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NITROUS ACID DEAMINATION OF 19-NORABIETA-8,11,13-TRIEN-4-AMINE[1]

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Abstract—The conversion of abieta-8,11,13-trien-19-oic acid I (R = COOH) to 19-norabieta-8,11,13-trien-4-amine I (R = NH_2) has been achieved in high yield. Nitrous acid deamination of the tertiary amine I (R = NH_2) gave a mixture of alkenes IV, V, VI together with a tertiary acetate I (R = OAc) and a tertiary alcohol I (R = OH). 18,19-Dinorabieta-8,11,13-trien-4-one II, a valuable intermediate in steroidal synthesis, was formed by oxidation of the alkene mixture with osmium tetroxide-sodium metaperiodate. The deamination products are discussed in the light of those products obtained from the nitrous acid deamination of other alicyclic systems.

SUITABLE precursors in the conversion of diterpenes to steroidal type compounds with potential pharmacological activity are those which possess a ketonic function at C-4.‡ Elaboration of the C-4 equatorial carboxyl group of dehydroabietic acid I (R = COOH) to a ketone has been previously carried out in varying success.[2–6] It was considered that nitrous acid deamination of 19-norabieta-8,11,13-trien-4-amine I (R = NH_2) might give rise to products suitable for the synthesis of 18,19-dinorabieta-8,11,13-trien-4-one II.

Of the methods available for the conversion of abietic acid III to abieta-8,11,13-trien-19-oic acid I (R = COOH),[7–15] the four-step synthesis of Jeger *et al.*[15] was found to be the most convenient. Purification of the acid I (R = COOH) was effected both by chromatography on silica gel and also by formation and subsequent halolysis of the methyl ester I (R = COOMe).

Although one would expect 19-norabieta-8,11,13-trien-4-amine I (R = NH_2) to be a suitable precursor for the elaboration of steroidal compounds, methods for its preparation in high-yields have been sparingly documented. Zeiss and Martin[4] state that action of mineral acids on the C-4 isocyanate I (R = NCO) gave unsatisfactory yields of the amine I (R = NH_2). While the Schmidt reaction[16] on the free acid I (R = COOH) gave considerable sulphonation of ring C[17], Stockel's[17] modification using polyphosphoric acid resulted in the formation of the amine I (R = NH_2) in 18·8% yield. Hofmann reaction[18] on the amide I (R = $CONH_2$) yielded a complex mixture, while hydrolysis of the carbamate I (R = NHCOOMe) gave the C-4 amino compound I (R = NH_2) in an overall yield of 50%.[17] In this present work, the

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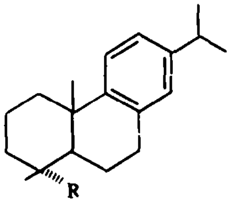
‡ Steroidal numbering system used throughout.

isocyanate I (R = NCO) was prepared by treatment of the acid chloride I (R = COCl) with sodium azide in acetone. Action of a cold ethereal solution of the isocyanate I (R = NCO) with 85% (w/w) sulphuric acid yielded the amine I (R = NH_2) in an overall yield of 66%.

Deamination of the tertiary amine I (R = NH_2) was carried out with saturated sodium nitrite at 4° for 24 hr and the product, on chromatography, yielded three compounds. The light petroleum eluates afforded a mixture of alkenes $C_{19}H_{26}$, b.p. 113–116°/0·01 mm, the NMR of which indicated the presence of: 19-norabieta-4(18), 8,11,13-tetraene IV (65%), 19-norabieta-3,8,11,13-tetraene V (26%) and 19-norabieta-4,8,11,13-tetraene VI (9%).



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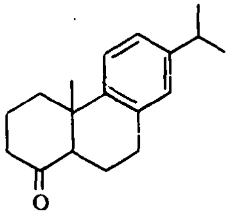

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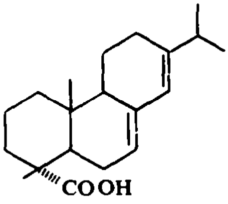

