[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. V.[1] The Synthesis of Adrenal Corticosteroids and Analogs from Allopregnan-3β-ol-20-one

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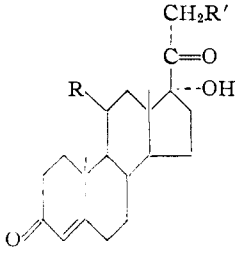
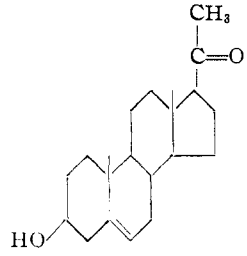
The discovery[2] of the dramatic therapeutic effect of Cortisone (17α-hydroxy-11-dehydrocorticosterone acetate) (I) in rheumatoid arthritis has greatly stimulated research on adrenal corticosteroids, particularly in regard to the synthesis of 11-oxygenated steroids. The main disadvantages of Cortisone are the clinical side effects, which accompany the continuous administration of high doses of such a potent hormone, and the present relative inaccessibility of the substance The recent report[3] on the marked clinical effectiveness of a simple 11-*desoxy*steroid, Δ⁵-pregnen-3β-ol-20-one (II) in arthritis, coupled by its lack of side effects, has emphasized the fact that the structural prerequisites for anti-arthritis activity are practically unknown. In an attempt to delineate these structural features, a program has been started in these Laboratories to synthesize a variety of steroids from readily available starting materials as potential anti-arthritic agents with possibly less severe side reactions in the patient. The present report deals with the synthesis of a number of 11-desoxy-17α-hydroxy-20-ketosteroids from *allo*pregnan-3β-ol-20-one 3-acetate (V), which is easily obtainable from various plant sources, with the aim of determining the biological effect of: (a) absence of an 11-oxygen function, (b) presence or absence of a 21-acetoxy group in 17α-hydroxy-20-ketones, (c) absence of the Δ⁴-3-keto moiety in ring A, and (d) variations in the α,β-unsaturated keto function of the adrenal hormones 17α-hydroxyprogesterone (III) and Reichstein's substance S acetate (IV) ("11-desoxycortisone").

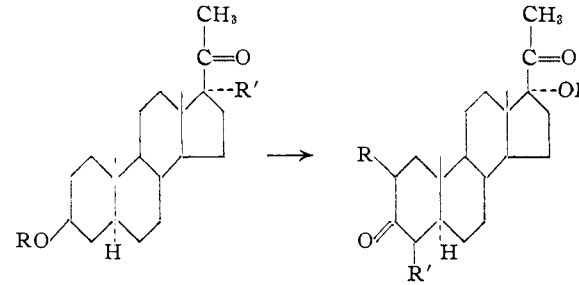


I, R = O, R′ = OAc
III, R = R′ = H
IV, R = H, R′ = OAc



II

In a preliminary communication,[4] Kritchevsky and Gallagher have described a very elegant method for the introduction of the 17α-hydroxyl group into 20-ketopregnane derivatives involving formation of an enol acetate[5] followed by reaction with perbenzoic acid in chloroform solution and hydrolysis. By a minor modification of this procedure, applicable to large scale runs as illustrated in the experimental section, *allo*pregnan-3β-ol-20-one acetate (V) was converted without isolation of intermediates in 70% yield to *allo*pregnane-3β,17α-diol-20-one (VI) (Reichstein's substance L)[6] and by acetylation to L acetate (VII). Gallagher's method[4] thus represents by far the simplest partial synthesis of this adrenal hormone.[7]



V, R = Ac, R′ = H
VI, R = H, R′ = OH
VII, R = Ac, R′ = OH

VIII, R = R′ = H
IX, R = Br, R′ = H
X, R = R′ = Br

Oxidation of Reichstein's substance L (VI) with N-bromoacetamide in *t*-butyl alcohol–pyridine solution afforded in *ca.* 80% yield the previously unknown *allo*pregnan-17α-ol-3,20-dione (VIII). It has been pointed out recently,[8] that whereas the corresponding *normal* isomer[4] can be utilized only for the preparation of 17α-hydroxyprogesterone (III), the corresponding A/B *trans* isomer VIII is more versatile in that it can be converted into three unsaturated derivatives. Thus monobromination of VIII in glacial acetic acid led to the 2-bromo derivative IX, which on boiling with collidine suffered dehydrobromination yielding Δ¹-*allo*pregnen-17α-ol-3,20-dione (XI), which represents a double bond isomer of 17α-hydroxyprogesterone (III). This Δ¹-isomer exhibited a maximum at 230 mu, typical of such ketones, and the $[\Delta]_{MD}$ value of +68 was in excellent agreement with that reported[9] (+67) for Δ¹-3-ketosteroids. Although further bromination could occur either in ring A or at C-21, a

