and *N*-bromosuccinimide (19.6 g., 0.11 mole) in 450 ml. of carbon tetrachloride was stirred and irradiated with a General Electric RS sunlamp for 2 hr. During this time, hydrogen bromide was evolved, and by the end of this period the solution had developed a dull red color. The succinimide was removed by filtration. The filtrate was evaporated to a pasty residue. Recrystallization of the residue from trichloroethylene gave greenish-yellow crystals, m.p. 150°, yield (13 g., 50%). Additional recrystallization of this material from trichloroethylene, benzene, xylene, or acetic acid–acetone (1:1) did not alter the melting point.

Purification of 2,5-dibenzylidene-3-cyclopentenone (I). The product I (14.7 g., 0.093 mole, m.p. 150°) described above was dissolved in the least possible volume of hot acetic acid–acetone (1:1). Uranyl acetate dihydrate (10 g.) dissolved in 3.8 ml. of hydrochloric acid was added to the hot solution. An orange-red precipitate began to form immediately. The solution was protected from light with aluminum foil and kept hot for 2 hr. The precipitated complex was filtered from the hot solution. This gave orange-red crystals (4.3 g., 5%) which did not melt below 300° and which showed infrared maxima identical to those of an authentic sample of the uranyl chloride-2,5-dibenzylidenecyclopentanone complex[3] (both spectra were taken in potassium bromide). Cooling of the filtrate gave greenish-yellow plates, m.p. 156–157°. This material gave, after two recrystallizations from trichloroethylene, 9 g. of I, m.p. 156–157°, λ_{max}^{EtOH} 316 mμ (38,900) and 232–234 mμ (11,700).

Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.45. Found: C, 88.12; H, 5.57.

2,5-Dibenzylidene-3-cyclopentenone thus purified did not give a precipitate on further treatment with uranyl chloride, and the material recovered from this second treatment had the same melting point, infrared spectrum, and ultraviolet spectrum as I purified by a single treatment with uranyl chloride.

Recovery of 2,5-dibenzylidenecyclopentanone from the uranyl chloride complex. The complex obtained above was washed with benzene to remove any organic material which had coprecipitated with it, and then warmed in ethanol with stirring until all of the orange-red complex had disappeared. During this process, a yellow precipitate formed which was collected by filtration and recrystallized from benzene giving bright yellow needles, m.p. 182–186° (authentic 2,5-dibenzylidenecyclopentanone m.p. 188–190°), mixed melting point with 2,5-dibenzylidenecyclopentanone 185–190°. This material had infrared and ultraviolet absorption spectra identical to those of authentic 2,5-dibenzylidenecyclopentanone.

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DEPARTMENT OF CHEMISTRY
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Synthesis of 7-Methyl Steroid Hormones. II. 7β-Methylcortisone Acetate and 7β-Methylhydrocortisone Acetate

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While a considerable number of alkylated steroid hormones have been described in recent years[1] no 7-alkylated cortisone derivatives have been prepared, and we therefore felt that the synthesis of these compounds would be of interest.

The effect on cortical activity associated with the substitution of methyl groups, or halogen (particularly fluorine) atoms, in place of hydrogen in the A, B, and C rings has been reviewed recently,[2] and may be summarized as follows.

If the methyl group or halogen atom is in an α-axial or α-equatorial configuration (2α-,[3] 6α-,[4] 9α-,[5] 12α-[6]) then retention or enhancement of physiological activity is observed.[7]

The paucity of β-axial and β-equatorial substituted corticoids prevents any generalization. The 6β-methyl- and halo-corticoids have been described, and it is established that these are less active than the parent compounds.[2] The only other case of a β-axial methyl substituted hormone is 8β,14α-dimethyl-18-nortestosterone[8] which is inactive as an androgen.

The 7β-methyl compounds described in this work provide the first example of *β-equatorial* substitution by methyl in corticoids[9] and it is therefore interesting to note that activity is lowered by such substitution.

An obvious starting point for the synthesis was the 3,20-bisethylene ketal of 7-ketocortisone acetate (II). Attempts to prepare (II) by *tert*-butyl chromate oxidation of the 3,20-bisethylene ketal (I)[10] led, in poor yield, to a substance showing an

(1) See Part I (C. H. Robinson, Olga Gnoj, W. Charney, M. L. Gilmore, and E. P. Oliveto, *J. Am. Chem. Soc.*, in press) for pertinent references.

(2) J. A. Hogg, 6th National Medicinal Chemistry Symposium of the American Chemical Society, Madison, Wis., June 23–25, 1958.

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

(4) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956). See also G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider, and J. A. Hogg, *J. Am. Chem. Soc.*, **79**, 1515 (1957).

(5) J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(6) D. Taub, R. D. Hofsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **79**, 452 (1957).

