291. *Triterpenoids. Part XI.* Some Stereospecific Reactions in the Lanostadienol (Lanosterol) Series.*

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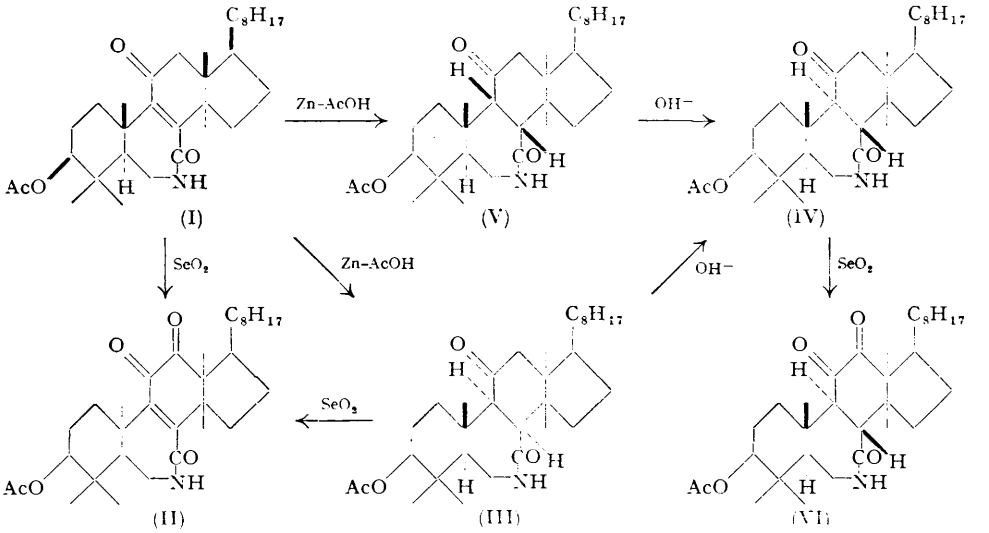
Reduction of 7 : 11-diketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate † by zinc dust and acetic acid affords both 8α : 9α- and 8β : 9β-7 : 11-diketo-6*a*-aza-B-homolanostan-3β-yl acetate. Both compounds are isomerised by alkali, to give, after re-acetylation, the corresponding 8β : 9α-isomer. The course of selenium dioxide oxidation of these and related compounds leads to the generalisation that ready conversion of ane-1 : 4-diones into ene-1 : 4-diones requires a *cis*-relation for the eliminated hydrogen atoms.

IN Part VII of this series (Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339; see also Falco, Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 2430) there is described the preparation of a number of nitrogenous derivatives of lanostadienol. In continuation of this work several observations of stereochemical interest have been made.

Oxidation of 7 : 11-diketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate † (I) with selenium dioxide gives the triketone (II) (Barnes *et al.*, *loc. cit.*), whereas reduction with zinc dust and acetic acid affords a saturated keto-amide, m. p. 184—185°. This is readily converted into (II) on selenium dioxide oxidation. The stereochemistry of this keto-amide is now regarded as 8α : 9α (III) on the basis of the following evidence. The zinc–acetic acid re-



duction of (I) also affords in minor amount a stereoisomeric amide, m. p. 284—286°. Both this amide and (III) are isomerised by methanolic potassium hydroxide to give, after re-acetylation, a further stereoisomer, m. p. 274—276°, which is the most stable of the four possible stereoisomers. Accordingly we formulate the isomer of m. p. 274—276° as the 8β : 9α-compound (IV) with a complete *trans-anti-trans* arrangement of asymmetric centres (cf. W. S. Johnson, *Experientia*, 1951, **7**, 315; *J. Amer. Chem. Soc.*, in the press).

Now whereas (III) is only isomerised slowly to (IV), the amide of m. p. 284—286° isomerises very rapidly (see Experimental section). It is logical therefore to regard the latter process as isomerisation at the α-position to the keto-group, and the former as isomerisation at the α-position to the amide function. On this basis the stereochemistry of

