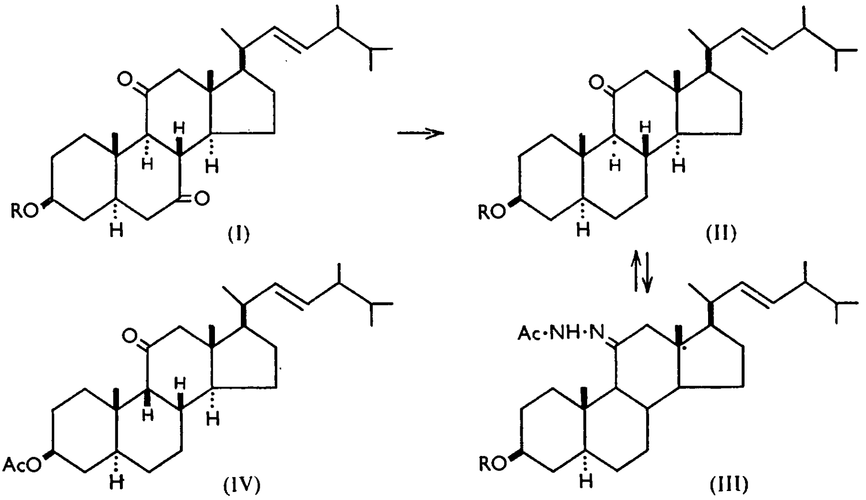
834. *Studies in the Synthesis of Cortisone. Part XIV.* Acetylhydrazones and Azines of Steroidal Ketones.*

By J. Elks and G. H. Phillipps.

In the preparation of 3β-acetoxyergost-22-en-11-one from 3β-acetoxyergost-22-ene-7 : 11-dione by Wolff–Kishner reduction and subsequent acetylation a by-product has been isolated and shown to be 3β-acetoxyergost-22-en-11-one acetylhydrazone. Acetylhydrazones and azines of some other steroidal ketones have been prepared for comparison of their infrared and ultraviolet spectra with those of the by-product.

The preparation of 3β-hydroxyergost-22-en-11-one (II; R = H) from 3β-acetoxyergost-22-ene-7 : 11-dione (I; R = Ac) by Wolff–Kishner reduction has been described [1,2] as part of procedures for the synthesis of cortical steroids from ergosterol. We have found that a method similar to that of Chamberlin *et al.*,[2] but done at 160° rather than 200° and involving chromatography of the acetylated crude product on alumina, gives the 11-ketone (II; R = Ac) in 65—70% yield and also some 7% of a more strongly adsorbed material.

The formulations of the by-product as the acetylhydrazone (III; R = Ac) of 3β-acetoxyergost-22-en-11-one, and of its alkaline hydrolysis product [which can be reacetylated to (III; R = Ac)] as (III; R = H) follow from elementary analysis and from the conversion of the acetylhydrazone acetate (III; R = Ac) into the ketone acetate (II; R = Ac) in low yield by hydrolysis with aqueous-alcoholic sulphuric acid or with pyruvic acid in acetic acid and subsequent acetylation. Further, the ketone (II; R = Ac) gave a low yield of the acetylhydrazone (III; R = Ac), under conditions similar to those used for the Wolff–Kishner reduction. Attempts to form the acetylhydrazone (III; R = Ac) from the ketone (II; R = Ac) by acethydrazide in refluxing alcohol or in diethylene glycol at 220° gave only unchanged starting material; the ketone was also unaffected by hydrazine hydrate in hot acetic acid.



The lack of reactivity of the 11-keto-group to carbonyl reagents [3] is well established; apart from reduction to 11-hydroxyl the only recorded reactions are Wolff–Kishner

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* Part XIII, preceding paper.

[1] Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106.

[2] Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1953, **75**, 3477.

[3] Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., New York, N.Y., 1949, pp. 409—410.

reduction,[1,4] formation of an ethylene ketal under forcing conditions,[5] and possibly Clemmensen reduction.[6] Although the 11-ketones of the 9β-hydrogen series have been reported as unreactive to carbonyl reagents,[7] a derivative of such a compound (containing also a 7 : 8-double bond, which may be of some significance) has since been prepared.[8]

The possibility was considered that the acetylhydrazone was a derivative of the 9β : 11-ketone (IV), which might exist in equilibrium with its 9α-epimer (II) under the enolising alkaline conditions. However, the ketone group in (IV) also failed to react with acethydrazide in refluxing alcohol. It therefore seemed most probable that the acetylhydrazone had structure (III; R = Ac) and that it arose from the 11-hydrazone, which itself must be an intermediate in the Wolff–Kishner reduction of the 7 : 11-diketone (I; R = Ac) to ergost-22-en-3β-ol.[1] That such a derivative would be expected to have infrared and ultraviolet absorption of the type found has been confirmed by examination of the spectra of other acetylhydrazones.

