The remainder of the material was evaporated to dryness, redissolved in 45 ml. of methanol, 18 ml. of 6N aqueous hydrochloric acid was added and the mixture was refluxed 1.5 hr. The cooled mixture was extracted with methylene chloride–hexane which on concentration gave 720 mg. of crystalline product, m.p. 173–190°. Recrystallization from ether gave blades, m.p. 192–197°. The analytical sample from hexane gave rosettes, m.p. 190–192°, $[\alpha]_D^{25}$ −20.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.62; H, 9.41.

11β-Hydroxy-3,5-androstadiene-17-one, VII. The mother liquors from the preceding preparations were evaporated to dryness, dissolved in benzene, and placed on a short column of Florisil. Elution with benzene gave a noncrystalline orange glassy material followed by 39 mg. of a crystalline fraction. Recrystallization of the latter from methanol and from aqueous methanol gave broad blades having a high vapor pressure near the melting point. The melting point under very slow temperature-rise conditions was 161.5–165°, but a moderate rate of heating on open microscope slide gave the value 178–179°, $[\alpha]_D^{25}$ +52.1°, $\tilde{\nu}_{max}^{CS_2}$, 3600 (single sharp), 1743 (v. strong), 821, 811, 865 cm.$^{-1}$, ultraviolet absorption bands occurred at 230, 237, 245 mμ, $\lambda_{max}^{CH_3OH}$ 237 mμ, ϵ = 21,900.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.61; H, 9.30.

Further elution of the column with ether gave 60 mg. of VI.

3β-Acetoxy-11β-hydroxy-5-androstene-17-one, VIa. The 3β,11β-dihydroxy-17-ketone, VI, 100 mg., was let stand 16 hr. in a mixture of 2 ml. of pyridine and 1 ml. of acetic anhydride. Dilution with water, extraction with ether, and washing the ether free of acetylation mixture with dilute hydrochloric acid and with dilute sodium bicarbonate gave, after evaporation, the required monoacetate. Recrystallization from hexane gave spindles undergoing transition beyond 200°. At 216° the primary crystal forms began to melt before transition of crystal form was completed. Decomposition and reddening supervened, the last crystal of the stable phase disappearing at 231°, $[\alpha]_D^{25}$ −17.1°. The analytical sample melted cleanly at 232°, after undergoing transition, but did not decompose.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.71; H, 8.61.

3β-Acetoxy-5-androstene-11,20-dione, V. (*a*) *From* VIa. 3β-Acetoxy-11β-hydroxy-17-ketone, VIa, 500 mg., was dissolved in 6 ml. of pyridine at 10° and treated with a slurry of 500 mg. of chromium trioxide in 6 ml. of cold pyridine.[19] After standing 16 hr. at room temperature the mixture was diluted with ice water and with ether. Dilute hydrochloric acid was added to make the aqueous phase distinctly acid, and enough dilute sodium bisulfite was added to reduce chromium to the trivalent state. At this point emulsified solid brown matter went into solution and the phases separated cleanly. The organic layer was separated and washed with water, dilute sodium bicarbonate, and saturated sodium chloride. The residue on evaporation gave 500 mg. of colorless crystalline residue, m.p. 163–167°. After crystallizing from methyl acetate and from methanol, the product melted from 172–174°, $[\alpha]_D^{25}$ +38°; Martin-Smith[13] gives m.p. 171°, $[\alpha]_D$ +38°.

Anal. Calcd. for $C_{21}H_{28}O_4$; C, 73.22; H, 8.19. Found: C, 72.81; H, 8.37.

(*b*) *From* IV. A 5-g. sample of the *N*-acetyl enamine, IV, was dissolved in 110 ml. of 5% ethanolic potassium hydroxide and refluxed for 1 hr. The cooled flask contents were diluted with water and extracted with ether. The organic layer was washed with 2*N* hydrochloric acid to remove yellow coloration, with dilute sodium bicarbonate, and with saturated sodium chloride. An aliquot of this material did not show persisting acetate infrared bands. The solvent was evaporated and the residue was acetylated with acetic anhydride–pyridine mixture at room temperature overnight. The product, crystallized from methanol, was obtained in 74% yield and was identical with the sample described in part (a).

