The 2,3,4,6-tetra-*O*-methyl-D-galactose obtained in the previously described hydrolysis had $[\alpha]^{21}D$ +107.8° (*c* 2.94, water); the literature[21] gives $[\alpha]D$ +109.5° (water). Its identity was confirmed by preparation of the anilide as follows. The sugar (100 mg.) was dissolved in 1.2 ml. of methanol and 0.5 ml. of freshly distilled aniline was added. The solution was refluxed 2 hr., then was left 24 hr. at +5°, and after dilution with a little ethanol the crystalline solid obtained was centrifuged and washed with cold methanol and with ethyl ether; yield 50 mg. of m.p. and m.m.p. 192°, $[\alpha]^{21}D$ −76.0° (*c* 0.092, acetone); lit.[22] m.p. 192°, $[\alpha]D$ −77.0° (acetone).

D. Methylation of 1,1-Bis(acetamido)-1-deoxycellobiitol.—This substance (500 mg.) was dissolved in 10 ml. of dimethylformamide, then 2.2 g. of barium oxide and 2 ml. of methyl iodide were added, and the suspension was shaken for 6 hr. The technique described under A for 1,1-bis(acetamido)-1-deoxylactitol was followed, and 610 mg. of octa-*O*-methyl-1,1-bis(acetamido)-1-deoxy-cellobiitol (VI) as a sirup finally was obtained in 97.4% yield. This sirup was purified first by chromatography on a cellulose column of 550 × 28 mm. and then by means of repeated dissolutions and evaporations from water and ethyl ether and filtering through activated charcoal until a colorless sirup was obtained. This sirrup had $[\alpha]^{21}D$ +27.0° (*c* 0.37, water).

Anal. (for a sample dried at 65° and 0.0001 mm.). Calcd. for $C_{24}H_{46}N_2O_{12}$: C, 51.98; H, 8.30; N, 5.05. Found: C, 52.00; H, 8.51; N, 4.91.

E. Methylation of 1,1-Bis(acetamido)-1-deoxymaltitol.—This substance (500 mg.) was methylated as described under D for the cellobiitol derivative. Octa-*O*-methyl-1,1-bis(acetamido)-1-deoxymaltitol (VII) (500 mg.) was obtained in 80% yield. The colored sirup was purified through a cellulose column employing water-saturated 1-butanol as eluent. The colorless sirup obtained was treated with water and filtered, and the solution was then evaporated and treated with ethyl ether to obtain a transparent solution. Evaporation of ether gave a sirup of $[\alpha]^{21}D$ +89.9° (*c* 1.35, water).

Anal. (for a sample dried at 65° and 0.0001 mm.). Calcd. for $C_{24}H_{46}N_2O_{12}$: C, 51.98; H, 8.30; N, 5.05. Found: C, 52.31; H, 8.39; N, 5.09.

F. Hydrolysis of VI and VII.—The separate hydrolysis of both substances employing the technique described under B gave the same pair of methylated monosaccharides, *i.e.*, 2,3,5,6-tetra-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose. Both monosaccharides have practically the same R_f and it was impossible to separate them by cellulose and alumina column chromatography. However, a cellulose column of 400 × 20 mm. was used to free the hydrolyzed mixture (100 mg.) from nonhydrolyzed material. The mixture obtained from the column, purified as usual, was submitted to a gas–liquid chromatography at 135° using a column packed with 1 part of Craig polyester (20% on Chromosorb W), 1 part of Apiezon M (20% on Chromosorb W), and 1 part of Apiezon M, 0.1% on glass beads (60–80 mesh). The carrier was argon at 140–150 cc./min. Both hydrolysates gave practically the same pattern. For the hydrolyzed compound VI, the proportion of 2,3,5,6-tetra-*O*-methyl-D-glucose in the mixture was 20.1 and 79.9% for the 2,3,4,6-tetra-*O*-methyl-D-glucose. For hydrolyzed compound VII, the percentages were 20.2 and 79.8%, respectively. The retention time for 2,3,5,6-tetra-*O*-methyl-D-glucose was 0.79, taking 2,3,4,6-tetra-*O*-methyl-D-glucose as reference compound.

G. Separation of 2,3,4,6,-Tetra-*O*-methyl-D-glucose from 2,3,5,6-Tetra-*O*-methyl-D-glucose on Anion-Exchange Resin.[15]—The resin was Permutit Deacidite FF, which was washed with 1 *N* sodium hydroxide and then with water free from carbon dioxide. The mixture of methylated sugars (120 mg.), obtained by hydrolysis of VII, was dissolved in 3 ml. of water and applied to the column (20 × 2 cm.). The elution was carried out with water and 16-ml. fractions were collected at a rate of 5 ml./hr. Evaporation of fractions gave 2,3,4,6-tetra-*O*-methyl-D-glucose (fractions 1–4, 50 mg.), $[\alpha]^{22}D$ +81.3° (*c* 0.92, water, final value); then a mixture of both methyl sugars was obtained (fraction 5, 15 mg.); and finally 2,3,5,6-tetra-*O*-methyl-D-glucose was obtained (fractions 6–10, 30 mg.), $[\alpha]^{22}D$ −11° (*c* 1.05, water). Both sugars gave on paper chromatography a single spot of R_g 1.

When the resin was prepared and allowed to stand 2 weeks under water free from carbon dioxide, the elution of the methyl sugars could not be carried out with water, and the use of pure methanol was necessary to elute the sugars from the column, but no separation was achieved.

(21) J. C. Irvine and A. Cameron, *J. Chem. Soc.*, **85**, 1071 (1904).

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The Addition of Ethanethiolic Acid to 3β-Acetoxy-5,16-pregnadien-20-one

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On irradiation with ultraviolet light ethanethiolic acid adds *trans* and stereospecifically to the double bonds of 3β-acetoxy-5,16-pregnadien-20-one. The initial attack of the acetylthio radical occurs from the most hindered side (β face) of the molecule. The structures of the adducts are proved by their n.m.r. spectra, rotatory dispersion curves, and chemical reduction products.