3β-Acetoxyergost-22-ene-7 : 11-dione (I; R = Ac), with acethydrazide in alcohol, gave a 7-acetylhydrazone, the reaction being slower than the formation of cholestanone acetylhydrazone. With hydrazine hydrate in acetic acid the ketones (I; R = H and Ac) gave the 7-azines, and cholestanone the 3-azine. The second of these azines was unstable in hot acetic acid, the ketone being re-formed. The 3β-hydroxyl group of the azine from the alcohol (I; R = H) could be acetylated, the molecule being otherwise stable to such conditions, unlike the azine from cholestanone, which gave a mixture of cholestanone and its acetylhydrazone.

Spectra of the Acetylhydrazones.—Acetylhydrazones of steroids have been prepared both directly[9] and from semicarbazones,[10] but the only available information about their infrared spectra is that pregnenolone acetylhydrazone and progesterone bisacetylhydrazone show bands at 1675 and 1677 cm.$^{-1}$, respectively. We find that the acetylhydrazones of acetone, cholestan-3-one, 3β-acetoxyergost-22-ene-7 : 11-dione, and the compounds (III; R = H and Ac) all show bands in their infrared spectra (in CS_2 solution or as Nujol mulls) at *ca.* 3150 cm.$^{-1}$ (N–H) and *ca.* 1665 cm.$^{-1}$ (C=O and C=N). The " amide II " band at *ca.* 1540 cm.$^{-1}$, probably best attributed[11] to C–N, was, however, present only in the spectra of Nujol mulls of the derivatives of acetone and cholestanone. Its absence from the spectra of the derivatives of the 7- and 11-ketones may possibly be explained, on steric grounds, as due to prevention of the assumption of partial double-bond character by the amido-carbon–nitrogen bond.[11] Nevertheless, the 7-semicarbazone of 3β-acetoxyergost-22-ene-7 : 11-dione (I) in Nujol does show an amide II band at 1568 cm.$^{-1}$.

The ultraviolet spectra of acetylhydrazones have been described, but for the only one comparable with our own, namely, acetone acetylhydrazone, the range examined just missed the position of maximum absorption.[12] The acetylhydrazone of pregnenolone has been reported to exhibit a maximum at 235 mμ, and that of progesterone at 242 and 275 mμ, but the extinction coefficients were not given.[9] We found, in our steroidal acetylhydrazones, as well as in that of acetone, that maxima appear at two wavelengths, *ca.* 215 and 235 mμ, and that compounds showing a maximum at only one position show an inflexion at the other. Thus the acetone and the cholestanone derivatives show a maximum at *ca.* 235 mμ, and the 11-ketone derivatives at *ca.* 215 mμ, whereas the 7-ketone derivative shows a double maximum. This variation, as with that in the infrared spectra, may be due to steric factors, but the number of examples is too small to give conclusive evidence on the point.

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[4] Moffett and Hunter, *J. Amer. Chem. Soc.*, 1951, **73**, 1973; Fieser, Herz, and Wei-Yuan Huang, *ibid.*, p. 2397; Fieser, Wei-Yuan Huang, and Babcock, *ibid.*, 1953, **75**, 116; Fieser and Wei-Yuan Huang, *ibid.*, p. 5356; Barton, Ives, and Thomas, *J.*, 1955, 2056.

[5] Magerlein and Levin, *J. Amer. Chem. Soc.*, 1955, **77**, 1904.

[6] Reichstein, *Helv. Chim. Acta*, 1939, **19**, 979; Steiger and Reichstein, *ibid.*, 1938, **21**, 161.

[7] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

[8] Inhoffen and Mengel, *Chem. Ber.*, 1954, **87**, 146.

[9] Reich, Sanfilippo, and Crane, *J. Biol. Chem.*, 1952, **198**, 713.

[10] Turner, *J. Amer. Chem. Soc.*, 1947, **69**, 875.

[11] Letaw and Gropp, *J. Chem. Phys.*, 1953, **21**, 1621; Freedman, *J. Amer. Chem. Soc.*, 1955, **77**, 6003; Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 185.

[12] Grammaticakis, *Bull. Soc. chim. France*, 1948, 973.

