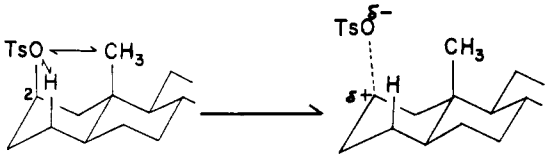
factor of 3.1 observed in the decalyl system, is in accord with this interpretation (IX, X).



IX X

From the results realized in these studies of the *trans*-decalyl and the cholestanyl systems, it appears that the reactivities of the individual isomers is readily interpretable in terms of 1,3-diaxial interactions. The fixed conformations realized in these systems greatly facilitates the analysis. It is hoped that these studies will be extended to other reactions and other derivatives to test the full utility of this approach in attaining a quantitative understanding of the influence of conformation on reactivity.

Experimental

Materials.—All carbinols were purified by utilizing the column chromatography followed by recrystallization.

Cholestan-3β-ol.—Cholestanone, prepared from cholesterol,[9,10] was reduced with metallic sodium in absolute ethanol; m.p. 139–140° (lit.[11] 140–141°). The Lieberman–Burchard test[9] proved that the compound was free from cholesterol.

Cholestan-3α-ol.—Cholestanone[9,10] was hydrogenated at 50° using platinum oxide as catalyst in acetic acid; m.p. 183–184° (lit.[12] 186–187°).

Cholestan-2-one was synthesized from cholestan-3-one by the route established by Ruzicka and co-workers[13,14]; m.p. 128–129° (lit.[15] 129–130°).

(9) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 191.

(10) *Ibid.*, p. 139.

(11) B. Heath-Brown, I. M. Heilbron and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

(12) L. Ruzicka, H. Brüngger, E. Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

Cholestan-2α- and 2β-ol were prepared according to the methods reported by Dauben and co-workers.[15] The 2α-ol melted at 177° (lit.[15] 177.1–178.9°) and the 2β-ol at 155° (lit.[15] 153–155°).

Cholestan-6-one was prepared from cholesterol by following the procedure of Shoppee and Summers[16]; m.p. 94–96° (lit.[16] 96–98°).

Cholestan-6α-ol.—The above ketone was reduced with metallic sodium in absolute ethanol; m.p. 129–130° (lit.[17] 128–129°).

Cholestanyl tosylates were prepared by the reaction of cholestanol with tosyl chloride in dry pyridine.[1] Cholestan-2α-, 3β- and 6α-ol reacted with molar equivalents of tosyl chloride for 2 days at 5°. Cholestan-3α ol reacted with two molar equivalents of tosyl chloride for 4 days at 5°. Cholestan-2β-ol was treated with three moles of tosyl chloride for 6 hours at 30°. The melting points of isomeric cholestanyl tosylates were: 3β, 135–136° (lit.[18] 136.5–137.5°); 3α, 138° (dec.); (lit.[18] dec.); 6α, 108–109° (lit.[16] 109–110°); 2α, 143.5–144; 2β, 114–115° dec.

Anal. Calcd. for $C_{34}H_{54}O_3S$: C, 75.22; H, 10.01. Found: (3α) C, 74.95; H, 10.10; 2α, C, 75.36; H, 10.17; 2β, C, 74.81; H, 9.93.

Rate Measurement.—Since the solubility of the cholestanyl tosylates was found to be low in acetic acid, the rate measurements were made at a concentration of about 0.01 mole/l. The methods of the measurement were the same as those of decalyl tosylate.[1]

Acknowledgment.—This work was partly supported by the Grant in Aid provided by the Ministry of Education for which I express my gratitude. I am also indebted to Professor Masuo Murakami, Professor Ichiro Moritani and Professor Herbert C. Brown for their valuable suggestions.

(13) L. Ruzicka, Pl. A. Plattner and R. Aeschbacher, *ibid.*, **21**, 866 (1938).

(14) L. Ruzicka, Pl. A. Plattner and M. Furrer, *ibid.*, **27**, 524 (1944).

(15) W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, THIS JOURNAL, **78**, 3752 (1956).

(16) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(17) R. Tschesche, *Ber.*, **65**, 1842 (1932).

(18) H. R. Nace, THIS JOURNAL, **74**, 5937 (1952).

SAKAI-SHI, OSAKA, JAPAN

[CONTRIBUTION FROM THE RESEARCH DIVISION OF CHAS. PFIZER AND CO., INC., GROTON, CONN.]

The Dehydrogenation of Corticosteroids with Chloranil[1]

BY E. J. AGNELLO AND G. D. LAUBACH

RECEIVED JANUARY 19, 1960

The reaction of tetrachloro-*p*-benzoquinone (chloranil) with a variety of steroid 3-ketones is described. Δ^4-3-Ketones are converted in one step to their Δ^6-dehydro or $\Delta^{1,6}$-bisdehydro derivatives depending on the reaction conditions employed. The scope, limitations and mechanism of the dehydrogenation are discussed.

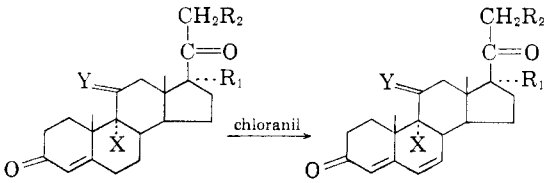
In the course of a study of new methods for the dehydrogenation of steroid 3-ketones, it was found that the treatment of Δ^4-3-ketosteroids with chloranil (tetrachloro-*p*-benzoquinone) can afford Δ^6-dehydro or $\Delta^{1,6}$-bisdehydro derivatives depending on the reaction conditions employed. A preliminary report of this single step method of synthesizing dehydro derivatives of corticosteroids from Δ^4-3-ketones has been published.[2] In the present communication additional data are presented with a discussion of the scope, limitations and mechanism of the reaction.

The first dehydrogenation of a corticosteroid with chloranil was performed on Δ^4-pregnene-17α,-21-diol-3,20-dione diacetate (I). The reaction afforded a product which was identical with a sample of the Δ^6-dehydro derivative, $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (II), prepared from I by the well-known bromination–dehydrobromination sequence.[3]

(1) Presented in part before the Division of Organic Chemistry of the International Congress of Pure and Applied Chemistry, Paris, France, July, 1957, and the Division of Organic Chemistry of the American Chemical Society at the 132nd National Meeting, New York, September, 1957.

(2) E. J. Agnello and G. D. Laubach, THIS JOURNAL, **79**, 1257 (1957).