Because of the ease[2] with which the Δ^{16}-20-oxo system of steroids adds nucleophilic reagents, a number of small molecules have been added in attempts to enhance certain desirable physiological properties of steroids. Acetone,[3] alcohols,[2,4] amines,[5] diethyl malonate,[6] haloforms,[7] hydrogen cyanide,[8] nitromethane,[9a] and mercaptans[10] have all been added in the presence of base. Ethanethiolic acid,[5b] hydrogen chloride,[9b,5b] mercaptans,[5b] nitromethane,[5b] and vinyl ethers[11] have been added under conditions of acid catalysis. Furthermore, diazomethane,[12] ethyl diazoacetate,[13] meth-

(1) Taken in part from the Ph.D. Thesis of J. R. D., June 1964. This research was partially supported by fellowships from the Sun Oil Co. and The National Science Foundation.

(2) D. F. Fukushima and T. F. Gallagher [*J. Am. Chem. Soc.*, **73**, 196 (1951)] have attributed the ready addition of alcohols to the relief of strain present in the *trans*-fused D-ring of Δ^{16}-20-oxo steroids.

(3) M. E. Wall, S. Serota, H. E. Kenney, and G. S. Abernethy, *ibid.*, **85**, 1844 (1963).

(4) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952).

(5) (a) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Herschberg, *ibid.*, **78**, 3158 (1956); (b) A. S. Hoffman, H. M. Kissman, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 962 (1962).

(6) P. Bladon, *J. Chem. Soc.*, 3723 (1958).

(7) E. Kaspar and R. Wiechert, *Ber.*, **91**, 2664 (1958).

(8) (a) R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959); (b) J. Romo, *ibid.*, **3**, 37 (1958).

(9) (a) R. M. Dodson, U. S. Patent 2,697,109 (Dec. 14, 1954); (b) R. M. Dodson and P. B. Sollman, U. S. Patent 2,708,201 (May 10, 1955).

(10) (a) J. Romo and G. Conteras, *Bol. Inst. Quim. Univ. Na. Auton. Mex.*, **4**, 101 (1952); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951); (c) J. Romo, G. Rosenkranz, and C. Djerassi, *ibid.*, **73**, 4961 (1951).

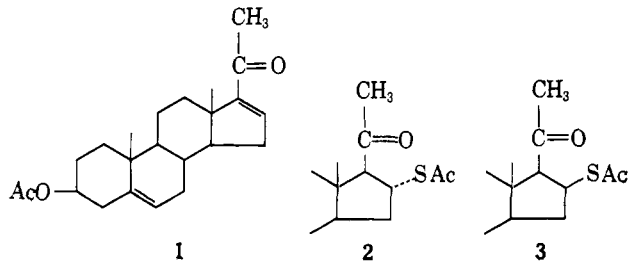
(11) S. Julia and H. Linares, *Compt. rend.*, **252**, 2560 (1961).

(12) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

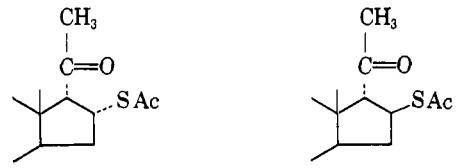
(13) G. P. Mueller and B. Riegel, *J. Am. Chem. Soc.*, **76**, 3686 (1954).

ylmagnesium iodide,[14] and methyl vinyl ether[15] have been added without benefit of added catalyst. To our knowledge, the only example of a homolytic addition to the Δ^{16}-20-oxo system is the recently reported addition of ethanol.[16] In each instance only one of the four possible stereoisomers, differing in configuration at C-16 and/or C-17, was isolated and was assigned the configuration having the substituents in the 16α and 17β positions. In many of these examples, the configuration of the product was assigned from rotational data or by analogy to earlier additions. However, there are enough examples where the configuration at C-16 and C-17 has been rigorously established to lend credence to the "attack from the rear" rule.

Five years ago we[17] isolated two of the four possible products from the addition of ethanethiolic acid to the 16 double bond of 3β-acetoxy-5,16-pregnadien-20-one one (**1**).[18] A third possible isomer was detected by paper chromatography, but could not be isolated for characterization. Compound **3**, m.p. 167–168°, $[\alpha]_D$ −32°, was less stable than, and was readily converted to, the other isolated product, compound **2**, m.p. 185–186°, $[\alpha]_D$ −55°, by treatment with anhydrous sodium acetate in acetic acid. Since these conditions were known[19] to epimerize asymmetric groups α to a ketone,



1 **2** **3**



4 **5**

this transformation suggested that the isomers differed only in their configuration at C-17. However, the molecular rotation of neither adduct was consistent with the large negative shift[20] characteristic of steroids possessing a 17α-acetyl side chain. This suggested that the two thiol acetates were isomeric at C-16. The positive Cotton effect[18,21] and n.m.r. spectrum[18,22] exhibited by the stable adduct was consistent with the assigned structure **2**. Furthermore the stable adduct was identical with the thiol acetate obtained by acetylating the thiol prepared by base-catalyzed addition of hydrogen sulfide to **1**—a reaction which almost certainly gave the 16α,17β isomer. The less stable adduct **3** exhibited a positive Cotton effect, indicative of a 17β-acetyl group,[21] but the amplitude was by far the smallest yet reported for a 17β-acetyl steroid. Furthermore, the chemical shift (n.m.r. spectrum) for the C-18 protons of **3** was downfield from that usually found for a 17β-acetyl steroid and was observed in that general region characteristic of 17α-acetyl steroids.[23] Although all these facts could be reconciled with the assigned structures **2** and **3**,[18] we did not feel that we could confidently assign the structures of the thiol acetates (in particular, of the unstable adduct) on the basis of this evidence alone.[24]

Desulfurization of the reduction products of the ethanethiolic acid adducts of **1** conclusively proved that they are both 17β-acetyl steroids and hence have the structures **2** and **3** as assigned.[18] In order to prevent any possible epimerization at C-17 *via* enolization during the desulfurization process, the C-20 carbonyl was first reduced by lithium aluminum hydride. The possibility that isomerization may occur during the reduction of the carbonyl seems highly unlikely in view of the reports[25] that reduction proceeds faster than any isomerization that may be induced by the basicity of the reagent. Reduction of **2**, followed by acetylation gave 16α-acetylthio-5-pregnene-3β,20β-diol diacetate (**9**). Desulfurization of **9** with Raney nickel afforded 5-pregnene-3β,20β-diol diacetate (**10**)[26] identical with an authentic sample prepared by sodium borohydride reduction of 3β-hydroxy-5-pregnene-20-on (**11**). When the same degradation scheme was applied to **3**, a difficultly separable mixture of the epimeric 20-acetates was obtained. The epimeric 20-acetates **12** and **13** were separated by fractional crystallization and desulfurized to **10** and **14**, respectively. 5-Pregnene-3β,20β-diol diacetate (**10**) obtained from **12** was identical with the above authentic sample; the physical properties of 5-pregnene-3β,20α-diol diacetate (**14**), m.p. 139–142°, $[\alpha]_D$ −54°, obtained from **13** agreed with those reported,[26] and the parent diol, obtained by saponification of **14**, was identical with an authentic sample of 5-pregnene-3β,20α-diol.[27]

These desulfurization experiments clearly demonstrated that both of the ethanethiolic acid adducts have

(14) G. E. Arth, D. B. R. Johnson, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarrett, *J. Am. Chem. Soc.* **80**, 3160 (1958).