Spectra of the Azines.—The ultraviolet absorptions of a few simple azines have been published. The closest analogy with our azines is to be found in those from acetaldehyde [$\lambda_{max.}$ 208 mμ (ε 10,000 in EtOH)] and butyraldehyde [λ_{max}: 205 (ε 13,000) and 208 mμ (ε 11,500 in EtOH)].[13] Azines of steroidal ketones have been described,[14] but the absorption in this region was not given. We find that the azines of cholestanone, 3β-hydroxyergost-22-ene-7 : 11-dione, and 3β-acetoxyergost-22-ene-7 : 11-dione show a main maximum at *ca.* 213 mμ (ε *ca.* 20,000).

In their infrared spectra these azines are free from N–H absorption and show a weak band at *ca.* 1635 cm.$^{-1}$, attributed to C=N. The azine from œstrone [14] showed a band at 1653 cm.$^{-1}$, but the different position is readily accounted for since it is a derivative of a 5-membered ring ketone.

EXPERIMENTAL

For general experimental information see Part XIII.

Wolff–Kishner Reduction of 3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione* (I; R = Ac).—The diketone (50 g.), sodium hydroxide (43 g.), diethylene glycol (430 ml.), and 90—95% hydrazine hydrate (15·5 ml.) were heated so that the temperature was raised to 160° during 1 hr., and held at 160° for a further 2 hr. A little water and hydrazine hydrate distilled during the reaction. The product was isolated by gradual addition of water (*ca.* 2 l.) to the stirred mixture at *ca.* 100°, and filtration of the flocculent precipitate after cooling. The crude total product was dried and then acetylated for 15 min. in boiling acetic anhydride (250 ml.). Most of the anhydride was removed by distillation *in vacuo*, and the residue treated twice with methanol to remove the rest and twice with benzene, the solvent being removed each time *in vacuo*.

The crude oily acetate was chromatographed in benzene on alumina (Peter Spence, Type H; 750 g.). Elution with benzene and crystallisation from methanol gave 3β-acetoxyergost-22-en-11-one (II; R = Ac) (31·2 g., 64·3%), m. p. 123—125°, $[\alpha]_D$ +11·5°. Heusser *et al.*[1] give m. p. 125—126°, $[\alpha]_D$ +12·5°, and Chamberlin *et al.*[2] m. p. 129—131°, $[\alpha]_D$ +11·9°. After elution of uncrystallisable oils by ether–benzene, methanol eluted 3β-*acetoxyergost*-22-*en*-11-*one* 11-*acetylhydrazone*, which crystallised from methanol and then acetic acid as needles (4 g., 7·3%), m. p. 202—204°, $[\alpha]_D$ +71° (Found: C, 74·8; H, 10·1; N, 5·5. $C_{32}H_{52}O_3N_2$ requires C, 75·0; H, 10·2; N, 5·5%), $\lambda_{max.}$ (in EtOH) 217·5 mμ (ε 14,000), $\lambda_{infl.}$ 232—236 mμ (ε 10,500), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), 1730 and 1242 (OAc), 1666 (CO·NH), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Hydrolysis of the acetate for 18 hr. with boiling 10% aqueous-alcoholic potassium hydroxide gave the *alcohol* which crystallised from methanol or ethanol as needles, m. p. 216—218°, $[\alpha]_D$ +81° (Found: C, 76·4; H, 10·7; N, 5·7. $C_{30}H_{50}O_2N_2$ requires C, 76·5; H, 10·7; N, 6·0%), $\lambda_{max.}$ (in EtOH) 218 mμ (ε 13,500), $\lambda_{infl.}$ 234—236 mμ (ε 10,080), $\nu_{max.}$ (in CS_2) 3640 (OH), 3200, 1666, and 970 cm.$^{-1}$.

The alcohol was re-acetylated by acetic anhydride in pyridine at 100° to the acetate (III; R = Ac).

Formation of the Acetylhydrazone from 3β-*Acetoxyergost*-22-*en*-11-*one*.—3β-Acetoxyergost-22-en-11-one (4·0 g.), sodium hydroxide (3·5 g.), diethylene glycol (35 ml.), and hydrazine hydrate (4·0 ml.) were heated at 150° for 2 hr. The cooled solution, from which a small amount of white solid had separated, was diluted to *ca.* 400 ml. with water, and the precipitate was collected, washed with water, and dried. The crude product was acetylated at 100° for 20 min. in acetic anhydride (25 ml.) and pyridine (25 ml.), then evaporated *in vacuo*. The residue was chromatographed in benzene on alumina (Peter Spence, Type H; 30 g.). The benzene eluate contained unchanged starting material (3·2 g., 80%). Elution with 1 : 1 ether–methanol and crystallisation from acetic acid (10 ml.) gave the acetylhydrazone (III; R′ = Ac) as needles (0·34 g., 7·5%), m. p. 202—204°, $[\alpha]_D$ +70° (*c* 0·9), with an infrared spectrum identical with that of the nitrogenous by-product of the Wolff–Kishner reduction. A mixed m. p. was undepressed.