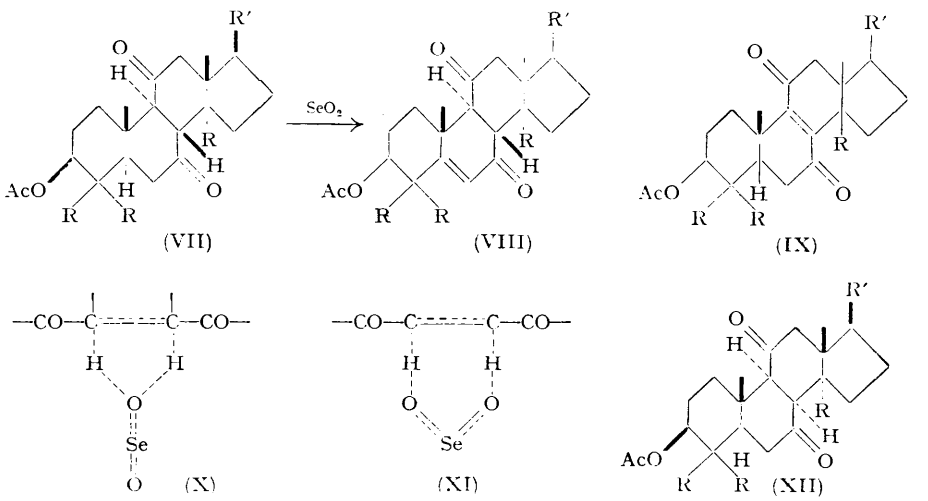
* Part X, *J.*, 1953, 576.

† We have now adopted steroid numbering for lanostadienol and its derivatives (cf. forthcoming paper by E. R. H. Jones, T. G. Halsall, and their collaborators). The adoption of steroid numbering also has the approval of Dr. J. F. McGhie.

(III) follows, and the amide, m. p. 284—286°, must be the 9-β-compound (V). The formation of the two amides (III) and (V) involves *cis*-addition of hydrogen. Such a stereochemical course for the reduction of ene-1 : 4-diones has already been exemplified (Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751) and may even be the normal mode of reduction, although frequently obscured by subsequent isomerisation to the more stable *trans*-form.

When the amide (IV) was subjected to selenium dioxide oxidation it gave in good yield 7 : 11 : 12-triketo-6*a*-aza-B-homolanostan-3β-yl acetate (VI). This reaction is in marked contrast with the course of the selenium dioxide oxidation of (III) (see above), where the double bond is readily reintroduced between $C_{(8)}$ and $C_{(9)}$. These observations, coupled with other considerations outlined below, lead us to the conclusion that the ready selenium dioxide oxidation of the system $-CO\cdot\overset{|}{C}H\cdot\overset{|}{C}H\cdot CO-$ is a stereospecific process in which the hydrogen atoms should be *cis* to each other.

Apart from the above-mentioned example, there are at least two other cases where the *trans*-stereochemistry of the hydrogen atoms of an ane-1 : 4-dione makes difficult selenium dioxide oxidation to an ene-1 : 4-dione. 7 : 11-Diketolanostanyl acetate (VII; R = Me, R′ = C_8H_{17}) gives 7 : 11-diketolanost-5-enyl acetate (VIII; R = Me, R′ = C_8H_{17}) (Dorée, McGhie, and Kurzer, *J.*, 1949, 570) and *not* 7 : 11-diketolanost-8-enyl acetate (IX; R = Me, R′ = C_8H_{17}). Similarly we have found that 7 : 11-diketoergostanyl acetate (VII; R = H,



R′ = C_9H_{19}) affords, although in poor yield, 7 : 11-diketoergost-5-enyl acetate (VIII; R = H, R′ = C_9H_{19}), and *not* 7 : 11-diketoergost-8-enyl acetate (IX; R = H, R′ = C_9H_{19}). Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) showed that whereas methyl 12 : 19-diketo-18α-oleananolate acetate was resistant to selenium dioxide oxidation, the stereoisomeric 18β-compound was readily oxidised. Such a difference in reactivity is in consonance with the present generalisation, for the 18α-compound has the $C_{(13)}$ and $C_{(18)}$ hydrogen atoms *trans*, and the 18β-compound has the *cis*-arrangement at these centres.

So far as the mechanism of the selenium dioxide oxidation is concerned the present results indicate that a molecular reaction with a cyclic transition state [(X) or (XI) or an equivalent] may be involved.

After the completion of our investigations as outlined above, Professor F. S. Spring, F.R.S., very kindly informed us of his preparation (with Budziarek; see *J.*, 1953, 956) of 7 : 11-diketo-8α-ergost-22-enyl acetate (XII; R = H, R′ = C_9H_{17}) by modified zinc dust reduction of 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate and related compounds. With Professor Spring's kind permission we have confirmed the reduction to (XII; R = H, R′ = C_9H_{17}) and have shown that, as expected, selenium dioxide oxidation (in ethanol solution) of the latter gives in excellent yield 7 : 11-diketo-

ergosta-8 : 22-dien-3β-yl acetate (IX; R = H, R′ = C_9H_{17}) with preferential *cis*-elimination of hydrogen. Under the same conditions 7 : 11-diketoergostan-3β-yl acetate was not attacked; it was even recovered unchanged after 24 hr. refluxing with an excess of selenium dioxide in ethanol.