(15) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. MacKellar, *J. Org. Chem.*, **28**, 2499 (1963).

(16) I. A. Williams and P. Bladon, *Tetrahedron Letters*, **No. 5**, 257 (1964).

(17) R. M. Dodson and P. B. Sollman, U. S. Patent 2,912,443 (Nov. 10, 1959).

(18) From the method of formation, compounds with the acetylthio group at C-17 were considered to be very improbable. L. L. Smith and D. M. Teller [*J. Med. Chem.*, **7**, 531 (1964)] have very recently had occasion to repeat, confirm, and extend our early work.

(19) R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Am. Chem. Soc.*, **82**, 4026 (1960).

(20) D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), 755 (1948).

(21) (a) C. Djerassi, *Bull. soc. chim. France*, 741 (1957); (b) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961); (c) P. Crabbé, *Tetrahedron*, **19**, 51 (1963); (d) P. Crabbé, F. McCapra, F. Comer, and A. I. Scott, *ibid.*, **20**, 2455 (1964).

(22) A. D. Cross and P. Crabbé, *J. Am. Chem. Soc.*, **86**, 1221 (1964).

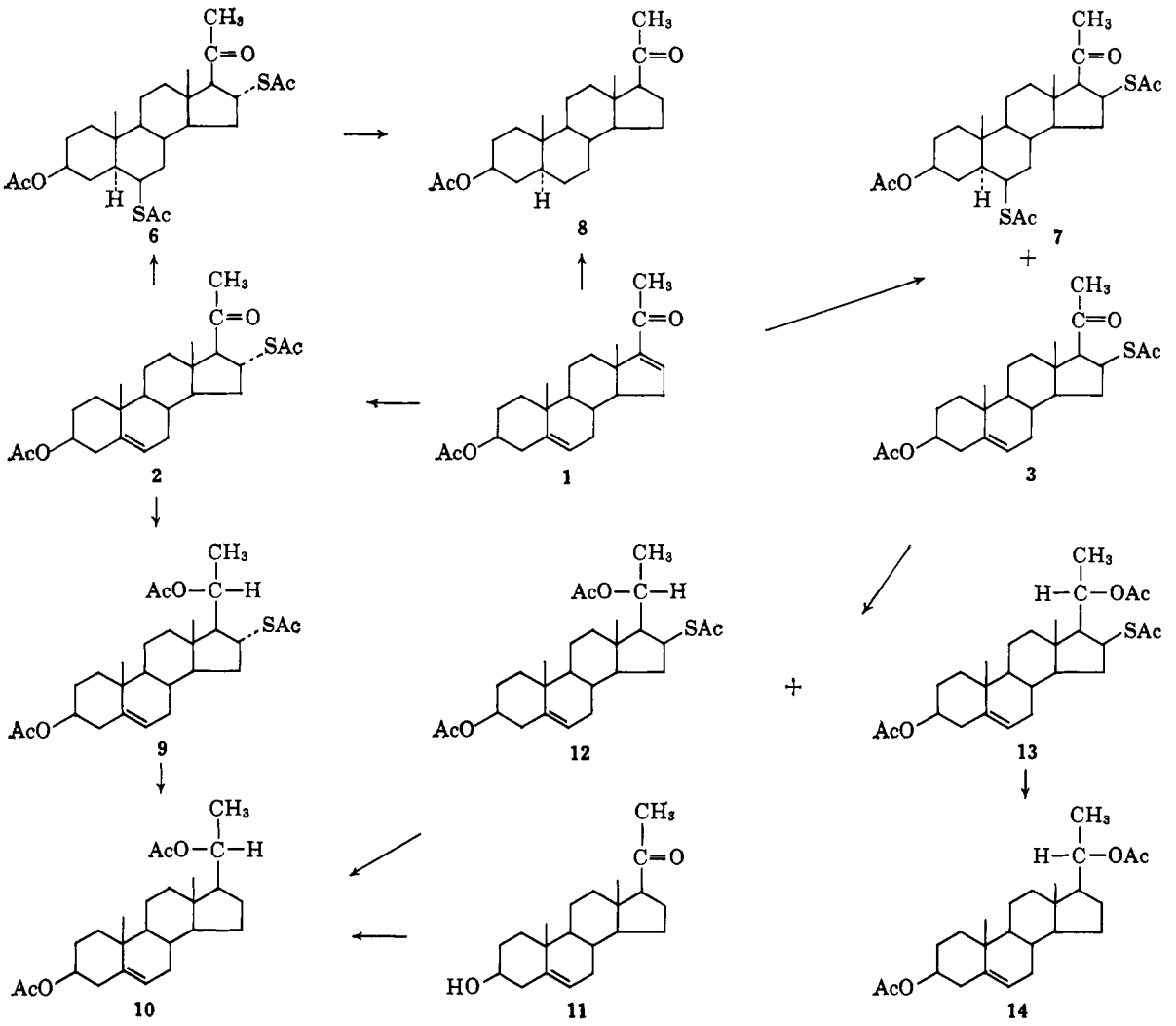
(23) (a) G. Slomp, private communication in *Mellon NMR Newsletter*, **31**, 8 (1961); (b) W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963); (c) J. E. Pike, G. Slomp, and F. A. MacKellar, *ibid.*, **28**, 2502 (1963); (d) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. MacKellar, *ibid.*, **28**, 2499 (1963).

(24) Since our O.R.D. and n.m.r. spectra of compounds **2** and **3** are in general agreement with those recently published by Smith and Teller (ref. 18), they are not presented or discussed in detail in this paper. Our interpretation of them was very similar to that of Smith and Teller (see ref. 1). Since the appearance of the publication by Cross and Crabbé (ref. 22), a more definitive assignment of structure can be made on the basis of the coupling constants ($J_{16,17}$) of the two isomers.