Acid Hydrolysis of 3β-*Acetoxyergost*-22-*en*-11-*one* 11-*Acetylhydrazone*.—(*a*) The acetylhydrazone (2·0 g.) was refluxed for 2 hr. in 80% alcohol (50 ml.) with concentrated sulphuric acid (5 ml.). The gummy product was isolated by precipitation with water and reacetylated with acetic anhydride in pyridine at 100°. The acetylating mixture was removed *in vacuo* and the residue chromatographed in benzene on alumina (Peter Spence, Type O; 30 g.). Elution

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[13] Barany, Braude, and Pianco, *J.*, 1949, 1898.

[14] Cohen, Bates, and Liebermann, *J. Amer. Chem. Soc.*, 1952, **74**, 3938.

with benzene and crystallisation from aqueous methanol gave 3β-acetoxyergost-22-en-11-one (II; R = Ac) as needles (50 mg., 2·8%), m. p. and mixed m. p. 118—121°. The infrared spectrum of the product showed that it was slightly impure.

(*b*) A mixture of the acetylhydrazone (2·0 g.), 90% pyruvic acid (6·0 g.), and sodium acetate (6·0 g.) in glacial acetic acid (60 ml.) was refluxed for 18 hr. The dark solution was poured into water (250 ml.), and the tarry product separated by filtration. A chloroform solution of the product was washed with water and dried (Na_2SO_4). The chloroform was removed *in vacuo*, and the residue purified as in (*a*), giving 3β-acetoxyergost-22-en-11-one as needles (100 mg., 5·6%), m. p. and mixed m. p. 117—122°, $[\alpha]_D$ +13°, slightly impure (infrared spectrum).

Cholestan-3-*one Azine*.—A solution of cholestanone (0·5 g.) in warm acetic acid (15 ml.) was treated with 90—95% hydrazine hydrate (1 ml.). The crystalline precipitate which was formed immediately was collected and washed with a little acetic acid. Crystallisation from 1 : 1 methanol–ethyl acetate (50 ml.) gave the *azine* as prisms, m. p. 222—226° (decomp.), $[\alpha]_D$ +63° (Found: C, 84·3; H, 11·9; N, 3·4. $C_{54}H_{92}N_2$ requires C, 84·4; H, 12·0; N, 3·6%), $\lambda_{max.}$ (in EtOH) 211·5 (ε 21,100) and 234 mμ (ε 5850), $\nu_{max.}$ (in CS_2) 1635 (C=N), and 1375 and 1360 cm.$^{-1}$ (CMe_2).

3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione* 7-*Azine*.—Reaction of 3β-acetoxyergost-22-ene-7 : 11-dione with hydrazine as in the preceding experiment and crystallisation of the crude product from ethyl acetate gave the 7-*azine* as needles, m. p. 300—305° (decomp.), $[\alpha]_D$ −230° (Found: C, 76·5; H, 9·6; N, 3·1. $C_{60}H_{92}O_6N_2$ requires C, 77·0; H, 9·9; N, 3·0%), $\lambda_{max.}$ (in EtOH) 213 mμ (ε 21,500), $\nu_{max.}$ (in CS_2) 1732 and 1240 (OAc), 1708 (CO), 1632 (C=N), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

When a similar mixture was heated at 100° for 2 hr. the azine redissolved and the product was unchanged starting material.

3β-*Hydroxyergost*-22-*ene*-7 : 11-*dione* 7-*Azine*.—Reaction of 3β-hydroxyergost-22-ene-7 : 11-dione with hydrazine as in the preceding experiments and crystallisation of the crude product from methanol gave the 7-*azine* as plates, m. p. 260—270° (decomp.), $[\alpha]_D$ −229° (Found: C, 79·0; H, 10·4; N, 3·7. $C_{56}H_{88}O_4N_2$ requires C, 78·9; H, 10·4; N, 3·3%), $\lambda_{max.}$ (in EtOH) 214·5 mμ (ε 20,000), $\nu_{max.}$ (in CS_2) 3630 and 1024 (OH), 1709 (CO), 1635 (C=N), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

Acetylation of the azine (1·0 g.) with acetic anhydride in pyridine at 100° and crystallisation of the product from ethyl acetate gave the 3β-acetoxy-7-azine as needles (0·9 g.), m. p. 315°, $[\alpha]_D$ −230°, with an infrared spectrum identical with that of the product of the previous experiment.