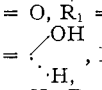
The broad scope[4] of the reaction was demonstrated by the successful application of the above or similar reaction conditions to the synthesis of the Δ^6-dehydro derivatives of a large variety of polyfunctional Δ^4-3-ketosteroids. Δ^4-Pregnene-11β,17α,21-triol-3,20-dione acetate (cortisol acetate, III) for example, was converted to its Δ^6-dehydro derivative (IV) in a variety of solvents, of which *t*-butyl alcohol and xylene were among the best. The structure of IV was proved by oxidation to the known $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,11,20-trione acetate (Δ^6-dehydrocortisone acetate, VI)[3] which also was prepared readily from cortisone acetate (V) by the action of chloranil. The known Δ^6-dehydro derivatives[5,6] of progesterone, cortexone



I, Y = H_2, R_1 = R_2 = OAc, X = H

III, Y =  , R_1 = OH, R_2 = OAc, X = H

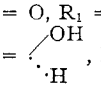
V, Y = O, R_1 = OH, R_2 = OAc, X = H

IX, Y =  , R_1 = OH, R_2 = OAc, X = F

II, Y = H_2, R_1 = R_2 = OAc, X = H

IV, Y =  , R_1 = OH, R_2 = OAc, X = H

VI, Y = O, R_1 = OH, R_2 = OAc, X = H

X, Y =  , R_1 = OH, R_2 = OAc, X = F

acetate and cortexolone acetate were also prepared by the chloranil method. Table I shows the yields obtained in the above and other representative transformations.

The magnitudes of the yields obtained in the experiments summarized in Table I indicate the selective action of the reagent on the Δ^4-3-ketone function. This selectivity makes possible the synthesis of many compounds heretofore available only with difficulty, if at all, by other methods. For example the synthesis of the Δ^6-dehydro derivatives of 11β-hydroxy-Δ^4-3-ketosteroids by the bromination–dehydrobromination sequence is not feasible due to the susceptibility of the 11-hydroxyl group to oxidative attack by the brominating agent. Another difficulty which is obviated by the chloranil method is the insolubility of highly oxygenated steroids in the solvents commonly employed for brominations (for example, carbon tetrachloride

TABLE I

	Product of Δ^4-3-ketosteroid and chloranil, acetate	Reaction solvent	Yield, %
(1)	$\Delta^{4,6}$-Pregnadiene-11β,17α,21-triol-3,20-dione (IV)	[a]	80
		[b]	66
(2)	$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,11,20-trione (VI)	[a]	70
		[b]	45
(3)	$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,20-dione	[a]	68
(4)	$\Delta^{4,6}$-Pregnadiene-21-ol-3,20-dione	[a]	40
(5)	$\Delta^{4,6}$-Pregnadiene-11β,14α,17α,21-tetrol-3,20-dione[c]	[a]	58
(6)	16,17α-Oxido-$\Delta^{4,6}$-pregnadiene-21-ol-3,20-dione[d]	[a]	58
(7)	$\Delta^{4,6}$-Pregnadiene-14α,17α,21-triol-3,20-dione[e]	[a]	46

[a] *t*-Butyl alcohol. [b] Xylene. [c] Starting material described in ref. 7. [d] Starting material described in ref. 8. [e] Starting material described in ref. 9.

when N-bromsuccinimide is the brominating agent). As has been indicated above the chloranil reaction can be carried out in solvents as diverse as xylene chlorobenzene *p*-dichlorobenzene, *n*-butyl acetate, *t*-butyl alcohol and acetic acid, to name a few.

The effectiveness of other quinones in dehydrogenating Δ^4-3-ketosteroids was also investigated. Among the readily available quinones which were found capable of converting Δ^4- to $\Delta^{4,6}$-3-ketosteroids were 2,6-dichloro-*p*-benzoquinone, 1,4-napthoquinone, 1,2-naphthoquinone, *p*-toluquinone and *p*-benzoquinone. However, chloranil effected the dehydrogenation more rapidly and afforded better yields of pure products than any of the above quinones. The superiority of chloranil in steroid-3-ketone dehydrogenations was not unexpected in view of the results of the elegant studies by Linstead and the late Braude and their co-workers[10] of the thermal transfer of hydrogen between hydroaromatic compounds and quinones. These investigators found that the effectiveness of quinones in the dehydrogenation of hydroaromatic compounds is enhanced by electron-attracting groups and reduced by electron-donating groups. Thus, chloranil, possessing four electron-attracting substituents and a consequently high oxidation–reduction potential,[11] was also one of the most reactive quinones in the group studied by Linstead.

Although all Δ^4-3-ketosteroids were converted to their Δ^6-dehydro derivatives in refluxing *t*-butyl alcohol, the closely related $\Delta^{1,4}$- and $\Delta^{4,6}$-3-ketosteroids and saturated 3-ketones were not affected by chloranil under these conditions. However, dehydrogenation of these more stable 3-ketones was accomplished under more vigorous conditions.

(3) See, for example, V. R. Mattox, E. L. Worock, G. A. Fleisher and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(4) The number of references to the use of this dehydrogenation method in the steroid field which have appeared since our original announcement[1,2] further attests the broad scope of the reaction. See, for example: (a) J. A. Campbell and J. C. Babcock, THIS JOURNAL, **81**, 4069 (1959); (b) R. M. Dodson and R. C. Tweit, *ibid.*, **81**, 1224 (1959); (c) H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, *ibid.*, **81**, 3485 (1959); (d) H. J. Ringold, J. Perez Ruelas, E. Batres and C. Djerassi, *ibid.*, **81**, 3712 (1959); (e) A. Bowers, L. C. Ibáñez and H. J. Ringold, *ibid.*, **81**, 5991 (1959).

(5) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

(6) F. Sondheimer, C. A. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5932 (1953).

(7) E. J. Agnello, B. M. Bloom and G. D. Laubach, *ibid.*, **77**, 4684 (1955).

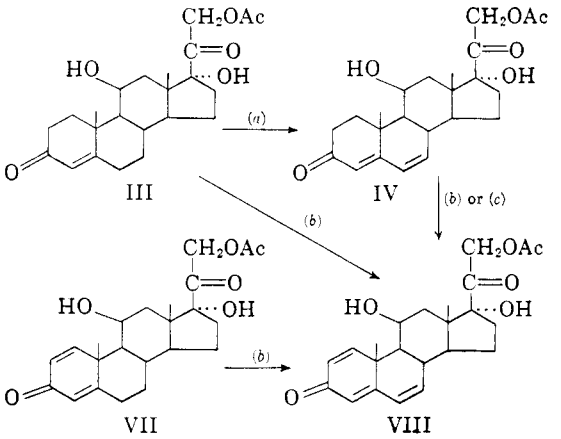
(8) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(9) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769, July 8, 1952.

(10) E. A. Braude and R. P. Linstead, *J. Chem. Soc.*, 3544 (1954); E. A. Braude, L. M. Jackman and R. P. Linstead, *ibid.*, 3548, 3564 (1954); E. A. Braude, A. G. Brook and R. P. Linstead, *ibid.*, 3569 (1954).

(11) See also L. F. Fieser and M. Fieser, "Organic Chemistry," Third Edition, Reinhold Publishing Co., New York, N. Y., 1956, pp. 710 ff., for a discussion of the effect of substituents on the oxidation-reduction potentials of quinones.