(25) (a) D. L. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **72**, 5743 (1950); (b) D. C. Ayres and P. J. S. Pauwels, *Proc. Chem. Soc.*, 388 (1961); *J. Chem. Soc.*, 5025 (1962).

(26) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949); W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950); J. Romo, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952). The melting point reported by R. B. Turner and D. M. Voitle [*J. Am. Chem. Soc.*, **73**, 2283 (1951)] for 5-pregnene-3β,20β-diol diacetate, m.p. 138.5–140°, differs from that found by us (m.p. 129–130°) and that listed in the other references (m.p. 125–126°, 130–131°, and 126–127°, respectively).

(27) We should like to thank Dr. J. Mihina for this sample.



a 17β-acetyl side chain[28] and therefore must be **2** and **3**. The assignment of structure **2** to the stable adduct, m.p. 185–186°, follows from its O.R.D. curve, n.m.r. spectrum, independent synthesis, and the greater relative stability of *trans* isomers over *cis* isomers.[29] The unstable adduct, m.p. 166–167°, must be 16β-acetylthio-3β-acetoxy-5-pregnen-20-one (**3**). The n.m.r. spectra of 16β,17β-disubstituted steroids has recently been discussed.[22] The reorientation of the usually preferred rotational conformation of the 20-carbonyl group, resulting from either steric or attractive forces between the 17β-acetyl and 16β-acetylthio groups, is probably responsible for the unexpected, low amplitude of the O.R.D. spectrum of **3**.[21d] Such an explanation would also account for the downfield shift of the C-18 resonance band in the n.m.r. spectrum.

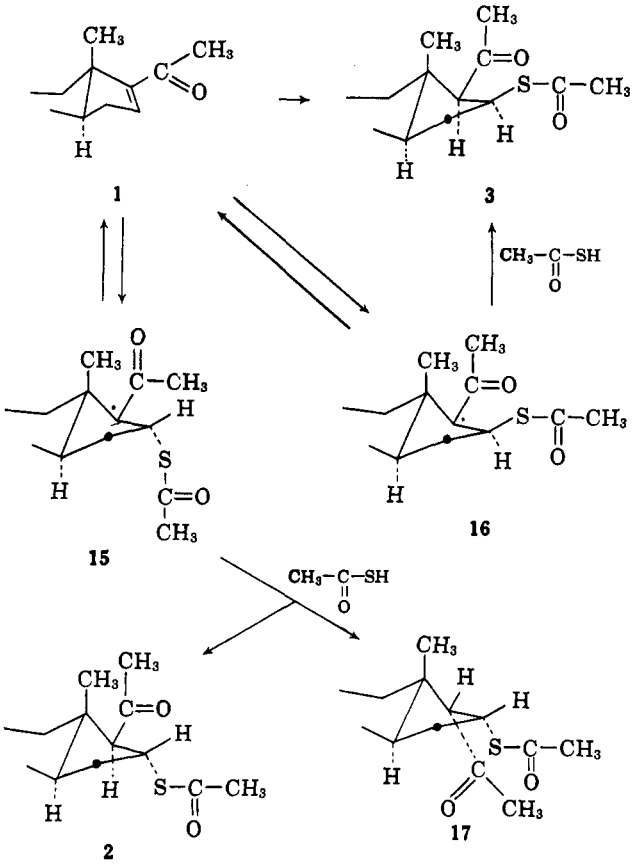
On repeating our earlier work[17] using unpurified ethanethiolic acid and irradiation, we isolated only the stable adduct **2**. Furthermore, we obtained an excellent yield of **2** at low temperature and short reaction time. In contrast to these results, when we used freshly distilled ethanethiolic acid and irradiation we obtained the unstable adduct **3** along with only a trace of **2** and some of the corresponding diadduct, 6β,16β-diacetylthio-3β-acetoxy-5α-pregnan-20-one (**7**). If we used the purified ethanethiolic acid without irradiation, we obtained a mixture which would not crystallize initially, but afforded the diadduct **7** and the stable diadduct, 6β,16α-diacetylthio-3β-acetoxy-5α-pregnan-20-one (**6**), after long standing (6 hr.).

The configurations of the substituents in ring D of the diadducts were assigned on the basis of the practically identical chemical shifts of the C-17, C-18, C-21, and —SCOCH$_3$ protons of **6** and **2** and of **7** and **3**. The presence of a low-field (τ 6.26) band in the n.m.r. spectra of both **6** and **7** showed that the acetylthio group was at C-6; the relatively small coupling with adjacent protons, as evidenced by the width at half-height of the absorption band for the C-6 proton, indicated that the proton was equatorial and that therefore the acetylthio group at C-6 was orientated β. Quite recently Shoppee and co-workers[30] have made the same stereochemical assignments to the acetylthio adducts of Δ^5-cholestenes. The configuration at C-5 in compound **6** was established by desulfurization to give 3β-acetoxy-5α-pregnan-20-one (**8**). The diadduct **6** was also obtained by irradiating a mixture of freshly distilled

(28) The possibility that the less stable adduct isomerized during the reduction step can be partially excluded by the observation that the three diacetoxy thiol acetates **9**, **12**, and **13** are different compounds; if the unstable adduct were **4**, isomerization would have given **2** and either **12** or **13** would have been identical with **9**. Only if the unstable adduct were **5** would isomerization and reduction have given the same pattern of products as was obtained. However, isomerization of **5** to **3** would probably involve isomerization of the more stable to less stable isomer (see ref. 22 and 29).

(29) (a) J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J. Chem. Soc.*, 4547 (1961); (b) P. Crabbé, *Tetrahedron*, **19**, 51 (1963); (c) P. Crabbé, L. M. Guerrero, J. Romo, and F. Sanchez-Viesca, *ibid.*, **19**, 25 (1963).

(30) C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *J. Chem. Soc.*, 877 (1964).



ethanethiolic acid and the monoadduct **2** with ultraviolet light.