Acetone Acetylhydrazone.[10]—This had m. p. 138°, and showed $\lambda_{infl.}$ (in EtOH) at 210 mμ (ε 7900) and $\lambda_{max.}$ at 229·5 mμ (ε 10,700), $\nu_{max.}$ (in CS_2) 3200 (NH), 1668 (CO·NH), and 1386 and 1362 cm.$^{-1}$ (CMe_2).

Cholestan-3-*one Acetylhydrazone*.—(*a*) A solution of cholestanone (0·4 g.) and acethydrazide (0·4 g.) in alcohol (40 ml.) was refluxed for 30 min. The *acetylhydrazone* separated on cooling as needles (0·3 g.), m. p. 223—225°, $[\alpha]_D$ +30° (Found: C, 78·9; H, 11·2; N, 6·6. $C_{29}H_{50}ON_2$ requires C, 78·7; H, 11·4; N, 6·3%), $\lambda_{infl.}$ (in EtOH) 211—218 mμ (ε 9100), $\lambda_{max.}$ 234·5 mμ (ε 10,400), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), and 1666 cm.$^{-1}$ (CO·NH).

(*b*) A solution of cholestanone azine (500 mg.) in acetic anhydride (10 ml.) and pyridine (10 ml.) was heated at 100° for 30 min., then evaporated *in vacuo*, and the residue crystallised from methanol to give cholestanone acetylhydrazone as needles (170 mg.), m. p. 219—221°, $[\alpha]_D$ +30°, with an infrared spectrum identical with that of material prepared by method (*a*). The mother-liquors from the crystallisation gave a second crop on dilution with water, which, crystallised from aqueous methanol, gave cholestanone as prisms, m. p. 130—131°, $[\alpha]_D$ +40°, with an infrared spectrum identical with that of authentic material.

3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione* 7-*Acetylhydrazone*.—A solution of 3β-acetoxyergost-22-ene-7 : 11-dione (5·0 g.) and acethydrazide (3·5 g.) in ethanol (150 ml.) was refluxed for 16 hr., and water (5 ml.) was then added. The crystals which separated on cooling were collected, washed, and dried to give the crude product (4·0 g.), m. p. 240—250°. Recrystallisation from methanol gave the 7-*acetylhydrazone* as needles, m. p. 249—250°, $[\alpha]_D$ −180° (Found: C, 73·2; H, 9·2; N, 5·3. $C_{32}H_{50}O_4N_2$ requires C, 73·0; H, 9·6; N, 5·3%), $\lambda_{max.}$ (in EtOH) 217·5 (ε 11,900) and 234 mμ (ε 12,400), $\nu_{max.}$ (in CS_2) 3200 and 3100 (NH), 1732 and 1240 (OAc), 1708 (CO), 1666 (CO·NH), and 970 cm.$^{-1}$ (*trans*-1 : 2-disubstituted ethylene).

3β-*Acetoxyergost*-22-*ene*-7 : 11-*dione* 7-*Semicarbazone*.—A solution of the diketone (2·0 g.), semicarbazide hydrochloride (2·0 g.), and crystalline sodium acetate (2·0 g.) in alcohol (90 ml.) and water (10 ml.) was refluxed for 90 min. The product, which separated during the reaction, was collected, washed with aqueous alcohol, and recrystallised from aqueous alcohol, to give the 7-*semicarbazone* as needles (1·2 g.), m. p. 259—263° (decomp.), $[\alpha]_D$ −214° (Found : C, 70·8; H, 9·1; N, 7·9. $C_{31}H_{49}O_4N_3$ requires C, 70·6; H, 9·4; N, 8·0%), $\lambda_{max.}$ (in EtOH) 205 (ε 10,000) and 230·5 mμ (ε 13,000), $\nu_{max.}$ (in $CHBr_3$) 3550, 3400, 3200, 1678, and 1578 ($NH{\cdot}CO{\cdot}NH_2$), 1710 and 1250 (OAc), and 1700 cm.$^{-1}$ (CO).

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[*Received, May* 14*th*, 1956.]