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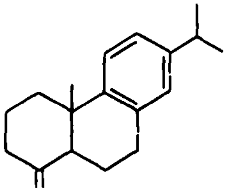
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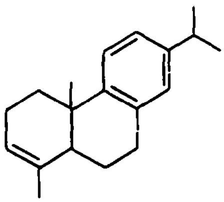
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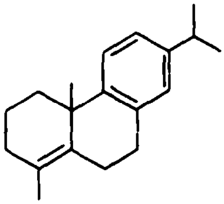
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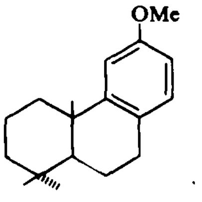
On elution with light petroleum-benzene (1:4), 19-norabieta-8,11,13-trien-4α-yl acetate I (*R* = OAc) was obtained as a non-crystallizable oil 6%. The assignment of the acetoxyl configuration was based upon the strong deshielding of the C-10 angular Me in the NMR, i.e. resonance occurs at 1·47 δ. This frequency can be compared with the normal values[19] of 1·15 δ (12-methoxypodocarpa-8,11,13-triene VII) and 1·18 (totarol VIII).[20] It has recently been shown[21] that 12-methoxy-16-norpodocarpa-8,11,13-trien-4α-yl acetate IX, which differs from 19-norabieta-8,11,13-trien-4α-yl acetate I (R = OAc) by the replacement of the C-12 OMe with a C-13 i-Pr group, gives rise to a signal in the NMR at 1·47 δ corresponding to the C-10 Me.

19 – Norabieta-8,11,13-trien-4α-ol I (R = OH) 10%, a viscous oil, was obtained on concentration of the benzene eluates. The 4α-ol configuration was deduced by



VII

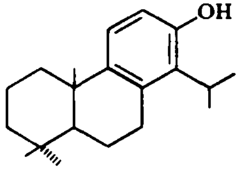
the chemical shift in the NMR of the C-10 Me peak. A 1,3-diaxial interaction of this Me and an OH group would have resulted in a marked deshielding as reported by Okamoto *et al.*[22] and Kawazoe *et al.*[23]

The C-4 ketone II, formed in high yield by OsO_4-sodium metaperiodate oxidation of the mixture of alkenes IV, V, VI was characterized by its IR and 2,4-dinitrophenylhydrazine derivative.

Studies into the nitrous acid deamination of cyclohexylamine,[24] aminodecalins,[25] and aminohydrindanes[26, 27] indicate that the reaction is conformationally specific:- in general equatorial amines yield equatorial alcohols with little or no olefin, while axial amines yield large amounts of olefin together with the equatorial alcohol. However, the work by Shoppee *et al.*[28, 29] on the deamination of aminosteroids, has disclosed an unexpected divergence from the above behaviour. Equatorial amines again give rise to the appropriate equatorial alcohol in almost quantitative yields but the axial amines display complete retention accompanied by elimination, with the major olefins being formed according not to the Hofmann rule, but to the Saytzeff rule.[30]

By contrast, *cis*-1-amino-*trans*-decalin and *trans*-2-amino-*trans*-decalin both yield 27% of the appropriate alcohol with inverted configuration and only 3% of that with retained configuration, accompanied by 70% olefins.

It has been suggested[28, 29] that this anomaly is due to the greater rigidity of the polycyclic steroid nucleus as compared with the decalin nucleus. Since this rigidity, which is reflected in both bond rotation and bond-angle deformation, is less in 19-norabieta-8,11,13-trien-4-amine I ($R = NH_2$) than in the steroidal amines, similar anomalous results might be expected in the deamination of this amine I ($R = NH_2$). Similarly, since the deamination of the C-4 amine I ($R = NH_2$) may be considered to proceed via the tertiary carbonium ion X, whilst that of the steroidal amines react via a secondary ion[31, 32] different resultant products might be anticipated.



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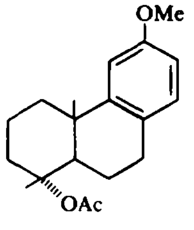

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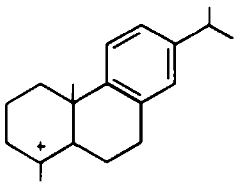

X

In this present work, the products obtained show little resemblance to those obtained from the deamination of the equatorial steroids. Instead of isolating the equatorial alcohol I ($R = OH$) in almost quantitative yield, the major product was a mixture of alkenes with the Hofmann elimination predominating. Preference for Hofmann product IV might indicate that the mechanism of alkene formation is a bimolecular mechanism,[30] whereas a unimolecular process would give rise to the Δ4 alkene VI as the major product. The formation of the 4α-alcohol I ($R = OH$) and the 4α-acetate I ($R = OAc$) may be explained by an attack of the nucleophile from the least hindered alpha side of the molecule.