In view of the ease with which ethanethiolic acid forms radicals, the light-initiated experiments above and the light-initiated additions of hydrogen bromide[31] and ethanethiolic acid[30] to Δ^4 and Δ^5 steroids must proceed *via* a *trans* homolytic mechanism, with the initial attack of the radical from the most hindered side of the molecule. This gives as the major product a thermodynamically unstable adduct. In contrast to the radical addition of ethanethiolic acid[30] and hydrogen bromide[31] to the Δ^5 double bond of steroids, the ionic addition of hypobromous acid or bromonium chloride is initiated by attack of the bromonium ion from the less hindered α face to yield the anti-Markovnikov product.[32] This difference indicates that ionic additions are more subject to steric effects than radical additions.

Two different explanations for the formation of **3** by free-radical addition of ethanethiolic acid to **1** can be given. In previous studies[30,31] it has been shown that a free radical attacks a double bond preferentially along a reaction coordinate that eventually produces an axial substituent. While the conformation of ring D in **1** closely approximates an envelope, it seems probable that the conformation in **3** is a half-chair. Thus the acetylthio radical attacks along that coordinate of the double bond that eventually leads to a pseudo-axial group. The final hydrogen transfer then occurs from the α side because of pronounced steric effects at the 17β position. It should be noted that hydrogen transfer at the 17β position would have led to the thermodynamically more stable compound (compare, *e.g.*, compounds discussed in ref. 22).

An alternate, and possibly more reasonable, explanation assumes initial but reversible[33] attack by the acetylthio radical from either side of the molecule to form **15** and **16**. The product then is determined by the relative rates of reaction of the slower hydrogen-transfer steps (**16** → **3** or **15** → **17** or **2**). Since hydrogen transfer to **16** occurs adjacent (*cis*) to the C-12 methylene group while hydrogen transfer to **15** must occur adjacent (*cis*) to the C-18 methyl group or adjacent (*cis*) to the C-12 methylene group and the C-16 acetylthio group, one could anticipate less steric interaction in the **16** → **3** hydrogen transfer. The choice between these mechanisms and details of mechanism must await further studies.

Experimental[34]

16α-Mercapto-3β-acetoxy-5-pregnen-20-one.—A solution containing *3β-acetoxy-5,16-pregnadien-20-one* (**1**, 10.00 g., 28.05 mmoles), pyridine (200 ml.), and piperidine (0.8 ml.) was saturated with hydrogen sulfide and stored for 64 hr. at room temperature. The solution was diluted with water (1 l.) and extracted with ether (1 l.). The ether extract was chromatographed on silica gel (300 g.). The material that was eluted with a 2% (v./v.) solution of ethyl acetate in benzene was crystallized from hexane to give 1.65 g. of the 16α-mercapto-3β-acetoxy-5-pregnen-20-one: m.p. 148–150° and 157–160°; $[\alpha]_D$ −3.4° (*c* 1.19); λ_{max}^{KBr} 5.80, 5.86, and 8.05 μ.

Anal. Calcd. for $C_{23}H_{34}O_3S$: C, 70.72; H, 8.77; S, 8.22. Found: C, 70.72; H, 8.61; S, 8.10.

16α-Mercapto-3β-hydroxy-5-pregnen-20-one. A. Hydrolysis of 16α-Acetylthio-3β-acetoxy-5-pregnen-20-one.—A solution containing **2** (12.0 g.), sodium hydroxide (12.0 g.), methanol (600 ml.), and water (24 ml.) was stored under nitrogen for 1.5 hr. at room temperature. The product was precipitated by the addition of dilute acetic acid, collected by filtration, and recrystallized from aqueous methanol to give 8.8 g. of the product, m.p. 181–182°. The analytical sample, obtained by recrystallization from aqueous ethanol, had m.p. 181–182°; $[\alpha]_D$ +2.5° (*c* 1.00); and λ_{max}^{KBr} 2.85, 3.94, and 5.90 μ.

Anal. Calcd. for $C_{21}H_{32}O_2S$: C, 72.36; H, 9.26; S, 9.20. Found: C, 72.37; H, 9.21; S, 8.72.

B. Hydrolysis of 16α-Mercapto-3β-acetoxy-5-pregnen-20-one.—A solution containing 16α-mercapto-3β-acetoxy-5-pregnen-20-one (0.30 g.), methanol (10 ml.), water (1 ml.), and sodium hydroxide (0.30 g.) was stored for 2 hr. at room temperature. The product was precipitated by the addition of 20 ml. of 10% acetic acid, collected by filtration, and recrystallized from aqueous methanol to give the product, m.p. 178–179°, identical (infrared) with the above material.

16α-Acetylthio-3β-acetoxy-5-pregnen-20-one (**2**). **A. Addition of Undistilled Ethanethiolic Acid to 1 without Irradiation.**—A mixture of 3β-acetoxy-5,16-pregnadien-20-one (**1**, 10.00 g., 28.05 mmoles) and cold ethanethiolic acid (10.00 ml.) was stirred for 15 min. in an ice bath; then the mixture was poured into water. The solid was collected by filtration and crystallized from methanol to give 6.90 g. (57%) of the stable adduct **2**, m.p. 185–186°. An additional 3.28 g. (27%) of lower melting material (1.96 g., m.p. 183–185°; 1.32 g., m.p. 174–179°) was obtained in two additional crops of crystals. The analytical sample, obtained from one recrystallization of the first crop from methanol, had m.p. 185–186°; $[\alpha]_D$ −55° (*c* 1.13)[17,18]; n.m.r. (10% in CCl_4) τ

(31) C. W. Shoppee and R. E. Lack, *J. Chem. Soc.*, 4864 (1960).

(32) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1961); M. Akhtar and D. H. R. Barton, *ibid.*, **84**, 1496 (1962); D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 2598 (1951); J. B. Ziegler and A. C. Shabica, *J. Am. Chem. Soc.*, **74**, 4891 (1952).

(33) For evidence of the reversibility of the reaction of thiyl radicals with olefins, see C. Walling and W. Helmreich [*ibid.*, **81**, 1144 (1959)] and N. P. Neureiter and F. G. Bordwell [*ibid.*, **82**, 5354 (1960)].

(34) Melting points were taken on a Fisher-Johns melting point block; rotations were determined in chloroform at 24 ± 2°. The n.m.r. spectra were determined by Dr. William B. Schwabacher on a Varian Associates V-4300B n.m.r. spectrometer operating at 56.44 Mc./sec.; the reported line positions are averages of three or more spectra.