PHILADELPHIA 18, PA.

(19) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

The Relative Stabilities of *cis* and *trans* Isomers. IX. A Study of the Importance of Conformational Transmission in Determining the Relative Stabilities of Hydrindanones in Steroidal Systems[1]

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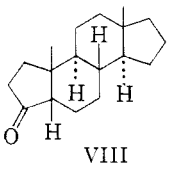
A-nor-5β-androstan-3-one (VIII) and A-nor-D-homo-5β-androstan-3-one (XIV) have been prepared. A comparison of their rotatory dispersion curves, together with the corresponding curves obtained from the epimeric mixtures which resulted when they were treated with base, showed that the strain induced in VIII by the *trans*-C/D fusion and conformationally transmitted to the A/B fusion was not of importance in determining the position of equilibrium at the latter juncture.

The hydrindane and hydrindanone systems, because of their apparent relative simplicity and wide occurrence in nature, have furnished a challenge to conformational analysis to interpret the relative stabilities of the *cis* and *trans* junctures. Although a large amount of work directed at such an interpretation has been carried out,[2] even a qualitative understanding of these systems is lacking in certain cases.

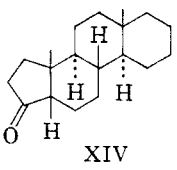
One effect which must in principle influence the stability of a hydrindanone juncture as in the A/B rings of a compound such as VIII and which has not previously been considered in this connection, is the effect of the strained *trans* C/D fusion as relayed

(1) Paper VIII, N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960).

(2) See ref. 1 for summary and references.



VIII



XIV

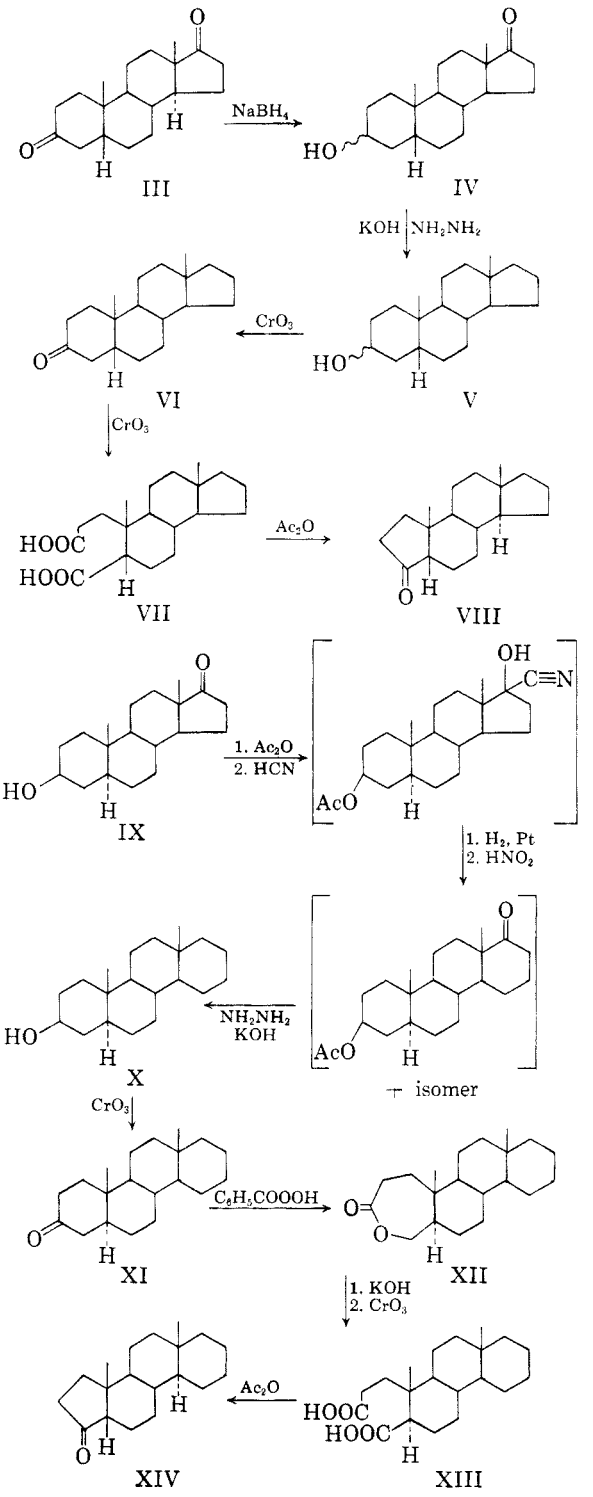
to the A/B fusion by conformational transmission.[3] While an effect of this kind can be assumed to occur, its importance in influencing the stability of the A/B juncture cannot be estimated from available data.