It is concluded that the wide variety of products obtained from the deamination of 19-norabieta-8,11,13-trien-4-amine I (R = NH_2) is due to the greater stability of the tertiary carbonium ion X over that of the secondary carbonium ion which is found in the deamination of the aminosteroids. The results obtained further illustrate the difficulty in predicting the course of deamination of alicyclic systems.

EXPERIMENTAL

IR spectra were measured on a Perkin–Elmer Infracord spectrophotometer and optical rotations on a Jasco ORD/UV-5 Optical Rotation Recorder. NMR were measured on a Perkin–Elmer R14 spectrophotometer (100 Mc/s) with TMS as an internal reference and, unless otherwise stated, $CDCl_3$ as solvent. Analyses are by Drs. Weiler and Strauss Oxford. Deactivated alumina refers to 5% deactivation. Melting points were taken on a Kofler block apparatus and are uncorrected.

Methyl abieta-8,11,13-*trien*-19-*oic acid* I (R = COOMe). Methylation of the acid I (R = COOH, 28 g; m.p. 168–170° (Lit.[7] 171–172°), $[\alpha]_D^{20}$ +63°, (Lit.[33] $[\alpha]_D^{20}$ +62°)) with diazomethane (15 g) in cold (0°) ether (450 ml) gave the ester I (R = COOMe, 14·2 g, 49%) as rods from MeOH–ether m.p. 54–55° (Lit[2] 59–61°); ν_{max}^{film} 1745, 1250 cm^{-1} (ester, C=O); δ 1·19 (C-4 Me), 1·20, 1·27 (i-Pr), 1·24 (C-10 Me), 3·66 (COOMe), 6·80–7·25 (aromatics).

The methyl ester I (R = COOMe, 11·8 g) and LiI (36·7 g) in dry pyridine (26 ml) was heated under anhydrous conditions for 24 hr. The soln was concentrated to a solid mass, which, after treating with a mixture of ice (200 g) and 2N HCl (50 ml) was taken up in ether. Acidification of the basic extract of this latter phase gave the acid I (R = COOH, 10·4 g, 92%) as needles for MeOH m.p. 171–172°; $\nu_{max}^{CCl_4}$ 2500–3500 (acid, O—H), 1710 cm^{-1} (acid, C=O); δ 1·18, 1·24 (i-Pr), 1·20 (C-4 Me), 1·26 (C-10 Me), 6·80–7·30 (aromatics).

Alternatively, the crude acid I (R = COOH) obtained from the preparation of Jeger *et al.*[15] may be purified by silica gel chromatography with benzene as eluant.

19-*Norabieta*-8,11,13-*trien*-4-*isocyanate* I (R = NCO). PCl_5 (10·7 g) was reacted with the acid I (R = COOH, 10·7 g) at 80° for 1 hr to give the acid chloride I (R = COCl, 10·9 g, 97%) as a pale-yellow oil; ν_{max}^{film} 1800 cm^{-1} (acid chloride, C=O); δ 1·20, 1·26 (i-Pr), 1·22 (C-4 Me), 1·38 (C-10 Me), 6·85–7·35 (aromatics).

To the acid chloride I (R = COCl, 4·1 g) in acetone (15 ml) at 15° was added NaN_3 (1 g) in water (4 ml) and after stirring was continued for a further 30 min, the mixture was poured into water. The dried benzene extract was refluxed for 3 hr resulting in the formation of the C-4 isocyanate I (R = NCO, 3·5 g, 99%) as a yellow oil; ν_{max}^{film} 2290 cm^{-1} (N=C=O); δ 1·16 (C-4 Me), 1·20, 1·27 (i-Pr), 1·37 (C-10 Me), 6·83–7·35 (aromatics).