9.34 (C-18), 8.97 (C-19), 8.05 (AcO), 7.94 (C-21), 7.78 (AcS), 7.48 (C-17, doublet, J = 9 c.p.s.), and 4.67 (C-6).[35]

B. Addition of Undistilled Ethanethiolic Acid to 1 with Irradiation.—A mixture of 3β-acetoxy-5,16-pregnadien-20-one (**1**, 5.00 g., 14.0 mmoles) and ethanethiolic acid (6.00 ml., Eastman Kodak practical grade) was irradiated with ultraviolet light for 2 hr.[36] The excess ethanethiolic acid was removed by distillation at reduced pressure, and the residue was triturated with ether (50 ml.). The undissolved solid was isolated by filtration and crystallized from a solution of ethyl acetate and petroleum ether (b.p. 60–68°) to give 2.55 g. (42%) of **2**, m.p. 185–186°. The ether solution and crystallization liquor afforded 2.01 g. of material, m.p. 122–147°. Repeated crystallization of this material from methanol afforded an additional 0.42 g. of **2**, m.p. 185–186°.

C. Isomerization of 16β-Acetylthio-3β-acetoxy-5-pregnen-20-one (3).—A solution containing 16β-acetylthio-3β-acetoxy-5-pregnen-20-one (1.00 g., m.p. 166–167°), anhydrous sodium acetate (1.00 g.), and acetic acid (10.0 ml.) was heated under reflux for 4 hr. The solution was cooled and diluted with water (50 ml.). The product **2** was collected by filtration and recrystallized from 10% (v./v.) benzene–hexane to give 0.50 g. of **2**, m.p. 185–186°.

D. Acetylation of 16α-Mercapto-3β-acetoxy-5-pregnen-20-one.—A solution containing 16α-mercapto-3β-acetoxy-5-pregnen-20-one (0.10 g.), acetic anhydride (1.5 ml.), and pyridine (1.5 ml.) was stored overnight at room temperature. Addition of water gave 0.10 g. of crude **2**, m.p. 182–184°. Recrystallization from a solution of ethyl acetate–hexane gave pure 16α-acetylthio-3β-acetoxy-5-pregnen-20-one (**2**), identical (infrared) with the above samples.

16β-Acetylthio-3β-acetoxy-5-pregnen-20-one (3).—3β-Acetoxy-5,16-pregnadien-20-one (**1**, 5.00 g., 14.0 mmoles) and freshly distilled ethanethiolic acid (5.00 ml., b.p. 85–86°) were irradiated in an open beaker with ultraviolet light. After irradiation for 1 hr. the mixture was crystallized from methanol (100 ml.) to give the following crops of material: crop 1, 2.35 g., m.p. 163–167°; crop 2, 0.09 g., m.p. 155–162°; crop 3, 0.06 g., m.p. 140–160°; crop 4, 0.03 g., m.p. 140–150°; crop 5, 0.39 g., m.p. 142–165°; crop 6, 0.20 g., m.p. 164–166°; and crop 7, 1.03 g., m.p. 135–155°. Attempts to obtain further crops of crystals gave only an oil that was discarded. The sixth crop, m.p. 164–166°, depressed the melting point of authentic samples of the two monoadducts **2** and **3** and of the starting material **1**. Recrystallization of crop 6 from methanol lowered the melting point to 162–167° and another recrystallization from a solution of ethyl acetate and petroleum ether gave 0.05 g. of the unstable adduct **3**, m.p. 166–167°. This material, m.p. 166–167°, was combined with the 2.35 g. from crop 1 and 0.10 g., m.p. 165–168°, obtained by recrystallizing crops 2 and 3 from methanol, for a total of 2.45 g. (41%) of **3**.[37] The analytical sample had m.p. 166–167°; $[\alpha]_D$ −33° (c 1.29)[17,18]; n.m.r. (10% in CCl_4) τ 9.13 (C-18), 8.98 (C-19), 8.05 (AcO and C-21), 7.73 (AcS), 7.29 (C-17, doublet, J = 9 c.p.s.), and 4.67 (C-6).[35]

Crop 4, probably a mixture of **2** and **3**, was discarded. Crop 5 was recrystallized from methanol to give 0.20 g., m.p. 182–184°, of **2** which was undepressed upon admixture with authentic 16α-acetylthio-3β-acetoxy-5-pregnen-20-one (**2**).

6β,16β-Diacetylthio-3β-acetoxy-5α-pregnan-20-one (7).—The 1.03 g. of crop 7 in the above experiment was repeatedly crystallized from methanol to give a pure sample of the diadduct **7**: m.p. 220–221°; $[\alpha]_D$ −65° (c 0.92); λ_{max}^{EtOH} 234 mμ (ε 10,200); λ_{max}^{KBr} 5.82, 5.88, 5.92, 8.03, and 8.80 μ; n.m.r. (10% in carbon tetrachloride) τ 9.08 (C-18 and C-19), 8.06 (AcO and C-21), 7.74 (AcS at C-6 and C-16), 7.30 (C-17, doublet, J = 9 c.p.s.), and 6.26 (C-6, w_H = 6.4 c.p.s.).[38]

Anal. Calcd. for $C_{27}H_{40}O_5S_2$: C, 63.74; H, 7.93; S, 12.61. Found: C, 63.36; H, 7.83; S, 12.70.

6β,16α-Diacetylthio-3β-acetoxy-5α-pregnan-20-one (6). A. By Addition of Ethanethiolic Acid to 2.—A solution of 16α-acetylthio-3β-acetoxy-5-pregnen-20-one (**2**, 1.98 g., 4.58 mmoles) in freshly distilled ethanethiolic acid (2.00 ml.) was irradiated for 1 hr. from the top of an open beaker with ultraviolet light. The hot solution was dissolved in methanol and fractionally crystallized. The head fractions afforded 0.68 g. (29%) of 6β,16α-diacetylthio-3β-acetoxy-5α-pregnan-20-one (**6**): m.p. 211–215°; $[\alpha]_D$ −53.5° (c 1.01); λ_{max}^{EtOH} 234 mμ (ε 9840); λ_{max}^{KBr} 5.78, 5.85, 5.92, 8.00, and 8.82 μ; n.m.r. (10% in CCl_4) τ 9.34 (C-18), 9.10 (C-19), 8.06 (AcO), 7.94 (C-21), 7.78 (AcS at C-16), 7.73 (AcS at C-6), 7.49 (C-17, doublet, J = 9 c.p.s.), and 6.23 (C-6, w_H = 6.4 c.p.s.).[38]

Anal. Calcd. for $C_{27}H_{40}O_5S_2$: C, 63.74; H, 7.93. Found: C, 64.04; H, 7.89.

