ring with the elimination of an alkyl group of the secondary amine, forming N-alkyl derivatives of 8-oxa-3-azabicyclo[3.2.1]-octane (III). The expected diamines IV also were formed.

The formation of intermediate cyclic quaternary salts II was postulated, followed by alkylation of the secondary amines (present in excess), forming the tosylates of the tertiary amines V and N-alkyl derivatives of 8-oxa-3-azabicyclo[3.2.1]octane (III).

This view now has been substantiated by the isolation of trimethylamine hydrobromide and 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) from the reaction of I with dimethylamine and by demonstrating that the reaction of the quaternary tosylate II (R = CH_3) with dimethylamine yields 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3).

An aqueous solution of the products from the reaction of I with pure dimethylamine in dry tetrahydrofuran was passed through a basic ion exchange resin. The expected 2,5-bis-(dimethylaminomethyl)-tetrahydrofuran (IV, R = CH_3) and 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3) were isolated by ether extraction of the effluent in 2 and 22% yields, respectively. The aqueous solution was concentrated by distillation in order to remove and collect the excess dimethylamine and any trimethylamine produced by alkylation. Neutralization of the concentrate with hydrobromic acid and evaporation to dryness gave the quaternary bromide VI (R = CH_3) in 50%

(1) A. C. Cope and B. C. Anderson, THIS JOURNAL, **77**, 995 (1955).