(1) Paper IV, Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(2) Hench, Kendall, Slocumb and Polley, *Proc. Staff Meet. Mayo Clin.*, **24**, 181 (1949).

(3) Freeman, Pincus, Johnson, Bachrach, McCabe and MacGilpin, *J. Am. Med. Assoc.*, **142**, 1124 (1950).

(4) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(5) Marshall, Kritchevsky, Lieberman and Gallagher, THIS JOURNAL, **70**, 1837 (1948).

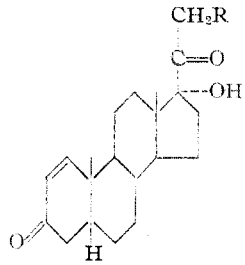
(6) Reichstein and Gätzi, *Helv. Chim. Acta*, **21**, 1497 (1938); V. Euw and Reichstein, *ibid.*, **24**, 418 (1941).

(7) For other syntheses, see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, 1949, Chapter V.

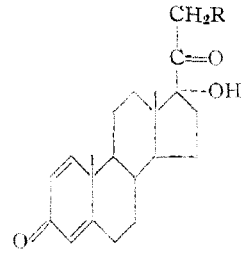
(8) Rosenkranz, Kaufmann, Pataki and Djerassi, THIS JOURNAL, **72**, 1046 (1950).

(9) Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

preliminary investigation of the dibromination of the ketone VIII in a polarimeter tube at 20° gave the typical curve (Fig. 1) observed previously[10] in the dibromination of 3-keto*allo*steroids, which indicated the intermediate formation of a 2,2-dibromo derivative ($[\alpha]^{20}D$ + 110°) followed by rearrangement to the 2,4-isomer X. Dehydrobromination of X with collidine resulted in the expected loss of two moles of hydrogen bromide and the formation of $\Delta^{1,4}$-pregnadien-17α-ol-3,20-dione (XIII), a new unsaturated analog of 17α-hydroxyprogesterone (III). Finally, employing the recently discovered sodium iodide procedure,[1] the 2,4-dibromo derivative X was converted to 2-iodo-17α-hydroxyprogesterone and thence by reduction to the desired adrenal hormone III itself.[11]