With this type of structure the equilibrium lies very far on the side of the *cis* isomer, compared with other apparently similar compounds and theoretical predictions.[1] If the strained C/D fusion were indeed responsible for the comparatively great stability of the *cis* forms in VIII, then compound XIV should not be analogous to VIII in this respect. An experimental comparison of the equilibrium points between the A/B *cis* and A/B *trans* forms of VIII and of XIV therefore seemed in order.

RESULTS AND DISCUSSION

A-nor-5β-androstane-3-one (VIII) has previously been described in the literature.[4] A new synthesis of it was used in the present work. This synthesis, which is outlined on the flow sheet, began from 5β-androstane-3,17-dione (III). The keto-group at C-3 was selectively reduced with sodium borohydride[5] to give IV. A Wolff-Kishner reduction[6] of IV gave V, which was oxidized[7] to VI and then to VII. This diacid was treated with acetic anhydride[4] which cyclized it to VIII.

The synthesis of XIV began from isoandrosterone (IX). The 3-hydroxyl was acetylated, and the ring expansion[8] was carried out in several steps, by forming the cyanohydrin[4] at C-17, catalytic reduction of the nitrile to the amine, and rearrangement by the Tiffeneau-Demjanov method upon treating the amine with nitrous acid. The resulting keto group was removed by the Wolff-Kishner method,[6] which gave the known D-homo-5α-androstan-3β-ol (X). Chromic acid oxidation of this alcohol yielded the 3-ketone (XI). Perbenzoic acid oxidation[9] of XI yielded a lactone



XII, to which the D-homo-4-hydroxy-3,4-seco-5α-androstan-3-oic acid lactone structure was assigned by analogy with the oxidation of cholestan-3-one.

The lactone (XII), upon treatment with alkali, opened to the corresponding hydroxy acid which was oxidized to the dioic acid (XIII) with chromium trioxide. Treatment of XIII with acetic anhydride[4] gave the ketone XIV.

(3)(a) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957). (b) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).

(4) L. Ruzicka, V. Prelog, and P. Meister, *Helv. Chim. Acta*, **28**, 1651 (1945).

(5) E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2814 (1952).

(6) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

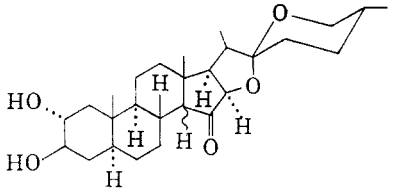
(7) B. Heath-Brown, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

(8)(a) R. O. Clinton, R. G. Christiansen, H. C. Neumann and S. C. Laskowski, *J. Am. Chem. Soc.*, **79**, 6475 (1957). (b) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940).