The tail fractions afforded 0.13 g. of starting material **2**, m.p. 182–185°, m.m.p. 182–185°. The intermediate fractions contained a mixture of **2** and **6**.

B. By Addition of Ethanethiolic Acid to 1.—A mixture containing 3β-acetoxy-5,16-pregnadien-20-one (**1**, 0.32 g., 0.90 mmole) and freshly distilled ethanethiolic acid (0.30 ml.) was stored in a dark hood at room temperature. After 1 hr. attempts to crystallize the oily residue from methanol all failed, even when the solution was seeded with **3**. Finally, after standing at room temperature for 6 hr., 0.12 g. of crystals, m.p. 188–196°, separated. This was recrystallized from methanol, then twice from a solution of ethyl acetate and petroleum ether, and finally from a solution of acetone and petroleum ether (b.p. 60–68°) to give a small amount of 6β,16α-diacetylthio-3β-acetoxy-5α-pregnan-20-one (**6**), m.p. 213–215°, identical (mixture melting point and infrared spectrum) with the material characterized above.

The mother liquors were applied to a silica gel (15 g.) column. Elution with a 5% (v./v.) solution of ethyl acetate in benzene gave a solid. Recrystallization of the solid from methanol (twice) afforded a sample of **6β,16β-diacetylthio-3β-acetoxy-5α-pregnan-20-one (7)**, m.p. 215–220°. This material did not depress the melting point of **7** prepared in the previous experiment but did depress the melting point of **6** prepared above.

Desulfurization of 16α-Acetylthio-3β-acetoxy-5-pregnen-20-one (2). A. Lithium Aluminum Hydride Reduction.—A solution of 16α-acetylthio-3β-acetoxy-5-pregnen-20-one (**2**, 3.27 g., 7.57 mmoles) in dry tetrahydrofuran (60 ml.) was added to a slurry of lithium aluminum hydride (1.56 g.) and dry tetrahydrofuran (25 ml.) over a period of 35 min. After being stirred an additional 6 hr. at room temperature, the excess lithium aluminum hydride was destroyed with ethyl acetate. The mixture was poured into dilute hydrochloric acid (3 N, 200 ml.) and extracted with ether (three 100-ml. portions). The combined ether extracts were washed with water (two 100-ml. portions), dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to a solid residue, m.p. 140–150°.

The residue was dissolved in pyridine (35 ml.) and acetic anhydride (35 ml.) and the solution was stored for 11 hr. at room temperature. The crude triacetate was precipitated by the addition of ice water (*ca.* 500 ml.), collected by filtration, and washed with water. Fractional crystallization of the damp solid from methanol afforded 1.55 g. (43%) of **16α-acetylthio-5-pregnene-3β,20β-diol diacetate (9)**, m.p. 199–204°. The analytical sample, obtained by crystallization from a solution of ethyl acetate and petroleum ether, consisted of small needles: m.p. 203–205°; $[\alpha]_D$ −157° (c 1.07); λ_{max}^{EtOH} 235 mμ (ε 5000); λ_{max}^{KBr} 5.78, 5.93, 8.02, and 8.78 μ; n.m.r. (10% in CCl_4) τ 9.26 (C-18), 9.00 (C-19), 8.72 (C-21, doublet, J = 7.9 c.p.s.), 8.05 (AcO at C-3 and C-20), 7.77 (AcS), and 4.63 (C-6).

Anal. Calcd. for $C_{27}H_{40}O_5S$: C, 68.03; H, 8.46; S, 6.73. Found: C, 67.95; H, 8.43; S, 6.85.

The residue (2.00 g.), obtained by evaporation of the mother liquors, was dissolved in benzene (100 ml.) and chromatographed on silica gel (70 g.). Elution of the column with a 2% (v./v.) solution of ethyl acetate in benzene afforded 0.99 g. of a solid that yielded 0.63 g., m.p. 202–205°, upon recrystallization from methanol. This material and 0.11 g., m.p. 195–201° (obtained from 0.38 g. of later eluents), did not depress the melting point of the analytical sample above. The 5 and 10% eluents removed 0.30 g. of an oil that was not investigated.

B. Desulfurization of 16α-Acetylthio-5-pregnene-3β,20β-diol Diacetate (9).—Raney nickel (*ca.* 3 g., W-2) was refluxed gently for 8 hr. with an ethanolic (95%, 60 ml.) solution of **9** (0.39 g., 0.84 mmole), and then the mixture was stored for 38 hr. at room

(35) Differences between our values and those reported by Smith and Teller[18] are probably due to difference in solvent used.

(36) An Hanovia 125-w. medium pressure mercury lamp (Type SH) was used without filter. It was directed into the mouth of a beaker containing the reagents.

(37) Smith and Teller[18] have reported ratios of the 16β isomer to 16α isomer as high as 13:1. However, for them results were erratic, and stereoselectivity was assumed to be dependent on the structure of the steroid and the thio acid. We believe variations in the purity of the thio acid and in exposure to light account for the variability of their results.

(38) w_H = full width at half-height.

temperature. The nickel was separated by filtration and washed with methanol (50 ml.). The filtrate and washings were evaporated at reduced pressure, and the resulting residue was recrystallized from methanol to give 0.14 g. (41%) of **5-pregnene-3β,20β-diol diacetate** (**10**), m.p. 127–128°. Subsequent crops gave an additional 0.15 g. (45%) of **10** that had m.p. 127–129°. Recrystallization of the first crop from methanol gave a pure sample, m.p. 129–130°.[26] A mixture of this material with a sample of 5-pregnene-3β,20β-diol diacetate, prepared *via* sodium borohydride reduction of 3β-hydroxy-5-pregnen-20-one and acetylation, showed no depression in melting point (infrared spectra identical).

Desulfurization of 16β-Acetylthio-3β-acetoxy-5-pregnen-20-one (3). A. Lithium Aluminum Hydride Reduction.—A solution of 16β-acetylthio-3β-acetoxy-5-pregnen-20-one (**3**, 1.78 g., 4.12 mmoles) in dry tetrahydrofuran (20 ml.) was added over a period of 15 min. to a slurry of lithium aluminum hydride (0.50 g.) and dry tetrahydrofuran (5.0 ml.). Dry ether (75 ml.) was added and the mixture was stirred at room temperature for 21.5 hr. After the excess lithium aluminum hydride was destroyed with ethyl acetate, the mixture was poured into dilute hydrochloric acid (3 *N*, 100 ml.) and extracted with ether (three 25-ml. portions). The combined organic phase was washed with water (two 30-ml. portions), dried (magnesium sulfate), and evaporated at reduced pressure.