When either $\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-3,-20-dione acetate (prednisolone acetate, VII) or $\Delta^{4,6}$ - pregnadiene - 11β,17α,21 - triol - 3,20 - dione acetate (IV) was treated with chloranil in refluxing amyl alcohol, a tri-unsaturated 3-keto-steroid, $\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione acetate (VIII), was isolated. The same compound was obtainable in one step from cortisol acetate (III) when it was subjected to the same treatment.



[a] Chloranil, *t*-butyl alcohol. [b] Chloranil, amyl alcohol. [c] Selenium dioxide.

The structure of VIII as the $\Delta^{1,6}$-bisdehydro derivative of cortisol acetate was orginally assigned on the basis of its ultraviolet absorption spectrum.[12] This formulation was supported by the discovery that VIII was also obtainable by the dehydrogenation of the $\Delta^{4,6}$-3-ketosteroid IV with selenium dioxide.[13] The physical constants of the alcohol obtained from VIII by saponification were also in good agreement with those reported by Gould, *et al.*, for $\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione prepared by another method.[14]

The single step conversion of a Δ^4-3-ketosteroid to its $\Delta^{1,6}$-bisdehydro derivative was also successfully performed on cortisone acetate (V) and appeared to be applicable to other Δ^4-3-ketones. However, the $\Delta^{1,6}$-bisdehydro derivative (XI) of 9α-fluorocortisol acetate (IX)[15] was more efficiently prepared by dehydrogenation of IX at C_6 with chloranil followed by treatment of the product with selenium dioxide to dehydrogenate at C_1.

The successful chloranil dehydrogenation of the large variety of Δ^4-3-ketosteroids mentioned above prompted the investigation of the effectiveness of this reagent with other types of steroids. Among the compounds subjected to chloranil in refluxing xylene or *t*-butyl alcohol were compounds which were presumed to be activated for dehydrogenation at $\Delta^{9(11)}$-, $\Delta^{20(22)}$- or Δ^4-, *i.e.*, Δ^7-5α-pregnene-3β-ol-20-one acetate (XIII), methyl 3α-acetoxy-12-keto-cholanate (XIV), 3α,12α-diacetoxybisnorcholanyl-diphenyl-ethylene (XV), and the enol acetate of cholestane-3-one (XVI). In none of the above cases was there any evidence of the formation of a dehydrogenation product and in most cases a good yield[16] of starting material was recovered.

Saturated 3-ketosteroids of both the 5α- and 5β-pregnane series were recovered unchanged from treatment with chloranil in refluxing *t*-butyl alcohol. However, when more vigorous conditions were employed (refluxing *sec*-amyl alcohol) dehydrogenation was effected. For example, the *cis* and *trans* isomers of 4,5-dihydrocortexolone acetate were each converted to two products. One of these was identical to the product (XIX)[17] obtained under the same conditions from cortexolone acetate (XVIII). The other product was most probably $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione acetate (paper chromatographic behavior and spectral properties).

The results which are summarized in Table II indicate the marked differences in the conditions required for the dehydrogenation of some representative steroids. All Δ^4-3-ketosteroids which have been subjected to the action of chloranil in refluxing *t*-butyl alcohol (b.p. 83°) have been dehydrogenated to their Δ^6-dehydro derivatives. Other 3-ketosteroids ($\Delta^{1,4}$-, $\Delta^{4,6}$- and saturated) were unaffected under the above mild conditions (*t*-butyl alcohol). All of them were converted to $\Delta^{1,4,6}$-3-ketosteroids under more vigorous conditions (*sec*-amyl or *n*-amyl alcohols). Compounds which were not 3-ketosteroids were unaffected by chloranil even under the more vigorous conditions.

TABLE II

Steroid	Reaction conditions and results: *t*-Butyl alcohol	*sec*-Amyl alcohol
Δ^4-3-Ketone	$\Delta^{4,6}$	$\Delta^{1,4,6}$
$\Delta^{1,4}$-3-Ketone	No reacn.	$\Delta^{1,4,6}$
$\Delta^{4,6}$-3-Ketone	No reacn.	$\Delta^{1,4,6}$
Satd. 3-ketone (5α or 5β)	No reacn.	$\Delta^{1,4,6}$
9α-Fluoro-Δ^4-3-ketone	$\Delta^{4,6}$	$\Delta^{4,6}$
Compounds XII to XVII	No reacn.	No reacn.

The above results and others contained in the Experimental section of this communication demonstrated the importance of not only the reaction temperature (*e.g.*, Δ^6-dehydrogenation in *t*-butyl alcohol, b.p. 83°, and $\Delta^{1,6}$-bisdehydrogenation in *sec*-amyl alcohol, b.p. 110–117°) but also of the nature of the solvent (compare results in xylene b.p. 135°, or chlorobenzene, b.p. 132° with *sec*-amyl alcohol, b.p. 110–117°).

In the course of the present investigation, we have made several observations which are pertinent to the formulation of a mechanism for the dehydrogenation of steroid 3-ketones. The observation that 3-ethoxy-$\Delta^{3,5}$-pregnadiene-17α,21-diol-20-one 21-acetate (the enol ether of cortexolone acetate) was dehydrogenated more readily than its parent Δ^4-3-ketone implicates an enolization step as the rate-determining one. Another result which lends support to this proposal was the more rapid dehydrogenation of Δ^5-cholestene-3-one when compared to Δ^4-cholestene-3-one, a result consistent

(12) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(13) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(14) D. Gould, *et al.*, THIS JOURNAL, **79**, 502 (1957).

(15) J. Fried and E. F. Sabo, *ibid.*, **76**, 1455 (1954).

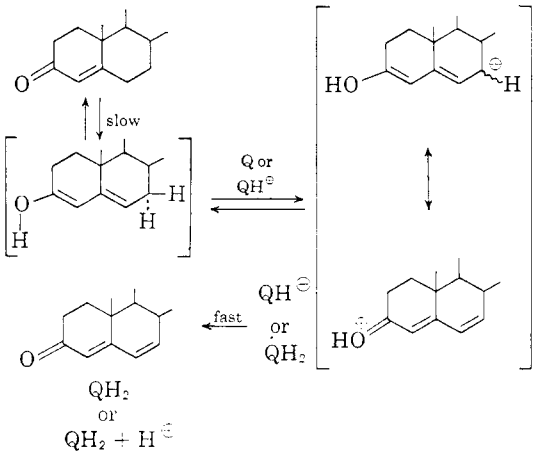
(16) Recovery yields: XIII, 40%; XIV, 90%; XV, 50%; XVI, 89%. Other compounds which were unaffected by chloranil are described in the Experimental section.

(17) The product was assigned the structure $\Delta^{1,4,6}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate on the basis of its spectral properties and by analogy with the conversion of III to VIII.

with the lower energy requirements for Δ^5-3-one to $\Delta^{3,5}$-dien-3-ol conversion.