(7) In apparent contradiction to this generalization, 11α-methylhydrocortisone acetate [G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 367 (1958)] is less active than the parent hydrocortisone acetate. However, the methyl group here has been introduced at the carbon bearing the 11β-hydroxyl group, and so the substitution differs from the others described which are α-, or vinylogously α-, to oxygen atoms at C-3 or C-11.

(8) P. Crabbé, G. Ourisson, and T. Takahashi, *Tetrahedron*, in press. J. F. Biellman, P. Crabbé, and G. Ourisson, *Tetrahedron*, in press.

(9) A patent has now appeared [J. C. Babcock and J. A. Campbell, U. S. Patent **2,838,534** (1958)] which outlines the preparation of 7-methyl cortical hormones. However, 7-methylcortisone and hydrocortisone are partially or not at all characterized, and no stereochemistry is assigned.

(10) See, for example, P. N. Rao and P. Kurath, *J. Am. Chem. Soc.*, **78**, 5660 (1956) and C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6308 (1957).

ultraviolet absorption maximum at 240 mμ. This material did not give a positive tetrazolium test, but gave a strong positive Zimmermann reaction. (Under the same conditions, the Δ^5-7-ketone grouping gave a weak Zimmermann reaction.) The infrared spectrum indicated the presence of an α,β-unsaturated ketone grouping, C-11 and C-17 carbonyl groups, and an ethylene ketal. Treatment of this substance with alkali produced a chromophore, λ_{max} 313 mμ, suggesting that a 3-substituted-$\Delta^{3,5}$-7-ketone system had been generated.[11] It seems reasonable to suppose that the substance in question is the 3-ethylene ketal of 5-androstene-3,7,11,17-tetrone.

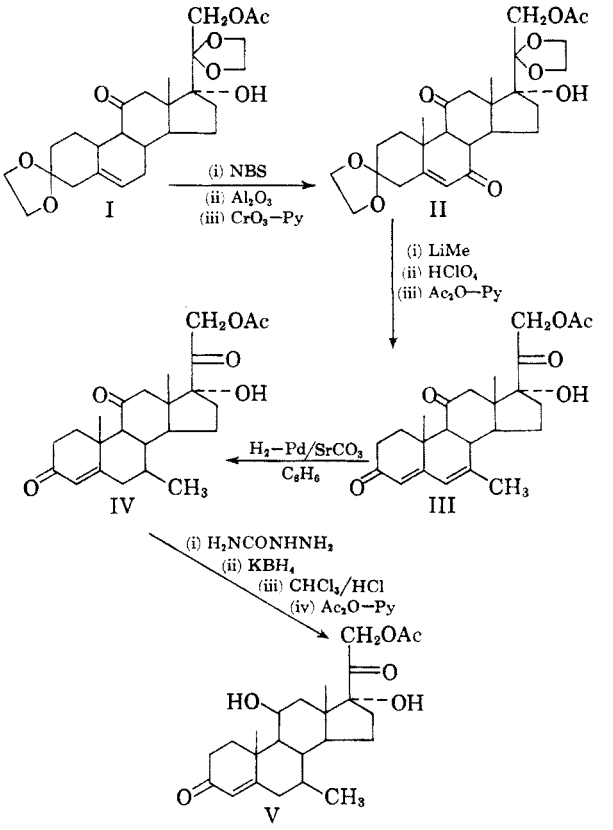
Attempts to oxidize the 3,20-bisketal (I) at C-7 with manganese dioxide[12] proved fruitless, while *N*-bromosuccinimide bromination followed by treatment with silver dichromate[13] led to oils showing ultraviolet absorption maxima at *ca.* 280 mμ, presumably due to formation of the $\Delta^{4,6}$-dien-3-one system.

The 7-ketobisketal (II) was best prepared from (I) in 37% overall yield, by successive Zeigler bromination, treatment with alumina, and chromic acid-pyridine oxidation.[11,14]

When the 7-ketone (II) was treated with lithium methyl in tetrahydrofuran ether, the crude product showed absorption maxima at 243 and 293 mμ. It was observed that heat or acid treatment led to disappearance of the 243 mμ band, with concomitant enhancement of the 293 mμ absorption. This suggests that during work-up the 3-ketal grouping had been lost, and that the crude product contained both the 3-keto-Δ^5-7-hydroxy-7-methyl and the 3-keto-$\Delta^{4,6}$-7-methyl systems. Indeed, treatment of the crude material described above with perchloric acid in methanol at room temperature gave a product which now showed a single ultraviolet maximum at 293 mμ. Regeneration of the 20-ketone had also occurred, as evidenced by the strong positive tetrazolium reaction. Acetylation at C-21 followed by chromatography gave 7-methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III), the ultraviolet (λ_{max} 293 mμ, ϵ 25,000) and infrared spectra (4,6-dien one system, 11-ketone and cortical side chain present) being in accord with the proposed structure.