Experimental

Unless specified to the contrary, rotations were determined in chloroform at room temperature and light-absorption maxima in ethanol.

For general experimental see Part VII (*J.*, 1952, 2339). Infra-red spectra were kindly determined by Dr. J. E. Page (of Glaxo Laboratories Ltd.) in carbon disulphide solution using a Perkin–Elmer double-beam instrument.

Reduction of 7 : 11-*Diketo*-6a-*aza*-B-*homolanost*-8-*en*-3β-*yl Acetate* (I).—The unsaturated amide (4 g.) was refluxed in " AnalaR " acetic acid (100 ml.), and zinc dust (5 g.) added during 1 hr. Chromatography over alumina (ether–benzene mixtures) afforded the 7 : 11-diketo-6*a*-aza-B-homo-8α-lanostan-3β-yl acetate (III) (3·5 g.), m. p. 184—185°, described in Part VII (*J.*, 1952, 2339). Crystallisation of the last (ether) eluted fractions from methanol afforded 7 : 11-*diketo*-6a-*aza*-B-*homo*-9β-*lanostan*-3β-*yl acetate* (V), m. p. 284—286°, $[\alpha]_D$ +70° (*c*, 1·07) (Found : C, 74·6; H, 10·15; N, 2·5. $C_{32}H_{53}O_4N$ requires C, 74·5; H, 10·35; N, 2·7%).

Alkaline Isomerisation of 7 : 11-*Diketo*-6a-*aza*-B-*homo*-8α- *and* -9β-*lanostan*-3β-*yl Acetate*.—The 8α-keto-amide (III) (600 mg.) in 10% methanolic potassium hydroxide was refluxed for 5 hr. The product was acetylated (pyridine–acetic anhydride at 100° for 30 min.). Recrystallisation from chloroform–methanol gave 7 : 11-*diketo*-6a-*aza*-B-*homolanostan*-3β-*yl acetate* (IV), m. p. 274—276°, $[\alpha]_D$ +4° (*c*, 2·20), +23° (*c*, 0·51 in MeOH; 2-dm. tube), $\lambda_{max.}$ 300 mμ (ε 60) (Found : C, 74·8; H, 10·3; N, 2·7. $C_{32}H_{53}O_4N$ requires C, 74·5; H, 10·35; N, 2·7%). Alkaline hydrolysis of the 9-β-keto-amide (V) followed by reacetylation gave the same product.

The 7 : 11-keto-amide acetate (IV) (100 mg.) was hydrolysed by refluxing 5% methanolic potassium hydroxide for 15 min. Crystallisation from benzene gave the *alcohol*, m. p. 138—145°, $[\alpha]_D$ −25° (*c*, 1·15), −15° (*c*, 1·03 in MeOH) (Found : C, 75·75; H, 10·65; N, 2·6. $C_{30}H_{51}O_3N$ requires C, 76·05; H, 10·85; N, 2·95%).

The rates of isomerisation of the above mentioned keto-amides were also determined on a more quantitative basis as follows. Methanolic potassium hydroxide (10·0 ml.; 5%) was added to the appropriate keto-amide (100 mg.), and the mixture rapidly brought to the b. p. At suitable time intervals (*t*, min.) the reaction was stopped by rapid cooling and the rotation determined. The following results were obtained : (III); t = 0, $[\alpha]_D$ +118° (*c*, 0·49; 2-dm. tube); t = 2, +100° (*c*, 1·00); t = 60, +97°; t = 180, +60°; t = 300, +50°; [using 10% potassium hydroxide t = 2, +99° (*c*, 1·00); t = 15, +82°; t = 180, +14°; t = 300, +7°, t = 600, −9°]. (V); t = 0, $[\alpha]_D$ +95° (*c*, 0·11; 4-dm. tube); t = 5, +11° (*c*, 1·00); t = 25, −10°; t = 60, −10°. (IV); t = 0, +20° (*c*, 0·54; 2-dm. tube); t = 15, −9° (*c*, 1·00); t = 60, −11°; t = 300, −11°.