The exact nature of the quinone-derived species which removes the C_7-hydrogen from the enol cannot be specified at present. However, in view of the fact that the dehydrogenation of Δ^4-cholestenone in acetic acid was accelerated by the addition of anhydrous hydrogen chloride and inhibited by a small amount of sodium acetate it appears that the quinone conjugate acid QH^+ is a more effective species for the removal of hydrogen than the quinone.

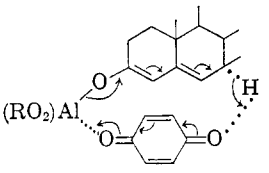
The observations cited above point to the following as a reasonable mechanism[18] for the dehydrogenation of steroid 3-ketones with quinones.



The recent report of Campbell and Babcock[4a] that 7β-methyl-Δ^4-3-keto steroids are readily dehydrogenated while the 7α-methyl derivatives resist dehydrogenation with chloranil sheds additional light on the mechanism by demonstrating the stereospecific abstraction of hydrogen.

Acknowledgments.—The authors gratefully acknowledge helpful discussions with Drs. B. M. Bloom and E. J. Corey and the technical assistance of Mrs. Mary Bolton Zopf and Mr. Bohdan Rakoczy.

(18) It has been proposed by L. Mandell, THIS JOURNAL, **78**, 3199 (1956), that the Wettstein modification[5] of the Oppenauer oxidation (the conversion of Δ^5-3-ols to $\Delta^{4,6}$-diene-3-ones by *p*-quinone in the presence of aluminum alkoxide) proceeds *via* a cyclic intermediate of type (a). According to Mandell, his observation that 1,4-naphthoquinone is an effective hydrogen acceptor in the Wettstein modification while 1,2-naphthoquinone (higher oxidation potential) is *not* effective implies a necessity for a 1,4-relationship of the two quinone carbonyl groups in the hydrogen acceptor. However, the present authors feel that the chloranil dehydrogenation reaction, occurring as it does under a different set of reaction conditions (in the absence of aluminum alkoxide), may proceed by a mechanism which does not require a cyclic intermediate of the type proposed for the Wettstein–Oppenauer oxidation. Our observation that 1,2-naphthoquinone *does* dehydrogenate a Δ^4-3-ketosteroid (see Experimental section) indicates that another mechanism (not involving 1,4-relationship of the two quinone carbonyl groups) is possible. Accordingly, the mechanism of the chloranil dehydrogenation reaction is formulated in the more general manner depicted in the text of this paper.



(a)

Experimental[19]

$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,20-dione Diacetate (II).—A stirred mixture of 5.0 g. of I[20] and 17.1 g. of chloranil in 350 ml. of *t*-butyl alcohol was heated at reflux temperature for 3 hours. The excess chloranil was filtered and the filtrate taken to dryness. The residue was taken up in chloroform (300 ml.) and the solution washed with 30-ml. portions of water (3 times), 5% sodium hydroxide (4 times) and again with water (4 times). Evaporation of the chloroform afforded a crystalline residue which, when triturated, yielded 3.07 g. of ivory microcrystals, λ_{max} 283 mμ (25,000). Recrystallization of this material from ethyl acetate afforded $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (II), m.p. 216–218°, λ_{max} 284 mμ (25,800).

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.8; H, 7.40.

The infrared spectrum of the above product was identical with that of a sample prepared from I by bromination with N-bromosuccinimide[3] and dehydrobromination with collidine[21] (I → 6-bromo-derivative → II).

$\Delta^{4,6}$-Pregnadiene-11β,17α,21-triol-3,20-dione Acetate (IV). a. In *t*-butyl Alcohol.—A mixture of 25 g. of cortisol acetate (III) and 45.7 g. of chloranil was heated with stirring in 1700 ml. of refluxing *t*-butyl alcohol for 3 hours. The reaction mixture, treated as above, afforded 21.4 g. of ivory solid from which 19.7 g. (80%) of crystalline product was isolated which exhibited an ultraviolet absorption band at 285 mμ (25,000). An analytical sample from ethyl acetate exhibited m.p. 199–202°, $[\alpha]^{25}D$ +193°, λ_{max} 284 mμ (25,000).

Anal. Calcd. for $C_{23}H_{30}O_6.CH_3COOC_2H_5$: C, 66.10; H, 7.81. Found: C, 66.4; H, 7.62.

Oxidation of 115 mg. of IV with chromic acid in acetic acid in the usual way afforded 75 mg. of crude crystalline product which, upon recrystallization from acetone, was identical to a sample of Δ^6-dehydrocortisone acetate (VI) prepared by the action of chloranil on cortisone acetate (V) (see below).

b. In Xylene.—A stirred mixture of 1.0 g. of cortisol acetate, 3.75 g. of chloranil and 75 ml. of xylene was heated at reflux for 3 hours. The reaction mixture was taken up in 1 liter of chloroform and the crude product isolated as described above. Trituration of the residue with ether–ethyl acetate (1:2) afforded 663 mg. of ivory-colored microcrystals. After 2 recrystallizations from ethyl acetate the sample was identical to the one prepared in *t*-butyl alcohol (above).

c. In *n*-Butyl Acetate.—A mixture of 404 mg. of cortisol acetate and 1.48 g. of chloranil in 30 ml. of *n*-butyl acetate was heated at reflux for 3 hours. Paper chromatographic analysis at the end of this time indicated the presence of about 30% of Δ^6-dehydrocortisol acetate and 70% of starting material.

d. In Chlorobenzene.—Treatment of cortisol acetate (404 mg.) in chlorobenzene (35 ml.) with chloranil (1.48 g.) for 3 hours at reflux resulted in a mixture which paper chromatographic analysis indicated to be approximately 15% Δ^6-dehydrocortisol acetate and 85% starting material.

$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,11,20-trione Acetate (VI). a. In Xylene.—A solution of 1.25 g. of cortisone acetate in 100 ml. of xylene was heated at reflux with 4.65 g. of chloranil for 2 hours. The crude product, isolated as described above, consisted of 1.15 g. of tan solid, λ_{max} 281 mμ (23,200),which, when triturated with ethyl acetate, afforded 0.56 g. of Δ^6-dehydrocortisone acetate,[3] m.p.

(19) All melting points are uncorrected. The rotations were determined in dioxane in 1-dm. tubes at concentrations of 1 to 5 mg./ml. and the ultraviolet spectra in 95% ethanol unless otherwise specified. The chloranil which was employed in these experiments was obtained from Matheson, Coleman and Bell (No. 5600) and recrystallized once from benzene before use. The *sec*-amyl alcohol was Coleman practical grade, b.p. 110–117°. All reactions were carried out under an atmosphere of nitrogen.

(20) R. B. Turner, THIS JOURNAL, **75**, 3489 (1953).