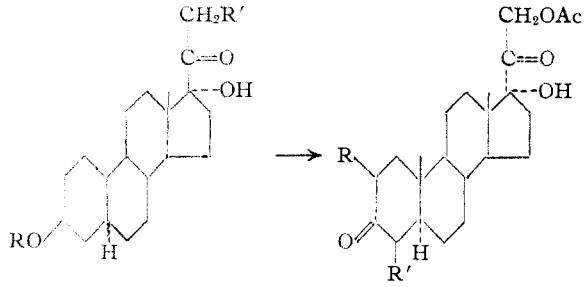


XI, R = H
XII, R = OAc



XIII, R = H
XIV, R = OAc

In a recent Communication to the Editor, Gallagher and co-workers[12] have outlined a synthesis of the 17-hydroxy-20-keto-21-acetoxy side-chain, characteristic of Cortisone (I) and Compound S (IV), in unspecified yield by converting a 17-hydroxy-20-ketone (*e. g.*, VII) to the corresponding 21-bromo derivative, followed by saponification with alkali and acetylation. In our hands, the alkaline saponification of 17-hydroxy-20-keto-21-bromo derivatives proceeded fairly satisfactorily (55% yield), but the following modified procedure for the introduction of the important dihydroxyacetone side chain was preferred, particularly on a larger scale. As mentioned above, bromination of the ketone VIII at 20° did not result in any perceptible reaction at C-21, but at 40°, substitution at C-21 could be accomplished readily. When applied to Compound L acetate (VII), 85% of the corresponding 21-bromo derivative XV was obtained, which on short treatment with sodium iodide in acetone followed by acetolysis of the intermediate iodo compound with potassium acetate in the same solvent led in 80% yield to *allo*pregnane-3β,17α,21-triol-20-one 3,21-diacetate (XVIII) (Reichstein's substance P diacetate)[13] which proved to be identical with the natural substance.[11] This modification of Gallagher's procedure[12] represents the most convenient partial synthesis[7] of this adrenal hormone at the present time. Since the completion of this work, Julian, *et al.*,[14] in a communication reported the direct acetolysis of a 21-bromo intermediate in the case of a 16,17-oxido-20-keto-5,6,21-tribromo steroid; the prior use of sodium iodide in ethanol–benzene effected debromination of the 5,6-dibromide as well as replacement of the 21-bromine atom by iodine.



XV, R = Ac, R′ = Br
XVI, R = H, R′ = Br
XVII, R = H, R′ = OAc
XVIII, R = Ac, R′ = OAc

XIX, R = R′ = H
XX, R = Br, R′ = H
XXI, R = R′ = Br

The remaining steps were similar to those outlined for the synthesis of the 17-hydroxy-20-ketosteroids XI and XIII: acid hydrolysis of XV afforded XVI which was converted to the previously unknown Reichstein's substance P 21-monoacetate (XVII) and thence by N-bromoacetamide oxidation to the saturated ketone XIX. Monobromination of the latter followed by collidine treatment gave Δ^1-*allo*pregnene-17α,21-diol-3,20-dione 21-acetate (XII), a Δ^1-isomer of Reichstein's substance S acetate (IV), while dehydrobromination of the 2,4-dibromo derivative XXI afforded the doubly unsaturated analog $\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV).

The results of various biological tests of the four, new unsaturated ketones XI to XIV and of several intermediates described in this paper will be published elsewhere.

Experimental[15,16]

*Allo*pregnane-3β,17α-diol-20-one (VI, Reichstein's Substance L).—The following procedure, based on Galla-

(10) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947); *J. Org. Chem.*, **13**, 697 (1948).

(11) No depression of the melting point was observed on admixture with the natural hormone isolated from adrenal glands. We are indebted to Prof. T. Reichstein, University of Basle, for carrying out the mixed melting point determination.

(12) Koechlin, Garmaise, Kritchevsky and Gallagher, THIS JOURNAL, **71**, 3262 (1949). We are grateful to Dr. T. F. Gallagher for informing us of the contents of this communication prior to publication.

(13) Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 546 (1938); Reichstein and Gaetzi, *ibid.*, 1185.

(14) Julian, Meyer, Karpel and Ryden, THIS JOURNAL, **71**, 3574 (1949).

(15) Melting points, marked Kofler, were determined on the Kofler block and are corrected; all others were carried out in capillaries and are uncorrected unless noted otherwise. Rotations were determined on *ca.* 60-100 mg. of substance in chloroform solution (unless marked otherwise) in a 2-dcm. tube of 10-cc. capacity. When two values are given, the first one refers to chloroform solution. Ultraviolet absorption spectra were measured in 95% ethanol solution on a Beckman Quartz Photoelectric Spectrophotometer.

(16) The microanalyses are due to Srta. Amparo Barba, while the Srtas. Ann Rochman and Paquita Revaque determined all spectra and rotations.

gher's communication,[4] proved to be satisfactory for large scale runs:

A mixture of 200 g. of *allo*pregnan-3β-ol-20-one 3-acetate (V), 92 g. of *p*-toluenesulfonic acid and 10 l. of acetic anhydride was distilled over a period of five hours, collecting 8.5 l. of distillate, and the residue was poured into ice water, extracted with ether, washed with dilute, cold alkali, water, dried and evaporated. The residual enol acetate[5] was adsorbed and eluted with 9 l. of hexane on 250 g. of ethyl acetate-washed alumina and the solvent was distilled. The oil was taken up in 2 l. of ether and allowed to stand overnight with an ethereal solution of 120 g. of monoperphthalic acid.[17] After washing with sodium iodide solution, sodium thiosulfate and water, the ether was dried, evaporated and the residue was saponified by refluxing for fifteen minutes with 100 g. of sodium hydroxide, 1 l. of water and 9 l. of methanol. Neutralization with acetic acid, concentrating and chilling afforded 130 g. (70%) of Reichstein's substance L, m. p. 245–250°, which was satisfactory for the next step. Recrystallization from dioxane afforded colorless crystals with m. p. 259–261° (Kofler), $[\alpha]^{20}D$ +32.5° (ethanol); reported: m. p. 257–259°, $[\alpha]^{25}D$ +31.7°[4]; m. p. 264–266°, $[\alpha]D$ + 30.6° (ethanol).[6]