Hydrogenation of the dienone (III) in benzene solution with palladium-strontium carbonate catalyst[15] until one mole of hydrogen was absorbed, gave 7β-methylcortisone acetate (IV). The configuration at C(7) is assigned on the basis of hydrogenation from the α-face.[16]

Conversion of 7β-methylcortisone acetate (IV) to the hydrocortisone derivative (V) was achieved by potassium borohydride reduction[17] of the 3,20-bissemicarbazone followed by regeneration of the carbonyl groups at C-3 and C-20, using a two phase chloroform aqueous hydrochloric acid procedure,[18] and finally reacetylation at C-21.



EXPERIMENTAL[19]

5-Pregnene-17α,21-diol-3,7,11,20-tetrone 21-acetate 3,20-bisethylene ketal (II). A solution of cortisone acetate bisethylene ketal (I, 5.5 g.) in carbon tetrachloride (300 ml.) and petroleum ether (50 ml.) together with potassium carbonate (1.1 g.) and *N*-bromosuccinimide (2.56 g.) was refluxed, with irradiation, for 4 min., using a 500-watt photoflood lamp (RFL-2, General Electric Co.). The mixture was cooled and filtered, and the filtrate was stirred with alumina (44 g. ethyl acetate–washed) for 2.5 hr., and filtered. Acetone (300 ml.) was then added and the mixture

(11) R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 989 (1956).

(12) P. Meunier, G. Zwingelstein, and J. Jouanneteau, *Bull. soc. chim. biol.*, **35**, 495 (1953).

(13) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(14) H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 331 (1952).

(15) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(16) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(17) E. P. Oliveto, R. Rausser, L. Weber, E. L. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1736 (1956).

(18) J. T. Day, U. S. Patent **2,781,367** (1957).

(19) Melting points were obtained on the Kofler block unless otherwise stated. Rotations were measured at 25° in dioxan solution, and at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infrared spectra, and rotations. Microanalyses were performed by Mr. Connor (Microanalytical Laboratory, Woodside, Long Island, N. Y.)

stirred overnight, then filtered. The filtrates were evaporated to dryness, and oxidized with a large excess of chromium trioxide–pyridine reagent at 25° overnight. Crystallization of the product from ethyl acetate–methanol gave the 7-ketone (II, 2.07 g.), plates m.p. 252–256°, $[\alpha]_D$ −6°, λ_{max}^{MeOH} 237 mμ (ε 11,000), λ_{max}^{Nujol} 2.92, 5.73, 5.88, 5.96, 6.10, 8.1, 9.08, 9.58 μ.

Anal. Calcd. for $C_{21}H_{36}O_6$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.02.

7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III). A solution of 3.0 g. of II in tetrahydrofuran (150 ml.) was added dropwise to an ethereal solution of methyllithium (from 3.45 g. of lithium and 14 ml. of methyl iodide in 300 ml. of ether), with stirring under nitrogen. The addition took 45 min., and the reaction mixture was then stirred under nitrogen for 20 hr. at 25°. The mixture was then poured slowly, with stirring, into iced 6% ammonium sulphate solution (1 l.). The product, isolated by extraction with ether, then methylene chloride, was an oil [λ_{max}^{MeOH} 243; 294 mμ (ε 6000; 5000)]. This material was dissolved in 0.27 *N* methanolic perchloric acid (175 ml.)[5] and left at room temperature for 19 hr., yielding 1.83 g. of a substance showing λ_{max}^{MeOH} 293 (ε 21,000). After acetylation (pyridine and acetic anhydride overnight at room temperature) and chromatography on Florisil, there was obtained, in the benzene ether eluates, 7-methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 466 mg.) as needles (acetone-hexane) m.p. 199–204°, $[\alpha]_D$ +362°, λ_{max}^{MeOH} 293 (ε 25,000). λ_{max}^{Nujol} 2.95, 5.72, 5.79, 5.84, 6.05, 6.19, 6.32, 8.15 μ.

Anal. Calcd. for $C_{24}H_{30}O_6.0.5(CH_3)_2CO$: C, 69.05; H, 7.50. Found: C, 69.20; H, 7.90.

7β-Methylcortisone acetate (IV). 7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 620 mg.) was hydrogenated in benzene (80 ml.) with palladized strontium carbonate (300 mg.) at room temperature until 1 mole of hydrogen had been absorbed. Chromatography of the product over Florisil afforded, in the benzene ether (3:2) eluates, 7β-methylcortisone acetate (IV; 173 mg.), m.p. 206–208° (from acetone-hexane), $[\alpha]_D$ +168°, λ_{max}^{MeOH} 239 mμ (ε 13,800); λ_{max}^{Nujol} 2.94, 5.78, 5.86, 6.02, 6.18, 8.12 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.60.