Selenium Dioxide Oxidation of 7 : 11-*Diketo*-6a-*aza*-B-*homo*-8α-*lanostan*-3β-*yl Acetate* (III).—The keto-amide (III) (100 mg.) was refluxed with selenium dioxide (150 mg.) in " AnalaR " acetic acid (10 ml.) for 3 hr. After crystallisation from chloroform–methanol, the product was identified as 7 : 11 : 12-triketo-6*a*-aza-B-homolanost-8-en-3β-yl acetate (II) (Barnes, Barton, Fawcett, and Thomas, Part VII, *loc. cit.*) by m. p., mixed m. p., rotation, and absorption spectrum.

Selenium Dioxide Oxidation of 7 : 11-*Diketo*-6a-*aza*-B-*homolanostan*-3β-*yl Acetate* (IV).—The keto-amide (IV) (100 mg.) was refluxed with selenium dioxide (200 mg.) in " AnalaR " acetic acid for 2 hr. Crystallisation from chloroform–methanol gave 7 : 11 : 12-*triketo*-6a-*aza*-B-*homolanostan*-3β-*yl acetate* (VI), m. p. 262—263°, $[\alpha]_D$ −9° (*c*, 0·60), $\lambda_{inflex.}$ *ca.* 320 mμ (ε 85), $\lambda_{max.}$ 430 mμ (ε 75) (Found : C, 72·5; H, 9·7; N, 2·4. $C_{32}H_{51}O_5N$ requires C, 72·55; H, 9·7; N, 2·65%). It gave no colour with ferric chloride. On chromatography in benzene solution over alumina this compound (1·0 g.) afforded 7 : 12-*diketo*-11-*hydroxy*-6a-*aza*-B-*homolanost*-9(11)-*en*-3β-*yl acetate* (720 mg.). Recrystallised from chloroform–methanol this had m. p. 274—276°, $[\alpha]_D$ −63° (*c*, 1·08), $\lambda_{max.}$ 283 mμ (ε 9000) (Found : C, 72·6; H, 9·55; N, 2·75. $C_{32}H_{51}O_5N$ requires C, 72·55; H, 9·7; N, 2·65%). It gave an immediate intense ferric chloride reaction.

Hydrogenation of 7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate*.—The ane-dione (5 g.) was hydrogenated over platinum in ethyl acetate (700 ml.) and 60% perchloric acid (2 drops) (cf. Hershberg, Oliveto, Rubin, Staeudle, and Kuhlen. *J. Amer. Chem. Soc.*, 1951, **73**, 1144). After reoxidation with chromium trioxide in acetic acid, the 7 : 11-*diketoergostan*-3β-*yl acetate* (VII;

R = H, R′ = C_9H_{19}), crystallised from methanol, had m. p. 194—195°, $[\alpha]_D$ −12° (*c*, 1·20), $\lambda_{max.}$ 300 mμ (ε 70) (Found: C, 75·7; H, 10·05. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%).

Selenium Dioxide Oxidation of 7 : 11-*Diketoergostan*-3β-*yl Acetate*.—The ane-dione (VII; R = H, R′ = C_9H_{19}) (2 g.) was refluxed with selenium dioxide (1·5 g.) in acetic acid for 3 hr. The product was chromatographed from benzene over neutralised alumina. Crystallisation from light petroleum (b. p. 60—80°) gave 7 : 11-*diketoergost*-5-*en*-3β-*yl acetate* (VIII; R = H, R′ = C_9H_{19}), m. p. 183—185°, $[\alpha]_D$ −48° (*c*, 0·97), $\lambda_{max.}$ 234 mμ (ε 10,500) (Found: C, 76·75; H, 10·05. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). In the infra-red the compound showed carbonyl bands at 1735 and 1235 (acetate), 1710 (saturated ketone in six-membered ring), and 1678 $cm.^{-1}$ (αβ-unsaturated ketone in six-membered ring).

Selenium Dioxide Oxidation of 7 : 11-*Diketo*-8α-*ergost*-22-*en*-3β-*yl Acetate* (XII; R = H, R′ = C_9H_{17}).—The ane-dione (150 mg.), prepared from 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (Budziarek, Johnson, and Spring, *J.*, 1952, 3410) by the method of Budziarek and Spring (*loc. cit.*), was refluxed with selenium dioxide (100 mg.) in absolute ethanol (25 ml.) for 30 min. The precipitated selenium was filtered off and the product crystallised from chloroform–methanol, to give 7 : 11-diketoergosta-8 : 22-dien-3β-yl acetate, m. p. 136—138°, $[\alpha]_D$ +26° (*c*, 0·90), $\lambda_{max.}$ 270 mμ, (ε 9500) (cf. Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2107; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396).

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