Acetylation with pyridine and acetic anhydride (one hour, steam-bath), followed by recrystallization from acetone gave 92% of Substance L acetate (VII) with m. p. 187–189°, $[\alpha]^{20}D$ + 18° (acetone); reported: m. p. 188–190°, $[\alpha]^{25}D$ + 16°[4]; m. p. 190–191°, $[\alpha]D$ 14.7° (acetone).[6]

***Allo*pregnan-17α-ol-3,20-dione (VIII).**—To a solution of 100 g. of substance L (VI) in 15 l. of *t*-butyl alcohol and 250 cc. of pyridine at 20° was added 74 g. of N-bromoacetamide. After standing for twenty hours, crystallization was induced by scratching and cooling, whereupon 68 g. of satisfactory material, m. p. 246–249°, was isolated. Concentration and dilution of the filtrate with water followed by recrystallization from a mixture of ethanol and chloroform yielded an additional 16 g. (total yield 83%) of equally pure material. The analytical sample had m. p. 251–253°, $[\alpha]^{20}D$ +24°, +50° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.95; H, 9.79.

2-Bromo*allo*pregnan-17α-ol-3,20-dione (IX).—The monobromination was carried out by adding slowly a solution of 14.7 g. of bromine in 150 cc. of glacial acetic acid to 30.5 g. of ketone (VIII) dissolved in 3 l. of acetic acid and containing a few drops of 4 *N* hydrogen bromide in acetic acid. After a few minutes, water was added to *partially* precipitate the product, yielding 23 g. (61%) of crystals melting at 182–185° (dec.); further addition of water afforded an additional 11.5 g. (32%) of somewhat inferior material with m. p. 175–179°. The analytical sample was recrystallized from ethanol; m. p. 188–190° (dec.), $[\alpha]^{20}D$ +47°.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.60. Found: C, 61.13; H, 7.38.

Δ^1-*Allo*pregnen-17α-ol-3,20-dione (XI).—The above bromo compound IX (21 g.) was refluxed with 60 cc. of redistilled γ-collidine for forty minutes, the mixture was cooled, poured into dilute sulfuric acid and filtered. The precipitate was taken up in ethyl acetate, washed well with dilute acid, water, dried, evaporated and the residue was chromatographed on 220 g. of ethyl acetate-washed alumina. Elution with benzene–hexane (6:4) mixtures followed by recrystallization from ethanol gave 5 g. (30%) of analytically pure Δ^1-*allo*pregnen-17α-ol-3,20-dione with m. p. 254–257° (cor.), $[\alpha]^{20}D$ +71° (dioxane), u. v. maximum at 230 mμ (log *E* 4.05).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.49; H, 9.33.

2,4-Dibromo*allo*pregnan-17α-ol-3,20-dione (X).—The dibromination in the polarimeter was carried out by the procedure described earlier[10] with 0.100 g. of ketone, 14.00 cc. of acetic acid and 1.2 cc. of bromine solution. The results are shown in Fig. 1 and demonstrate the intermediate formation of the 2,2-dibromo ketone.

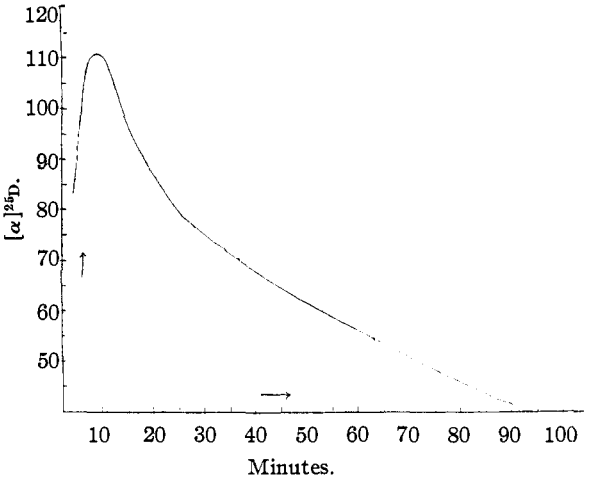


Fig. 1.—Dibromination of *allo*pregnan-17α-ol-3,20-dione (VIII) in the polarimeter.