(21) See, for example, C. Djerassi and C. R. Scholz, *ibid.*, **69**, 2404 (1947).

220–221° dec. An analytical sample exhibited m.p. 221–222° dec., λ_{max} 282 mμ (25,000), $[\alpha]_D$ +275°.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.8; H, 6.97.

b. In *t*-Butyl Alcohol.—From 10.0 g. of cortisone acetate, 18.3 g. of chloranil and 680 ml. of *t*-butyl alcohol (3 hours at reflux) there was obtained 8.8 g. of crude crystals which afforded, upon trituration, 7.8 g. of Δ⁶-dehydrocortisone acetate, λ_{max} 281 mμ (22,400), identical by infrared spectral comparison to VI prepared as described above.

c. In *o*-Dichlorobenzene.—Cortisone acetate (402 mg.) and chloranil (490 mg.) in 70 ml. of *o*-dichlorobenzene at reflux for 18 hours afforded 310 mg. of crude Δ⁶-dehydrocortisone acetate.[3] Recrystallization from acetone yielded 72 mg. of VI, m.p. 235–236°, $[\alpha]_D$ +265°, λ_{max} 281 mμ (25,400), identical in all respects to the sample described above.

Δ⁴,⁶-Pregnadiene-3,20-dione.—Progesterone (629 mg.) and chloranil (980 mg.) in 72 ml. of xylene were heated at reflux for 18 hours. The crude triturated crystalline product, 170 mg., isolated as above, exhibited m.p. 133–135°, λ_{max} 283 mμ (25,000), $[\alpha]_D$ +181° (chlf.). Recrystallization from ethyl acetate afforded Δ⁶-dehydroprogesterone,[5] m.p. 143–145°, $[\alpha]_D$ +167° (chlf.), λ_{max} 283 mμ (25,400).

Δ⁴,⁶-Pregnadiene-21-ol-3,20-dione Acetate.—The reaction of 5.0 g. of cortexone acetate, 19.7 g. of chloranil, 350 ml. of *t*-butyl alcohol and 5.6 ml. of glacial acetic acid (3 hours at reflux) afforded, after the usual work-up, 3.3 g. of crude residue. Trituration of the crude product with acetone gave 2.5 g. of crystalline Δ⁶-dehydrocortexone acetate,[5] m.p. 110–112°, λ_{max} 284 mμ (22,000).

Δ⁴,⁶-Pregnadiene-17α,21-diol-3,20-dione Acetate.—Treatment of 25.0 g. of cortexolone acetate with 53.1 g. of chloranil in refluxing *t*-butyl alcohol (1700 ml.) and acetic acid (28 ml.) for 3 hours afforded after the usual work-up and trituration of the crude residue with 2:1 ether–ethyl acetate, 16.8 g. of crystalline Δ⁶-dehydrocortexolone acetate,[6] λ_{max} 285 mμ (24,500). An analytical sample exhibited m.p. 220–221°, λ_{max} 283 mμ (26,200).

Δ⁴,⁶-Pregnadiene-11β,14α,17α,21-tetrol-3,20-dione 21-Acetate.—Treatment of 420 mg. of Δ⁴-pregnene-11β,14α,17α,21-tetrol-3,20-dione 21-acetate[7] with 1.48 g. of chloranil in refluxing *t*-butyl alcohol (30 ml.) and acetic acid (0.5 ml.) for 3 hours afforded 204 mg. of triturated crystalline product, λ_{max} 283 mμ (22,000). Recrystallization from ethyl acetate yielded the analytical sample which exhibited m.p. 245–247° dec., $[\alpha]^{24}_D$ +230°, λ_{max} 283 mμ (24,800).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.4; H, 7.20.

Δ⁴,⁶-Pregnadiene-14α,17α,21-triol-3,11,20-trione 21-Acetate.—A mixture of 500 mg. of Δ⁴-pregnene-14α,17α,21-triol-3,11,20-trione 21-acetate,[7] 1.76 g. of chloranil and xylene was heated at its reflux temperature for 2 hours. The total crude product, obtained as described above, readily afforded 118 mg. of ivory crystals, λ_{max} 280 mμ (24,500) when triturated with ethyl acetate. An analytical sample, obtained from ethyl acetate, exhibited m.p. above 260°, $[\alpha]^{20}_D$ + 292°, λ_{max} 282 mμ (24,300).

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.6; H, 6.89.

Δ⁴,⁶-Pregnadiene-14α,17α,21-triol-3,20-dione 21-Acetate.—Treatment of 404 mg. of Δ⁴-pregnene-14α,17α,21-triol-3,20-dione 21-acetate (14α-hydroxycortexolone acetate)[9] with 1.48 g. of chloranil in refluxing *t*-butyl alcohol (30 ml.) and glacial acetic acid (0.5 ml.) for 3 hours gave 187 mg. of triturated crystals, λ_{max} 283 mμ (25,000). An analytical sample of the Δ⁶-dehydro derivative, obtained from ethyl acetate, exhibited m.p. 227–229°, λ_{max} 283 mμ (25,400), $[\alpha]^{20}_D$ +152°.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.1; H, 7.39.

16,17α-Oxido-Δ⁴,⁶-pregnadiene-21-ol-3,20-dione 21-Acetate.—Treatment of 10 g. of 16,17α-oxido-Δ⁴-pregnene-21-ol-3,20-dione 21-acetate[8] with 45 g. of chloranil in 700 ml. of refluxing *t*-butyl alcohol and 11 ml. of glacial acetic acid for 3 hours afforded 4.2 g. of triturated crystalline product, λ_{max} 283 mμ (25,000). An analytical sample, recrystallized from ether, exhibited m.p. 172°, $[\alpha]^{26}_D$ +127°, λ_{max} 284 mμ (25,200).

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.7; H, 7.15.

9α-Fluoro-Δ⁴,⁶-pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate.—A mixture of 1.1 g. of 9α-fluoro-Δ⁴-pregnene-17α,21-diol-3,11,20-trione 21-acetate[15] and 1.93 g. chloranil in 75 ml. of *t*-butyl alcohol was heated at reflux temperature for 3 hours. The crude product consisted of 391 mg. of amorphous brown solid which, upon trituration with 2:1 ether–ethyl acetate, afforded 156 mg. ivory microcrystals, λ_{max} 278 mμ (22,500). An analytical sample, recrystallized from 4:1 ethyl acetate–ethanol, exhibited m.p. 242–243°, λ_{max} 279 mμ (26,500).

Anal. Calcd. for $C_{23}H_{27}O_6F$: C, 66.01; H, 6.50. Found: C, 66.2; H, 6.46.