19-*Norabieta*-8,11,13-*trien*-4-*amine* I (R = NH_2). To a stirred soln of the isocyanate I (R = NCO, 6·3 g) in ether (64 ml) at 0° was added H_2SO_4 (85% w/w, 6·3 ml) dropwise during 1 hr. The mixture was diluted with water and the ether extracts discarded. Basification of the aqueous phase yielded the tertiary amine I (R = NH_2, 4·2 g, 73%) as a clear mobile oil; $\nu_{max}^{CCl_4}$ 3300, 1620 cm^{-1} (primary amine); δ 1·10 (C-4 Me), 1·18 (C-10 Me), 1·18, 1·25 (i-Pr) 6·85–7·30 (aromatics); picrate m.p. 218–220° (Lit.[17] 222–223°).

Nitrous acid deamination of 19-*norabieta*-8,11,13-*trien*-4-*amine* I (R = NH_2). Compound I (R = NH_2, 6·4 g) in 5% (v/v) aqueous AcOH (100 ml) at 4° was treated with $NaNO_2$ (1·8 g) in water (100 ml) at 4° for 24 hr. The reaction mixture was extracted with ether and washed to give a neutral oil (2·3 g) which was chromatographed on deactivated alumina. Elution with light petroleum afforded an alkene mixture as a clear oil (1 g, 45%) b.p. 113–116°/0·01 mm. (Found: C, 89·5, H, 10·5, $C_{19}H_{26}$ requires; C, 89·7, H, 10·3%); $\nu_{max}^{CS_2}$ 3100, 890 cm^{-1} (=CH_2); NMR in CCl_4 indicated the presence of 65% of 19-*norabieta*-4(18), 8,11,13-*tetraene* IV δ 0·98 (C-10 Me), 1·19, 1·25 (i-Pr), 4·58, 4·80 (C-4 =CH_2), 6·70–8·30 (aromatics), 26% of 19-*norabieta*-3,8,11,13-*tetraene* V δ 1·03 (C-10 Me), 1·19, 1·25 (i-Pr), 1·34 (C-4 Me), 5·38 (C-3 H), 6·70–8·30 (aromatcs) and 9% of 19-*norabieta*-4,8,11,13-*tetraene* VI δ 1·19, 1·25 (i-Pr), 6·70–8·30 (aromatics).

Further elution with light petroleum–benzene (1:4) gave I (R = OAc, 140 mg, 6%) as a pale-yellow oil which resisted purification because of concomitant elimination of the acetoxy function; $\sigma_{max}^{CS_2}$ 1745, 1250 cm^{-1} (ester, C=O), δ (CCl_4) 1·15, 1·24 (i-Pr), 1·25 (C-4 Me), 1·47 (C-10 Me), 1·88 (C-4 OCOMe), 6·70–7·35 (aromatics).

Concentration of the benzene washings resulted in the isolation of 19-*norabieta*-8,11-13-*trien*-4α-ol I (R = OH, 220 mg, 10%) as an oil b.p. 148–152°/0·005 mm. (Found: C, 83·6, H, 10·1, $C_{19}H_{28}O$ requires: C, 83·8, H, 10·4%); $\nu_{max}^{CS_2}$ 3450, 1130 cm^{-1} (alcohol, O – H); δ 1·13 (C-4 Me), 1·19, 1·25 (i-Pr), 1·21 (C-10 Me), 6·83–7·35 (aromatics). After standing at room temp for 3 months, the alcohol slowly crystallized m.p. 91·5–92·5° but its extreme solubility prevented further recrystallization.

Oxidation of alkene mixture. OsO_4 (10 mg) was added to a stirred soln of the alkenes (627 mg) dissolved in a mixture of dioxan (50 ml), water (15 ml) and AcOH (10 ml). A saturated aqueous soln of sodium metaperiodate (1·2 g) was added over 30 min and stirring continued for a further 21 hr. The reaction mixture was poured into water, the ether extract washed with base and the neutral soln concentrated to give II (460 mg, 75%) as a pale-brown oil purified by alumina chromatography with benzene as eluant. The IR ($\nu_{max}^{CCl_4}$ 1718 cm^{-1} (C=O)) was superimposable onto that recorded by Zeiss and Martin;[4] δ (CCl_4), 1·02 (C-10 Me), 1·21, 1·30 (i-Pr), 6·83–7·30 (aromatics).

The 2,4-dinitrophenylhydrazone had m.p. 94–96° (Lit.[4] 94–96°). δ 1·08 (C-10 Me), 1·21, 1·30 (i-Pr), 6·83–7·49 (aromatics).

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