A. Dibromination of the Alloketone VIII.—A solution of 30 g. of the ketone VIII in 3 l. of glacial acetic acid was treated at 22° with a few drops of hydrogen bromide followed by slow addition of a solution of 30.5 g. of bromine in 200 cc. of acetic acid. At the end of the reaction, 1 cc. of 4 *N* hydrogen bromide in acetic acid was added and the solution was allowed to stand overnight. Dilution with 8 l. of water, filtration and recrystallization from ethyl acetate–hexane gave 19.1 g. of colorless crystals of the dibromo ketone X with m. p. 178–182° (dec.). Since from the filtrate on evaporation to dryness and heating for one hour with zinc dust in acetic acid there was recovered 9.45 g. of saturated ketone (VIII), the yield of dibromo ketone was 63%. The decomposition point depended on the rate of heating and the analytical sample after recrystallization from hexane–acetone crystallized in long needles which had m. p. 183–185° (dec.) when inserted at 160°, 180–182° (Kofler), $[\alpha]^{20}D$ 0°.

Anal. Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17. Found: C, 51.64; H, 5.88.

B. Monobromination of the 2-Bromoalloketone IX.—A solution of 5.08 g. of the bromoketone IX in 180 cc. of acetic acid was treated with a solution of 1.98 g. of bromine in 25 cc. of acetic acid. After working up as in (A), there was obtained 2.62 g. of X, m. p. 183–185° (dec.), $[\alpha]^{20}D$ 0°.

$\Delta^{1,4}$-Pregnadien-17α-ol-3,20-dione (XIII).—The dehydrobromination of the 2,4-dibromo derivative was carried out exactly as described above for the monobromo compound and afforded 31% of analytically pure dienone XIII, which crystallized as colorless needles from chloroform–ethyl acetate; m. p. 232–234° (cor.), when inserted at 220°, $[\alpha]^{20}D$ +38.5°, u. v. maximum at 244 mμ (log *E* 4.14).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.96; H, 8.21.

2-Iodo-17α-hydroxyprogesterone.—A solution of 21 g. of 2,4-dibromo ketone X in 1 l. of acetone was refluxed with 26 g. of sodium iodide for two hours, the sodium bromide was filtered (8.2 g.) and the filtrate was refluxed for an additional eighteen hours. After concentration to approximately 400 cc., the iodine color was removed by the addition of thiosulfate and the product was precipitated with water, filtered and washed well; yield 79–86%. The crystals became brown at *ca.* 85° and decomposed at approximately 105–120°. A sample was recrystallized twice from methanol and then dried at room temperature at 0.01 mm. for eighteen hours. The colorless crystals turned yellowish-brown at 95° and decomposed at ap-

(17) "Organic Syntheses," **20**, 70 (1940).

proximately 112–115° depending on the rate of heating; $[\alpha]^{20}D$ +71°, u. v. maximum at 244 mμ (log *E* 4.15).

Anal.[18] Calcd. for $C_{21}H_{29}O_3I$: I, 27.81. Found: I, 28.32.

17α-Hydroxyprogesterone (III).—The deiodination was accomplished by adding in a current of carbon dioxide a solution of chromous chloride (prepared from 40 g. of chromic chloride[1]) to 3.5 g. of 2-iodo-17α-hydroxyprogesterone dissolved in 100 cc. of acetone. After five minutes, the product was precipitated with water and filtered. A chloroform solution of the solid was dried over sodium sulfate, evaporated, the residue triturated with ether and filtered; yield, 2.09 g. (83%) m. p. 207–212°, $[\alpha]^{20}D$ +102° (acetone), u. v. maximum 240 mμ (log *E* 4.19). The analytical sample of 17α-hydroxyprogesterone (III) was obtained from ethanol–chloroform as colorless rhombic blades with m. p. 220–222° (cor.) when inserted at 200° (Prof. Reichstein[11] reported m. p. 220–223° (Kofler) for our sample), $[\alpha]^{20}D$ +103° (acetone), u. v. maximum 241 mμ (log *E* 4.30); lit.[19] m. p. 218–220° or 222–223°, $[\alpha]^{20}D$ +98.8° ±5° (acetone).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.17; H, 8.90.