9,11β-Oxido-Δ⁴,⁶-pregnadiene-17α,21-diol-3,20-dione 21-Acetate.—9,11β-Oxido-Δ⁴-pregnene-17α,21-diol-3,-20-dione 21-acetate[22] (402 mg.) and 1.4 g. of chloranil in 35 ml. of *t*-butyl alcohol was heated under reflux for 4 hours. The total crude product, 276 mg., when triturated with 2:1 ether–ethyl acetate, afforded 105 mg. of ivory crystals, λ_{max} 283 mμ (25,000). An analytical sample, recrystallized from ethyl acetate, exhibited m.p. 205–206°, λ_{max} 283 mμ (26,900), $[\alpha]^{22}_D$ +149°.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.6; H, 7.09.

Treatment of 8.0 g. of the 9,11β-oxido-Δ⁴,⁶-pregnadiene-17α,21-diol-3,20-dione 21-acetate obtained in this reaction with anhydrous hydrogen fluoride in tetrahydrofuran-chloroform[23] afforded 6.1 g. of 9α-fluoro-Δ⁴,⁶-pregnadiene-17α,21-diol-3,20-dione 21-acetate, λ_{max} 282 mμ (25,200), identical by infrared spectral comparison to X, prepared by the reaction of chloranil with 9α-fluorocortisol acetate (see below).

9α-Fluoro-Δ⁴,⁶-pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (X). a. In *t*-Butyl Alcohol.—Treatment of 422 mg. of 9α-fluoro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione acetate[15] (IX) with 0.74 g. of chloranil in 30 ml. of *t*-butyl alcohol (4 hours at reflux temperature) and isolation of the product as above afforded 100 mg. of ivory crystals, m.p. 207–210°, λ_{max} 282 mμ (23,400), and with absorption bands in the infrared spectrum in agreement with those reported.[24]

b. In *sec*-Amyl Alcohol.—A mixture of 1.0 g. of IX and 2.48 g. of chloranil in 35 ml. of *sec*-amyl alcohol was heated at its reflux temperature for 10 minutes. Paper chromatographic analysis indicated complete conversion to the Δ⁶-dehydro derivative X. Heating was continued for 3 hours. No change occurred. The product isolated (127 mg. of triturated crystals) was identical to X obtained from IX in *t*-butyl alcohol.

Δ¹,⁴,⁶-Pregnatriene-11β,17α,21-triol-3,20-dione 21-Acetate (VIII). a. From III with Chloranil.—A mixture of 404 mg. of cortisol acetate (III), 1.48 g. of chloranil and 15 ml. of *sec*-amyl alcohol was heated at its reflux temperature for 3 hours. The mixture was filtered and the filtrate evaporated to dryness. A chloroform solution of the residue was washed with 10-ml. portions of water (3 times), 5% sodium hydroxide (3 times) and with water (4 times), then dried and concentrated to dryness. Trituration of the crude residue (285 mg.) with 1:1 ethyl acetate–ether afforded 150 mg. (37%)[25] of ivory microcrystals; λ_{max} 221 mμ (10,500), 264 mμ (10,500), 293 mμ (13,500). The infrared spectrum of this product was identical to VIII prepared from the Δ⁶-dehydro derivative IV by treatment with either chloranil or selenium dioxide and from the Δ¹-dehydro derivative VII with chloranil (see below).

b. From IV with Chloranil.—A mixture of 402 mg. of Δ⁶-dehydrocortisol acetate (IV), 1.48 g. of chloranil and 15 ml. of *sec*-amyl alcohol was heated at its reflux temperature for 3 hours. The reaction mixture was filtered, the filtrate was evaporated to dryness and the residue was chroma-

(22) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

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

(24) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955).

(25) Dr. W. T. Moreland (W. T. Moreland and E. J. Agnello, U. S. Patent 2,883,379, April 21, 1959) of this Laboratory improved the yield of this conversion to approximately 65% by the addition to the reaction mixture of finely divided substances such as calcium carbonate, germanium or ground glass.

tographed on Florisil using methylene chloride and methylene chloride–acetone mixtures. A crystalline compound, isolated in low yield (5%), was identical to VIII prepared from III. Some starting material was also recovered.

c. **From VII with Chloranil.**—From 402 mg. of prednisolone acetate (VII) in *n*-amyl alcohol (15 ml.) with 1.48 g. chloranil under the same conditions and using the same isolation procedure, 5% of crystalline product was obtained which was identical to VIII prepared from III or IV.

d. **From IV with Selenium Dioxide.**—A mixture of 3.2 g. of IV and 660 mg. of selenium dioxide in 50 ml. of phenetole was heated at its reflux temperature for 0.75 hour. The hot reaction mixture was filtered and diluted with 300 ml. of ethyl acetate. The solution was washed with sodium bicarbonate and water and dried over sodium sulfate. The dry solution was stirred with precipitated silver (2 g.) and Darco-G-60 (2 g.) for 2 hours, filtered and concentrated to dryness. A solution of the residue in a small volume of methylene chloride crystallized as pale yellow crystals (514 mg.), $[\alpha]^{25}D$ +135°, λ_{max} 222 mμ (11,000), 253 mμ (9,300), 300 mμ (11,000). Recrystallization from ethyl acetate afforded $\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate, m.p. 210–211°, $[\alpha]^{25}D$ +131°; λ_{max} 223 mμ (13,400), 253 mμ (10,500), 301 mμ (13,300).

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.3; H, 7.12.

Saponification of 32 g. of VIII with potassium carbonate in aqueous methanol afforded 26.8 g. of the 21-hydroxyl compound; λ_{max} 223 mμ (11,520), 254 mμ (9,800) and 300 mμ (11,600). An analytical sample, obtained from ethanol, exhibited m.p. 235°, $[\alpha]^{21}D$ +99°; λ_{max} 222 mμ (11,300), 254 mμ (9,200), 301 mμ (10,900).[26a]

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.9; H, 7.29.

$\Delta^{1,4,6}$-Pregnatriene-17α,21-diol-3,11,20-trione 21-Acetate.—Heating 402 mg. of cortisone acetate (V) with 1.48 g. of chloranil in 15 ml. of refluxing *sec*-amyl alcohol for 3 hours afforded, after the usual work-up, 251 mg. of crude residue. The crystalline product (107 mg., 27%) was obtained by triturating the residue with ethyl acetate. Recrystallization from ethyl acetate afforded an analytical sample of $\Delta^{1,4,6}$-pregnatriene-17α,21-diol-3,11,20-trione 21-acetate, m.p. 222–226°, $[\alpha]^{22}D$ +284°; λ_{max} 223 mμ (10,200), 255 mμ (9,800), 297 mμ (12,100).[26b]

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.4; H, 6.62.

9α-Fluoro-$\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione 21-Acetate (XI). a. **From X with Selenium Dioxide.**—A mixture of 140 mg. of X and 172 mg. of selenous acid (in two portions) in *t*-butyl alcohol (15 ml.) and acetic acid (0.15 ml.) was heated at its reflux temperature for 6.5 hours. The solvent was evaporated, the steroid was taken up in ethyl acetate and the solution washed successively with water, ammonium sulfide and water. The crude product, after the removal of solvent and trituration with ethyl acetate, afforded the crystalline product (40 mg.). An analytical sample, recrystallized from methanol, exhibited m.p. 238–239° dec., λ_{max} 220 mμ (12,600), 250 mμ (9,700), 299 mμ (13,000).