(9) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

The ketones isolated (VIII and XIV) can both be assigned the 5-β configuration (A/B *cis*) on the basis of their rotatory dispersion curves. The curves are nearly identical for the two ketones, and quite similar but epimeric with those of the model compound XV.[10] The alternative 5α structures would be expected to yield curves similar to those found for XVI.[10] The assignments are unambiguous, as the molecular amplitudes are large (over 10,000°) and for VIII and XIV the predicted sign of the Cotton effect is positive, as found, while for the 5α-epimers it would be negative.

If the peracid rearrangement had gone with migration of the other possible alkyl group, then XI would have led eventually to A-nor-D-homo-5α-androstan-2-one instead of to XIV. Qualitatively the Cotton effect curve for this compound would be similar to that of XIV but the amplitudes would differ considerably. Closely similar models (2-keto-A-norcholestane and 3-keto-A-norcholanic acid respectively[10]) have [α] + 23,300 and [α] + 14,350 respectively. The value for XIV is [α] + 12,700 which is additional support for the structure assigned.



XV 14β
XVI 14α

Earlier studies[1] have shown the ease and accuracy of measuring equilibrium constants by means of optical rotations in the ultraviolet. The rotatory dispersion curves of pure VIII and the equilibrium mixture obtained upon treatment of VIII with base were measured and were nearly identical. It can therefore be estimated that the equilibrium mixture contains more than 95% of the 5β epimer under the conditions used. This is a larger percentage than the theory[1] calls for and is analogous to what was found with the previously studied A-nor system. When the curves for XIV and the equilibrium mixture of epimers obtained by treatment of XIV with base were compared, again the equilibrium amount of the 5β epimer was >95%.

Therefore it may be concluded that the equilibrium point in the epimerization at C-5 is not noticeably affected by the presence or absence of a strained C/D fusion, and conformational transmission does not appear to be important in effecting this equilibrium.

(10) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956). For further details of this rotatory dispersion approach see C. Djerassi, *Optical Rotatory Dispersion Applications to Organic Chemistry*, McGraw-Hill, New York, 1960, p. 41.

EXPERIMENTAL

17β-Acetoxy-5β-androstan-3-one (I). The synthesis of this compound was carried out beginning with testosterone. Hydrogenation of testosterone acetate furnished a mixture of isomers epimeric at carbon 5 from which 17β-acetoxy-5β-androstane-3-one was isolated[11] in 52% yield, m.p. 139–144°; lit.[11] m.p. 143–145°.

5β-Androstane-17β-ol-3-one (II). Compound I, 9.77 g., was heated for 1 hr. in a refluxing solution containing 8.4 g. of potassium hydroxide in 115 ml. of 85% methanol. The reaction mixture was poured into water and extracted with chloroform. The chloroform extracts were dried, the solvent was evaporated, and the residue was crystallized from ether–petroleum ether (b.p. 60–90°) to yield 7 g. (82%) of II in two crops, m.p. 140–143° (lit.[12] m.p. 142–143°).

5β-Androstane-3,17-dione (III). Compound II, 1 g., in 5 ml. of acetic acid was treated with 0.24 g. of chromium trioxide in 10 ml. of 90% acetic acid. The mixture was allowed to stand for 2 hr. at room temperature and was then diluted with 100 ml. of water The resulting solution was kept at 0° overnight and the solid was collected, wt. 0.79 g. (79%), m.p. 122–128° (lit.,[12] m p. 131–132°).