Alternate reduction methods[1] were equally successful.

21-Bromo*allo*pregnane-3β,17α-diol-20-one 3-Acetate (XV).—A solution of 31 g. of Reichstein's compound L acetate (VII) in 800 cc. of acetic acid was treated at 40° with a few drops of hydrogen bromide and 13.9 g. of bromine in 200 cc. of acetic acid. After one-half hour, the solution was poured into much water, the product was collected and recrystallized from acetone–water; yield, 32 g. (85%), m. p. 185–188°, $[\alpha]^{20}D$ +35.6°; lit.,[12] m. p. 184–187°.

***Allo*pregnane-3β,17α,21-triol-20-one 3,21-Diacetate (XVIII, Reichstein's Substance P Diacetate).**—Twenty-five grams of the above 21-bromo derivative XV was boiled for fifteen minutes with 15 g. of sodium iodide and 850 cc. of acetone, the precipitate of sodium bromide was filtered and the acetolysis was carried out by adding to the acetone solution a mixture of 125 g. of potassium bicarbonate and 75 cc. of glacial acetic acid and refluxing for twelve hours. The latter mixture proved superior to the use of anhydrous potassium acetate. At the end of the reaction, the product was precipitated with water, dried with benzene, treated for one-half hour with acetic anhydride–pyridine and then crystallized from methanol–chloroform; yield, 20.3 g. (82%), m. p. 200–205° (cor.). One recrystallization from benzene (19.1 g. 77% yield) raised the m. p. to 208–210° (cor.), $[\alpha]^{20}D$ +41.5°. Prof. T. Reichstein[11] found m. p. 211–214° (Kofler) for our sample and 210–213° for a mixture with natural Substance P diacetate (XVIII) (m. p. 209–211°); the color reaction with sulfuric acid and the silver oxide reduction were identical. A specimen for analysis was sublimed at 180° and 0.002 mm.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.42; H, 8.82.

21-Bromo*allo*pregnane-3β,17α-diol-20-one (XVI).—After twenty hours at room temperature, a solution of 14.4 g. of the above 3-acetoxy-21-bromo derivative XV in 1.5 l. of methanol and 15 cc. of concd. hydrochloric acid was treated with 8 g. of sodium bicarbonate and 200 cc. of water, concentrated under reduced pressure, the product precipitated with water and recrystallized from methanol; yield, 10.4 g. (80%), m. p. 212–216° (dec.). Further recrystallization raised the m. p. to 227–229° (dec. cor.), $[\alpha]^{20}D$ +55.7°.

Anal. Calcd. for $C_{21}H_{33}O_3Br$: C, 61.01; H, 8.05. Found: C, 61.25; H, 8.31.

***Allo*pregnane-3β,17α,21-triol-20-one 21-Acetate (XVII, Reichstein's Substance P 21-Monoacetate).**—A solution of 10 g. of the 3-hydroxy-21-bromo derivative XVI in 600 cc. of acetone was treated with 6 g. of sodium iodide and subsequently with 40 g. of potassium bicarbonate and 24 cc. of acetic acid as described above for substance P diacetate (XVIII); 7.8 g. (82%) of substance P 21-monoacetate with m. p. 232–236° was thus obtained which does not appear to have been described previously in the literature. The analytical sample was recrystallized several times from methanol; m. p. 235–236° (cor.), $[\alpha]^{20}D$ +44°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.62; H, 9.31.

***Allo*pregnane-17α,21-diol-3,20-dione 21-Acetate (XIX).**—The oxidation was carried out with 5.65 g. substance P 21-monoacetate (XVII), 1 l. of *t*-butyl alcohol, 5 cc. of pyridine and 3 g. of N-bromoacetamide for sixteen hours, whereupon the product crystallized directly from solution; yield, 4.82 g. (85%), m. p. 241–244°. Recrystallization from ethanol followed by sublimation afforded crystals with m. p. 249–251° (Kofler), $[\alpha]^{20}D$ +61° (dioxane).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.46; H, 8.55.