Anal. Calcd. for $C_{23}H_{27}O_6F$: C, 66.01; H, 6.50. Found: C, 65.9; H, 6.44.

b. **From 9α-Fluoro-$\Delta^{1,4}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (XII).**—A mixture of 420 mg. of XII and 1.48 g. of chloranil was heated in 15 ml. of *sec*-amyl alcohol at its reflux temperature for 3 hours. Aliquots taken each hour for paper chromatographic analysis indicated the presence of increasing amounts of product XI and decreasing amounts of starting material. The crude amorphous product (292 mg.) exhibited λ_{max} 240 and 295 mμ (ratio of optical densities, 2:1), indicating the presence of both product and starting material. Trituration with 1:1 ethyl acetate–ether afforded 104 mg. of tan microcrystals with the same ultraviolet absorption spectrum.

$\Delta^{1,4,6}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XIX).—Treatment of 388 mg. of XVIII in 25 ml. of *sec*-amyl alcohol with 1.48 g. of chloranil at reflux temperature for 3 hours afforded 171 mg. of crude triturated microcrystals. The presence of a small amount of Δ^6-dehydro derivative was indicated by paper chromatographic and spectral analysis: λ_{max} 222 mμ (10,000), 263 mμ (10,800), 295 mμ (14,500).

b. **From 5α-Pregnane-17α,21-diol-3,20-dione 21-Acetate.**—Treatment of 5α-pregnane-17α,21-diol-3,20-dione acetate (390 mg.) with chloranil (1.48 g.) in 15 ml. of *sec*-amyl alcohol at reflux temperature for 3 hours afforded a crude mixture (amorphous) of Δ^6- and $\Delta^{1,6}$-dehydro derivatives of XVIII. Trituration of the crude residue with ethyl acetate–ether gave 16 mg. of crystals which were identical to the product isolated by procedure (a) above.

c. **From 5β-Pregnane-17α,21-diol-3,20-dione 21-Acetate.**—5β-Pregnane-17α,21-diol-3,20-dione 21-acetate was treated as in (b) above and the total reaction mixture subjected to paper chromatographic analysis. The same products, Δ^6- and $\Delta^{1,6}$-dehydro derivatives of XVIII, were indicated (not isolated).

Dehydrogenation Rate: Comparison of a Δ^4-3-Ketosteroid with an Enol Ether. a. **Δ^4-3-Ketosteroid.**—A mixture of 774 mg. of Δ^4-pregnene-17α,21-diol-3,20-dione-21 acetate and 2.96 g. of chloranil in 30 ml. of *t*-butyl alcohol was heated at its reflux temperature for *10 minutes* and the total crude steroid recovered in the usual way. It consisted of 895 mg. of slightly moist white glass which exhibited a single major peak in the ultraviolet (λ_{max} 240 mμ) with a very minor peak at 280 mμ (less than 10% of the optical density at 240 mμ). Trituration of the crude product with 1:4 ethyl acetate–ether afforded 664 mg. of white crystals which were identical to starting material by infrared spectral comparison.

b. **Enol Ether.**—Treatment of 804 mg. of 3-ethoxy-$\Delta^{3,5}$-pregnadiene-17α,21-diol-20-one 21-acetate with 2.96 g. of chloranil in 30 ml. of *t*-butyl alcohol for 10 minutes as in (a) above and isolation of the product in the usual way afforded 624 mg. of an amorphous ivory glass which exhibited a major ultraviolet absorption band at 285 mμ and a shoulder at 240 mμ (ratio approximately 4:1). Trituration of the crude product with ether afforded 415 mg. of crystalline product which was also a mixture of Δ^4- and $\Delta^{4,6}$-3-ketones (ratio of optical density at 285 mμ to that at 240 mμ was approximately 3:1).

Dehydrogenation Rate: Effect of Acid and Base.—A mixture of 1.0 g. of Δ^4-cholesten-3-one and 1.94 g. of chloranil in 50 ml. of glacial acetic acid was heated at 80° and aliquots (5 ml.) were removed at 20, 60 and 90 minutes and the total crude steroid isolated as follows. The acetic acid was removed *in vacuo*. The residue was taken up in 50 ml. of ether and the solution washed successively with water, 5% sodium hydroxide and water (4 times each). The product was isolated from the dried ether solution. The weights of the steroids isolated from each aliquot and the optical densities at 233 mμ (Δ^4-3-ketone) and 275 mμ ($\Delta^{4,6}$-3-ketone) are tabulated below. The above experiment was repeated twice, once with hydrogen chloride (200 mg./ml.) and once with sodium acetate (9 mg./ml.) added to the acetic acid.

Reaction medium	Time, min.	Steroid Weight, mg.	Optical density 233 mμ	Optical density 275 mμ
Acetic acid	20	91	2.40	0.00
	60	78	1.14	0.48
	90	86	0.80	1.84
Acetic acid + hydrogen chloride	20	82	0.63	2.75
	60	72	.55	2.10
	90	77	.50	1.83
Acetic acid + sodium acetate	20	86	1.52	0.00
	60	75	1.52	.00
	90	91	1.99	.05

Steroids other than Δ^4-3-Ketones.—The following results were obtained from the action of chloranil on compounds that were not Δ^4-3-ketosteroids. (a) Recovered unchanged (yield, solvent, reflux time): 5α-pregnane-17α,21-diol-3,20-dione 21-acetate, 5β-pregnane-17α,21-diol-3,20-dione 21-acetate, 5α-pregnane-17α,21-diol-3,11,20-trione 21-acetate, 3-acetoxy-Δ^2-cholestene and 3β-acetoxy-Δ^5-cholestene-7-one (90 to 100%, *t*-butyl alcohol, 3 hours); cholesterol (52%, xylene, 2 hours); Δ^5-pregnene-3β-ol-20-one (100%, xylene, 5 hours); methyl 3α-acetoxy-12-ketocholanate

(26a) The constants are in good agreement with those reported by D. Gould, *et al.*,[14] for (a) Δ^6-dehydroprednisolone prepared by another method; (b) Δ^6-dehydroprednisone acetate prepared by another method.

(90%, xylene, 18 hours); Δ^7-5α-pregnen-3β-ol-20-one acetate (40%, xylene, 16 hours); 3α,12α-diacetoxybisnorcholanyldiphenyl ethylene (50%, *o*-dichlorobenzene, 16 hours).

(b) Δ^5-Cholestene-3-one was completely converted to $\Delta^{4,6}$-cholestadiene-3-one in 20 minutes when treated with chloranil in *t*-butyl alcohol.