3,4-Seco-5β-androstan-3,4-dioic acid (VII). Sodium borohydride reduction of III according to Elisberg, Vanderhaeghe, and Gallagher[5] gave a mixture of 3α-hydroxy- and 3β-hydroxy-5β-androstan-17-one in 82% yield. Two grams of this material was heated under reflux for 1 hr. with 25 ml. of diethylene glycol containing 1.2 g. of 95% hydrazine and 4 g. of potassium hydroxide. The condenser was then removed and the mixture was allowed to distill until the temperature of the vapors reached 190°. After heating the mixture under reflux for an additional 4 hr. it was cooled, poured into water, neutralized with hydrochloric acid, and the solution was extracted with ether. The ether solution was washed and dried, and the ether was evaporated. The resulting mixture of 3α-hydroxy- and 3β-hydroxy-5β-androstanes was then taken up in 25 ml. of acetic acid and mixed with a solution composed of 10 ml. of 90% acetic acid and 0.5 g. of chromium trioxide. The mixture was allowed to stand at room temperature for 1 hr. and was then poured into water and the solution was extracted with ether. The ether phase was dried and the solvent was evaporated. The residue was found by chromatographic examination still to contain considerable 3-hydroxy-5β-androstane. The crude ketone, 1.3 g., was dissolved in 40 ml. of 90% acetic acid containing 1.5 g. of chromium trioxide, and the solution was heated under reflux for 3 hr.[7] The cooled solution, diluted with 6*N* sulfuric acid, was extracted with ether. The ether layer was then extracted with dilute sodium hydroxide. Extraction of the aqueous phase with ether furnished 200 mg. of neutral material. The basic solution was acidified and extracted with ether. The dried ether extracts gave crude VII, which was recrystallized from ether-pentane, wt. 370 mg. (18%), m.p. 242–245° (lit.[4] m.p. 253–255°).

A-Nor-5β-androstan-3-one (VIII). Compound VII was converted to VIII in 30% yield following the known procedure,[4] m.p. 91–92°, lit.,[4] m p. 89–91°. R. D. in methanol (*c* 0.09): [α]$_{700}$ +98°, [α]$_{589}$ +142°, [α]$_{310}$ +2550°. [α]$_{272.5}$ −1806°, [α]$_{260}$ −1190. After this curve was obtained a drop of 40% aqueous potassium hydroxide was added, the solution was allowed to stand overnight, and the curve was redetermined. The equilibrium curve was very similar to the original one, [α]$_{312.5}$ +2352°, [α]$_{277.5}$ −1638°.

3β-Acetoxy-5α-androstan-17-one. Compound IX, 2.0 g., was converted to the acetate by heating with 2 ml. of acetic anhydride at 60° for 8 hr. The cooled mixture was diluted with water and the mixture was extracted with ether. The ether solution was washed in turn with dilute hydrochloric

(11) Private communication from Dr. O. Mancera of Syntex, S. A.

(12) L. F. Fieser and W.-Y. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953).

acid, sodium bicarbonate solution, and water. The solution was dried, the ether was evaporated, and the residue was the crude acetate, 2.2 g. (96%), m.p. 110–114° (lit.[13] m.p. 103–104°).

D-Homo-5α-androstan-3β-ol (X). Compound IX. 2.2 g., was dissolved in 35 ml. of ethanol and the solution was cooled to −5°. Potassium cyanide, 12.8 g., was added and then 9.6 ml. of acetic acid was added during a few minutes with stirring. The mixture was then stirred and allowed to come to room temperature. After standing overnight, the mixture was poured into water. The resulting mixture was extracted with ethyl acetate. The organic phase was separated, filtered, treated with charcoal, and the solvent was evaporated. The residue was dissolved in 75 ml. of acetic acid, 0.5 g. of platinum oxide was added, and the nitrile was hydrogenated at atmospheric pressure. The uptake of hydrogen ceased at the theoretical point, and the catalyst was removed by filtration. The bulk of the acetic acid was evaporated at reduced pressure, the residue was dissolved in water and the aqueous solution was filtered through a Celite pad and concentrated to a volume of 50 ml. Two milliliters of acetic acid was then added, the solution was cooled in ice, and an aqueous solution containing 1 g. of sodium nitrite was added. The resulting solution was allowed to stand overnight and the precipitate was collected, washed with water, and dried, wt. 1.4 g. A total of 3.9 g. of this crude material from combined runs was reduced with 3 g. of anhydrous hydrazine using 9 g. of potassium hydroxide in 60 ml. of diethylene glycol as described for the preparation of V. The product was isolated as before, taken up in benzene, and chromatographed on 100 g. of alumina with benzene. Two fractions were obtained, and separately purified by crystallization from benzene-pentane. The first fraction yielded 0.5 g., m.p. 158–163° (lit.[4] for the 3α isomer, m.p. 168–169°), and the second yielded 1.0 g., m.p. 146–150° (lit.[4] for 3β isomer, m.p. 143–143.5°).