2-Bromo*allo*pregnane-17α,21-diol-3,20-dione (XX).—The bromination was carried out exactly as described for the ketone IX, except that twice as much acetic acid was necessary; the crude product had m. p. 184–188° which was raised on recrystallization from methanol to m. p. 200–203° (dec.), $[\alpha]^{20}D$ +82° (dioxane).

Anal. Calcd. for $C_{23}H_{35}O_5Br$: Br, 16.99. Found: Br, 17.24.

Δ¹-*Allo*pregnene-17α,21-diol-3,20-dione 21-Acetate (XII).—Collidine dehydrobromination of 30 g. of the monobromo compound XX in the usual manner afforded 11 g. (44%) of crude Δ¹-ketone XII with m. p. 236–240°; one recrystallization from ethanol raised the m. p. of the colorless crystals (8.5 g., 34%) to 255–258°. The analytical sample was obtained from ethyl acetate, m. p. 260–263° (cor.), $[\alpha]^{20}D$ +97° (dioxane), u. v. maximum at 230 mμ (log *E* 4.04).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.34. Found: C, 70.82; H, 8.38.

Δ¹,⁴-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XIV).—The required 2,4-dibromo derivative XXI was obtained as described above for the analogous 17-hydroxy-20-ketone X (procedure B), as needles from hexane–acetone, m. p. 173–176° (dec., Kofler), $[\alpha]^{20}D$ +40°.

Anal. Calcd. for $C_{23}H_{32}O_5Br_2$: Br, 29.15. Found: Br, 28.66.

The above dibromo derivative was refluxed with collidine for forty-five minutes, which resulted in the loss of nearly two moles of hydrogen bromide on the basis of collidine hydrobromide isolated (91%). After the usual work-up and several recrystallizations from hexane–acetone, 32% of the desired dienone XIV was obtained with m. p. 216–218° (Kofler), $[\alpha]^{20}D$ + 88°, u. v. maximum at 244 mμ (log *E* 4.26).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.66; H, 7.85.

Summary

The synthesis of a number of 11-desoxy-17α-hydroxy-20-ketosteroids has been described. *Allo*pregnan-3β-ol-20-one 3-acetate (V), a readily available starting material from plant sources, has been converted through Reichstein's substance L (VI) to *allo*pregnan-17α-ol-3,20-dione VIII and thence to the adrenal hormone 17α-hydroxyprogesterone (III) by the recently discovered sodium iodide method.[1] The saturated ketone VIII through its 2-bromo and 2,4-dibromo derivatives, respectively, served also as the key intermediate for the preparation of the Δ¹-isomer XI and the doubly unsaturated analog XIII of 17α-hydroxyprogesterone.

(18) Analysis by Mr. Joseph F. Alicino, Metuchen, New Jersey.

(19) v. Euw and Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941); Prins and Reichstein, *ibid.*, 945.

Starting with Reichstein's substance L acetate, now readily available, a convenient partial synthesis of Reichstein's substance P 21-monoacetate (XVII) and 3,21-diacetate (XVIII) is described. The former was carried through the same transformations as performed in the corresponding 21-desoxy series and afforded two new analogs (XII and XIV) of the important cortical hormone 17α-hydroxy-11-desoxycorticosterone (Reichstein's substance S).

Several of these substances are being subjected to a variety of biological tests particularly in regard to their potential usefulness as anti-arthritic agents.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

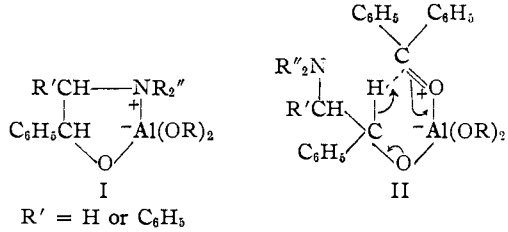
Factors Interfering with the Oppenauer Oxidation of Amino Alcohols[1]

BY ROBERT E. LUTZ, ROBERT H. JORDAN,[2a] AND WILLIAM L. TRUETT[2b,c]

In recent attempts[3] we found that, like quinine,[4a] several typical aliphatic 1,2-amino alcohols did not undergo the Oppenauer oxidation with aluminum *t*-butoxide and benzophenone or cyclohexanone. However, aluminum isopropoxide reductions of the corresponding, and other, α-amino ketones have proceeded without difficulty in all cases tried except the α-(N-alkyl-ethanolamino)-ketones which are cyclic.[5] It follows that under the oxidizing conditions the equilibria[6] lie well over on the side of the reductants.