7β-Methylhydrocortisone acetate (V). A solution of 7β-methylcortisone acetate (125 mg.) in methanol (5 ml.), pyridine (0.15 ml.), and water (1.25 ml.) containing semicarbazide hydrochloride (207 mg.) was refluxed for 15 hr. The solution was then concentrated *in vacuo*, diluted with water, and filtered, giving 130 mg. of 3,20-bissemicarbazone. Extraction of the filtrate with ether gave an additional 14 mg. (total yield 144 mg.). The bissemicarbazone (144 mg.) was dissolved in tetrahydrofuran (5 ml.) and water (2.5 ml.), potassium borohydride (150 mg.) was added, and the mixture was refluxed overnight. Cooling and acidification to *p*H 5.5 with acetic acid, followed by heating on the steam bath for 0.5 hr., then dilution with water, filtration, washing with water, and drying, gave 57 mg. of crude bissemicarbazone of 7β-methylhydrocortisone. Extraction of the filtrate with methylene chloride and ethyl acetate, after addition of saturated sodium chloride solution, yielded a further 22 mg. (total yield 79 mg.). The infrared spectrum of this material (Nujol) indicated substantially complete reduction of the 11-ketone group.

Cleavage of the 3,20-bissemicarbazone was now carried out by adding the steroid (79 mg.) to 14 ml. of a 3:2 chloroform-tetrahydrofuran mixture and 7.4 ml. of 1.25 *N*-hydrochloric acid. The two-phase system was stirred vigorously at room temperature for 1.5 hr. The organic phase was then separated, and the aqueous phase was extracted four times with chloroform. The chloroform extracts and the original chloroform phase were combined, washed with water, and evaporated *in vacuo* to give a solid. Acetylation overnight at room temperature with pyridine–acetic anhydride, followed by chromatography of the acetylated product furnished 7β-methylhydrocortisone acetate (V, 11 mg.), needles (from acetone-hexane) m.p. 185–190°, $[\alpha]_D$ +131°, λ_{max}^{MeOH} 243 mμ. (ε 15,000); λ_{max}^{Nujol} 3.0, 5.74, 5.82, 6.15, 8.15 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.38; H, 7.94.

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Quaternary 2-Oxomorpholinium Salts[1]

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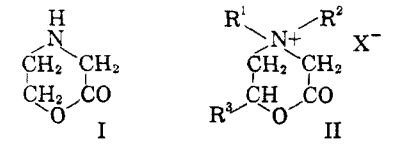
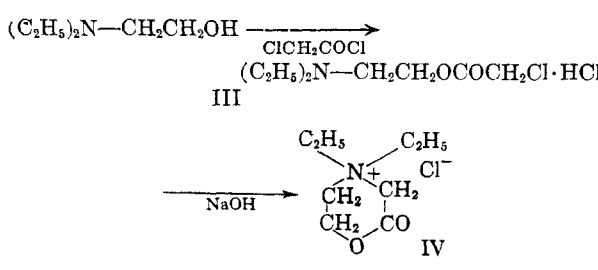
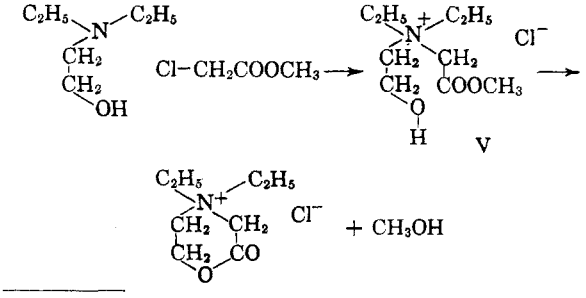
Quaternary 2-oxomorpholinium salts are based on the ring system of 2-oxomorpholine (I) which also might be called morpholactone to emphasize its lactone nature. The quaternary diethyl derivative of II ($R^1 = R^2 = C_2H_5$; $R^3 = H$; X = Cl) has been synthesized by Blicke and Faust[2] the following way.





The hydrochloride III gave 4,4-diethyl-2-oxomorpholinium chloride (IV) in a yield of 26%, m.p. 198–199.° Before the paper of Blicke and Faust appeared we had already synthesized IV and several related compounds by a condensation of β-dialkylamino alcohols and haloacetic esters. Presumably this reaction proceeds in two steps. The first step is the formation of the quaternary



(1) The larger part of these experiments has been performed at the B. F. Goodrich Research Center, Brecksville, Ohio.

(2) F. F. Blicke and J. A. Faust, *J. Am. Chem. Soc.*, **76**, 3158 (1954).