Other Quinones.–Treatment of cortisol acetate (III) with various quinones at reflux temperature in the solvents indicated and examination of the ultraviolet absorption spectra of the crude products, isolated in the usual manner, gave the results described below:

(a) ***p*-Toluquinone in *n*-Amyl Alcohol.**—After 3 hours the product was a mixture of approximately 70% starting material III and 30% Δ^6-dehydro derivative IV.

(b) **1,2-Naphthoquinone in *n*-Amyl Alcohol.**—After 3 hours the product was a mixture of approximately 50% starting material III and 50% Δ^6-dehydro derivative IV.

(c) **2,6-Dichloro-*p*-benzoquinone in *sec*-Amyl Alcohol.**—After 2 hours the product was a mixture of approximately 50% each of Δ^6-bisdehydro and $\Delta^{1,6}$-bisdehydro derivatives (IV and VIII). No starting material was detected.

(d) **2,6-Dichloro-*p*-benzoquinone in *o*-Dichlorobenzene.**—After 3 hours the product was a mixture of approximately 40% starting material III and 60% Δ^6-dehydro derivative IV.

(e) ***p*-Benzoquinone in *n*-Amyl Alcohol.**—After 2 hours paper chromatographic analysis indicated the crude mixture contained Δ^6-dehydro derivative IV and starting material III in a ratio of 1:3.

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

Proximity Effects. XIX. Solvolysis of 4-Cycloöcten-1-yl Brosylate with Trifluoroacetic Acid[1,2]

BY ARTHUR C. COPE, J. MARTIN GRISAR AND PAUL E. PETERSON[3]

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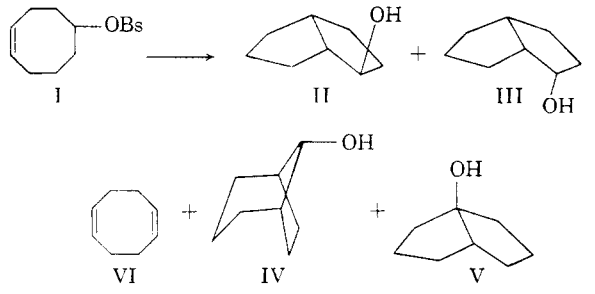
Solvolysis of 4-cycloöcten-1-yl brosylate (I) with trifluoroacetic acid followed by hydrolysis gave the known alcohols *exo*- and *endo*-bicyclo[3.3.0]octan-2-ol (II and III) and the hitherto unknown alcohols *exo*-bicyclo[3.2.1]octan-8-ol (IV) and *cis*-bicyclo[3.3.0]octan-1-ol (V). Evidence for the structure and configuration of the unknown alcohols is presented and includes the synthesis of *endo*-bicyclo[3.2.1]octan-8-ol (X) from bicyclo[3.2.1]octan-8-one (VII) and *cis*-bicyclo[3.3.0]octan-1-ol (V) from bicyclo[3.3.0]oct-1(5)-ene oxide (XX). Solvolysis of *exo-cis*-bicyclo[3.3.0]oct-2-yl brosylate (XIV) also gave *exo*-bicyclo[3.2.1]octan-8-ol (IV) providing a basis for assignment of configuration to that alcohol. *trans*-2-Vinylcyclohexanol (XXIII) is obtained from solvolysis of 3-cycloöcten-1-yl brosylate but not from solvolysis of the 4-isomer I. 3-Cycloöcten-1-ol is therefore postulated to be a precursor of *trans*-2-vinylcyclohexanol (XXIII) in the solvolysis of *cis*-cyclooctene oxide and in the reaction of 1,5-cycloöctadiene (VI) with strong acids.

The solvolysis of 4-cycloöcten-1-yl brosylate (I) with acetic acid at 80° recently has been reported to give in 35% yield acetates of the alcohols *exo*- (32%) and *endo-cis*-bicyclo[3.3.0]octan-2-ol (48%) (II and III) and 4-cycloöcten-1-ol (20%).[4] The solvolysis of the brosylate I with trifluoroacetic acid and proof of the structure of two of the products are reported in this paper.

The solvolysis of 4-cycloöcten-1-yl brosylate (I) with trifluoroacetic acid at 25–30° followed by hydrolysis gave in 55% yield products that consisted of *exo*- (40%) and *endo-cis*-bicyclo[3.3.0]octan-2-ol (11%) (II and III), *exo*-bicyclo[3.2.1]-octan-8-ol (31%) (IV), *cis*-bicyclo[3.3.0]octan-1-ol (12%) (V) and 4-cycloöcten-1-ol (6%).



The crystalline brosylate I was solvolyzed by adding it to a twenty-fold molar excess of trifluoroacetic acid that contained sodium acetate to neutralize the *p*-bromobenzenesulfonic acid formed. The solvolysis products were separated from the reaction medium, hydrolyzed and distilled, and analyzed by gas chromatography. Alcohols III and V were isolated as separate fractions by distillation through a spinning band column, and IV was isolated from a distillation fraction that contained it together with II by repeated low temperature recrystallization. *exo*-Bicyclo[3.2.1]octan-8-ol (IV) was also obtained from 1,5-cycloöctadiene (VI) by treatment with 75% sulfuric acid. *exo*- and *endo-cis*-bicyclo[3.3.0]octan-2-ol (II and III) were identified by preparation of derivatives and comparison with authentic specimens.[5] The assignment of structures to alcohols IV and V is described in the following paragraphs.

***exo*-Bicyclo[3.2.1]octan-8-ol (IV).**—The structure of *exo*-bicyclo[3.2.1]octan-8-ol (IV) is shown by its oxidation to bicyclo[3.2.1]octan-8-one (VII). Its infrared spectrum is identical to that of the ketone obtained in 3.8% yield from cyclization of 2-(ω-bromopropyl)-cyclopentanone (VIII) following the procedure of Mayer, Wenschuh and Töpelmann.[6] The 2,4-dinitrophenylhydrazones of the ketone obtained by the two routes also had identical infrared spectra and showed no mixed melting point depression. To obtain evidence for the carbon skeleton of bicyclo[3.2.1]octan-8-one (VII), it was converted to its ethylenethioketal and desulfurized with Raney nickel to the known[7] bicyclo[3.2.1]octane (IX). The 8-position of the

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(2) Paper XVIII, A. C. Cope, S. Moon and P. E. Peterson, THIS JOURNAL, **81**, 1650 (1959).

(3) National Institutes of Health Postdoctoral Fellow, 1956–1958.

(4) A. C. Cope and P. E. Peterson, THIS JOURNAL, **81**, 1643 (1959).

(5) A. C. Cope, M. Brown and H. E. Petree, *ibid.*, **80**, 2852 (1958).

(6) R. Mayer, G. Wenschuh and W. Töpelmann, *Chem. Ber.*, **91**, 1616 (1958).

(7) M. S. Newman and Y. T. Yu, THIS JOURNAL, **74**, 507 (1952), and references cited therein.