D-Homo-5α-androstan-3-one (XI). One gram of D-homo-5α-androstan-3β-ol was oxidized with 0.24 g. of chromium trioxide in 25 ml. of 90% acetic acid by allowing the mixture to stand overnight. The reaction product was isolated by diluting the mixture with water and extracting with ether. The ether extracts were washed and dried; evaporation of the ether gave 0.9 g. (90%) of XI, m.p. 164–166° (lit.[4] m.p. 168.5–170°).

D-Homo-4-hydroxy-3,4-seco-5α-androstan-3-oic acid lactone (XII). Compound XI, 1.37 g., was allowed to stand overnight at 5° in a chloroform solution containing 1.31 g. of perbenzoic acid. The remaining perbenzoic acid was then destroyed by shaking the solution with excess potassium iodide in 5% sulfuric acid followed by sodium thiosulfate. The organic layer was washed and dried and the solvent was evaporated. The residue was crystallized from methylene chloride–hexane and gave 700 mg. of material, m.p. 210–215°, and a second crop, 200 mg., m.p. 205–210°. A sample was recrystallized from hexane several times, m.p. 217–218°.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 77.80; H, 10.31.

D-Homo-3,4-seco-5α-androstan-3,4-dioic acid (XIII). Compound XI, 700 mg., was saponified by heating under reflux in methanol with 2 g. of potassium hydroxide. The cooled solution was diluted with water and extracted with ether. The ether phase was dried, the solvent was evaporated, and the residue was taken up in 30 ml. of acetic acid. To this solution was added 700 mg. of chromium trioxide in 7 ml. of 90% acetic acid. The solution was left at room temperature for several hours, and the product was isolated as described for XI. After crystallization from ethyl acetate there was obtained 330 mg. (43%) of material, m.p. 222–227°. A small sample was recrystallized for analysis, m.p. 224–226°.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.38; H, 9.59. Found: C, 70.96; H, 9.37.

A-nor-D-homo-5β-androstan-3-one (XIV). Compound XIII, 330 mg., was dissolved in 5 ml. of acetic anhydride and the mixture was heated under reflux for 1 hr. The excess acetic anhydride was distilled at reduced pressure, and the residue was heated under reflux for a few minutes at a pressure of 100 mm. The pressure was then lowered to 20 mm. and the mixture was distilled. The distillate was dissolved in ether and the solution was washed first with dilute sodium hydroxide, then with water. The ether solution was dried and the solvent was evaporated. The residue was sublimed to yield XIV, wt. 100 mg., m.p. 118–121°. After chromatography on alumina with hexane-ether, the material was crystallized from hexane, m.p. 124–125°. The compound showed a strong carbonyl band at 5.72 μ in chloroform. R. D. in methanol (*c* 0.09): $[\alpha]_{700}$ +70°, $[\alpha]_{589}$ +130°, $[\alpha]_{312.5}$ +2600°, $[\alpha]_{272.5}$ −2040°, $[\alpha]_{262.5}$ −1640°. After this curve was obtained, a drop of 40% aqueous potassium hydroxide was added to the solution. The basic solution was allowed to stand overnight and the rotatory dispersion curve was redetermined. This curve was nearly identical with the original one, $[\alpha]_{312.5}$ +2620° and $[\alpha]_{272.5}$ −2120°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.33; H, 11.04.

Acknowledgment. The authors are indebted to Dr. Carl Djerassi of Stanford University for obtaining the rotatory dispersion curves reported herein, and for furnishing the compounds used as starting materials in this work, and to the Public Health Service (Grant E-2267) for financial support.

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(13)(a) T. Reichstein and A. Lardon, *Helv.*, **24**, 955 (1941). (b) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).