The explanation offered for this phenomenon, involving acid–base combination between nitrogen and aluminum,[4] did not seem to us to explain adequately why the alcoholic group, which would still be free, did not undergo the oxidation with reasonable speed when the solubility of the complex was appreciable, and it did not seem to be consistent with the facility of aluminum isopropoxide reductions of α-amino ketones where presumably similar complexes might be formed.

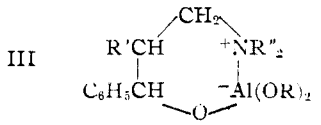
The phenomena may be explained in terms of stable cyclic complexes of the type (I) which if formed would cause displacement of the equilibrium sharply in favor of the amino alcohol, and which would be expected to interfere seriously with hydrogen transfer if the reaction were an intramolecular one involving a quasi-ring intermediate or transition state such as II.[4,7] Five-membered



I
R′ = H or C_6H_5

II

ring complexes (I) might well involve a significant degree of added stabilization through second order or "no bond" resonance. Analogous six-membered ring complexes (III) based on 1,3-amino alcohols would be conceivable although resonance stabilization would be excluded or at least greatly diminished because of the break in conjugation involved in the extra methylene group. Larger rings or linear polymeric complexes presumably would not be stable. Thus the amino alcohols might fall



III

into three categories; the 1,2-types which should not undergo the standard Oppenauer oxidation; 1,4 and 1,5 and longer amino alcohols which should generally be oxidizable without difficulty; and the intermediate 1,3-amino alcohols where a less predictable reaction might depend on structural and steric effects. Preliminary studies, successful as far as they have gone, have been made to test these predictions.

Nine typical 1,2-amino alcohols (IVa-c, V, and XIII–XVII of Table I) including one diasteroisomeric pair (IVb and c), were recovered unchanged employing aluminum *t*-butoxide and benzophenone or cyclohexanone; three of these were used in the form of the free bases, four as the hydrochlo-

(1) The work of this paper was supported in part by a grant-in-aid from the National Institutes of Health, recommended by the National Cancer Institute, and it stemmed from the program of syntheses of 1,2-amino alcohols as tumor-necrotizing agents.

(2) (a) Post-doctorate Fellow[1]; (b) Philip Frances du Pont Fellow; (c) assisted by Preston H. Leake and Rosser L. Wayland, Jr.

(3) The first unsuccessful Oppenauer oxidations in this laboratory were carried out by Dr. R. S. Murphey using aluminum isopropoxide. Mr. C. R. Bauer then used aluminum *t*-butoxide on IVa which will be described in a later publication.

(4) (a) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945). *Cf.* (b) Doering and Aschner, *ibid.*, **71**, 838 (1949). (c) Doering and Young, *ibid.*, **72**, 631 (1950).

(5) (a) Lutz, Freek and Murphey, *ibid.*, **70**, 2015 (1948); (b) Lutz and Jordan, *ibid.*, **71**, 996 (1949).

(6) Concerning the reversibility of this reaction, *cf.* (a) Wilde, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178; (b) "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, p. 155; (c) Adkins, Elofson, Rossow and Robinson, THIS JOURNAL, **71**, 3622 (1949); (d) Adkins and Cox, *ibid.*, **60**, 1151 (1938); (e) Baker and Adkins, *ibid.*, **62**, 3305 (1940); (f) Baker and Schafer, *ibid.*, **65**, 1675 (1943).

(7) (a) Baker and Linn, *ibid.*, **71**, 1399 (1949); (b) Lutz and Gillespie, *ibid.*, **72**, 344 (1950); (c) Jackman and Mills, *Nature*, **164**, 789 (1949).