The residue (1.55 g., m.p. *ca.* 65–200°) was acetylated by heating with acetic anhydride (20 ml.) and pyridine (20 ml.) for 1 hr. on a steam bath. The product was precipitated with ice-water (150 ml.) and extracted from the mixture with methylene chloride (three 25-ml. portions). The methylene chloride extracts were washed with dilute hydrochloric acid (3 *N*, two 25-ml. portions), saturated sodium bicarbonate solution (two 25-ml. portions), and water (two 25-ml. portions), dried (magnesium sulfate), and evaporated at reduced pressure to an oil. The oil was dissolved in methanol and fractionally crystallized. From the head fractions was obtained 0.18 g. of **16β-acetylthio-5-pregnene-3β,20α-diol diacetate** (**13**): m.p. 187–188°; $[\alpha]_D$ −56° (*c* 0.78); n.m.r. (7% in CCl_4) τ 9.24 (C-18), 8.99 (C-19), 8.73 (C-21, doublet, J = 6.5 c.p.s.), 8.12 (AcO at C-20), 7.98 (AcO at C-3), 7.74 (AcS), and 4.63 (C-6).

Anal. Calcd. for $C_{27}H_{40}O_5S$: C, 68.03; H, 8.46. Found: C, 68.24; H, 8.38.

From the tail fractions was isolated 0.09 g. of **16β-acetylthio-5-pregnene-3β,20β-diol diacetate** (**12**): m.p. 178–179°; $[\alpha]_D$ −32° (*c* 0.87); n.m.r. (7% in CCl_4) τ 9.31 (C-18), 9.01 (C-19), 9.06 (C-21, doublet, J = 6 c.p.s.), 8.06 (AcO at C-3 and C-20), 7.73 (AcS), and 4.68 (C-6).

Anal. Calcd. for $C_{27}H_{40}O_5S$: C, 68.03; H, 8.46. Found: C, 67.85; H, 8.31.

Investigation of the mother liquors yielded an additional trace (*ca.* 3 mg.) of **13** and 0.11 g. of **12**. No new material could be found.

B. Desulfurization of 16β-Acetylthio-5-pregnene-3β,20α-diol Diacetate (**13**).—Deactivated (by refluxing for 1 hr. in acetone) Raney nickel (0.25 teaspoon) was stirred for 16 hr. with **13** (0.09 g., 0.2 mmole) in acetone (40 ml.). Unchanged starting material, m.p. 186–188°, m.m.p. 186–188°, was isolated from the filtrate after separation of the nickel. This material was retreated for 4 hr. with deactivated Raney nickel (0.25 teaspoon) in refluxing ethanol. Isolation as above gave an oil that crystallized from aqueous methanol to give 0.01 g. of **5-pregnene-3β,20α-diol diacetate** (**14**), m.p. 139–142°, $[\alpha]_D$ −54° (*c* 0.43) (lit.[26] m.p. 142–143°, $[\alpha]_D$ −56°). Later crops gave material melting over a wide range.

The identity was confirmed by saponification of the above 0.01 g. to 5-pregnene-3β,20α-diol which was identical with an authentic sample (mixture melting point) provided by Dr. Mihina.

C. Desulfurization of 16β-Acetylthio-5-pregnene-3β,20β-diol Diacetate (**12**).—The triacetate **12** (0.25 g., 0.52 mmole) and Raney nickel (*ca.*0.5 teaspoon) were suspended in ethanol (95%, 100 ml.) and refluxed gently with stirring for 15 hr. The nickel was separated by filtration and washed with ethanol (100 ml.). Concentration of the filtrate and then chilling afforded 0.20 g., m.p. 122–127°. After attempts to purify the sample by crystallization were unsuccessful, the 0.20 g. was chromatographed on silica gel (10.0 g.). The product (0.13 g.) eluted with a 2% (v./v.) solution of ethyl acetate and benzene was recrystallized from methanol to give 0.09 g. of **5-pregnene-3β,20β-diol diacetate**, m.p. 128–130°, identical with the authentic sample (mixture melting point and infrared spectrum).

3β-Acetoxy-5α-pregnan-20-one (**8**).—6β,16α-Diacetylthio-3β-acetoxy-5α-pregnan-20-one (**6**, 0.10 g., 0.20 mmoles) was heated under reflux in acetone (100 ml.) for 1 hr. with deactivated Raney nickel (0.5 teaspoon, refluxed 1 hr. with 100 ml. of acetone). The nickel was separated by filtration and washed with methanol (100 ml.). Evaporation of the filtrate gave *ca.* 0.09 g. of an amorphous solid. The solid was dissolved in benzene and chromatographed on silica gel (4 g.). A 2% (v./v.) solution of ethyl acetate in benzene eluted the crude product. Recrystallization from aqueous methanol and then aqueous acetone gave 0.02 g. of the 3β-acetoxy-5α-pregnan-20-one, m.p. 147–148°, m.m.p. 147–149° with an authentic sample.

Reduction of Organic Compounds by Carbon Monoxide. I. The Reductive Coupling of Aromatic Nitro Compounds[1]

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The reductive coupling of several aromatic nitro compounds to the corresponding azo derivatives was effected in the presence of carbon monoxide and catalytic quantities of iron pentacarbonyl. Azoxybenzene was isolated as an intermediate in the transformation of nitrobenzene to azobenzene. Carbon monoxide is the reductant and is oxidized to carbon dioxide in the process.

The conversion of nitrobenzene to azobenzene has been effected in numerous ways since the uses of iron and acetic acid[2] or zinc and aqueous sodium hydroxide[3] were described. The latter system has since become the method of choice for laboratory-scale syntheses. Other interesting and novel methods of producing azobenzene and its derivatives include reduction of the corresponding nitro aromatic by carbohydrates,[4,5] electrolytically produced amalgams,[6] sodium aluminum hydride,[7] silicon,[8] and carbon monoxide.[9]

Carbon monoxide has been used to effect the reduction of many inorganic compounds, but its use in reduction of organic compounds has not been widely explored. Murahashi and co-workers[10] obtained a low

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