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SESQUITERPENOIDS—IV

THE REACTION OF CYANIDE ION WITH SOME CONJUGATED KETONES IN THE EUDESMANE SERIES

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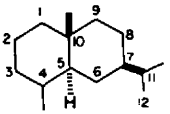
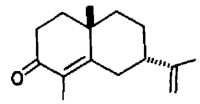
Abstract—The reactions of cyanide ion with (+)-7β(H)-eudesm-4,11-dien-3-one (II), (+)-eudesm-4,11-dien-3-one (XI), and (+)-eudesm-4,6-dien-3-one (XVI) are discussed.

THIS paper describes the reaction of cyanide ion with some unsaturated ketones in the eudesmane series. The nomenclature as in previous papers in this series[1] is based upon the eudesmane (I) with the absolute configuration shown.

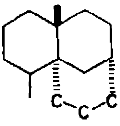
The reaction of cyanide ion with (+)-7β(H)-eudesm-4,11-dien-3-one (II) was investigated in the first place as a possible point of departure for the preparation of a series of tricyclic compounds with the basic carbon skeleton (III). For from the 5α-cyano-derivative of II it should be possible, by suitable chemical transformations both of the cyano-group and the 7α-isopropenyl group followed then by cyclization, to construct the new carbocyclic ring shown in III. However neither the ketone (II) nor its 11,12-dihydro-derivative reacted with cyanide ion under conditions which gave high yields of cyano-derivatives (or in certain cases the corresponding amides) from (+)-carvone (IV),[2] testosterone (V) and its acetate,[3] and the octalone (VI).[4]



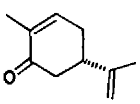
I



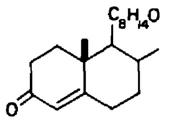
II



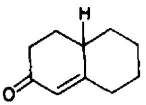
III



IV



V



VI

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[1] Part III, *Tetrahedron* **20**, 2593 (1964).

[2] C. Djerassi, R. A. Schneider, N. Vorbrueggen and N. L. Allinger, *J. Org. Chem.* **28**, 1632 (1963).

[3] A. Bowers, *J. Org. Chem.* **26**, 2043 (1961); A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.* **85**, 3223 (1963).

[4] W. L. Meyer and N. G. Schnautz, *J. Org. Chem.* **27**, 2011 (1962).

In fact no conditions were discovered under which any reaction would occur. This at first sight untoward result can be satisfactorily explained by taking account of the stereochemistry of the transition states which are involved in the attack of the cyanide ion at the β-carbon atom of the $\alpha\beta$-unsaturated ketone system in II.

Two preliminary points must be disposed of first. One, it is reasonable to suppose that in the transition state of the reaction between the nucleophilic cyanide ion and the conjugated enone system, the cyanide ion approaches the β-carbon atom of minimum electron density in either of the directions indicated in Fig. 1, for these are the directions in which bond formation can most easily develop.[5] It is from these directions perpendicular to the plane defined by C_β—C_α—C—O, that the cyanide ion can most effectively displace the π-electrons of the conjugated system towards the carbonyl oxygen atom.

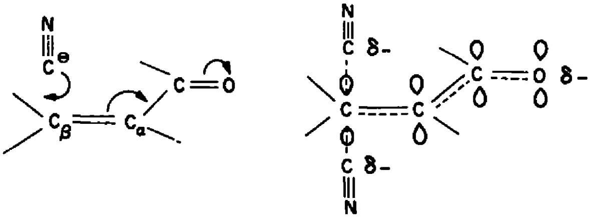


FIG. 1

The second point is that there is considerable evidence to show that the steric interactions of the axial 7α-isopropenyl or -isopropyl groups are severe, severe enough to affect both the chemistry and the physical properties of compounds in which they are present.[6,9] Accordingly, any transition state which involves an axial 7α-isopropenyl or -isopropyl group is likely to be energetically unfavourable.

The transition state involved in the 5α-attack of cyanide ion upon the ketone (II) can be represented by VII. In this, considerable interaction between the axially approaching cyanide ion and the 7α-isopropenyl group is bound to develop during the approach of the reagent and more particularly as bond formation occurs, and such interaction would be likely to render such a course for the reaction energetically unfavourable. The transition state (VIII) for a 5β-attack of cyanide ion is also energetically unacceptable since as bond formation develops, severe nonbonded interaction between the 7α-isopropenyl group and $C_{(4)}$ is bound to arise, the eventual product having the conformation IX. It might be thought that a 5β-attack of cyanide ion should be feasible on the grounds that the final product of such an attack could exist in the conformation X in which these severe steric interactions of the 7α-isopropenyl group have been eliminated. [Any *cis*-decalin system can in principle exist in two conformations, which in this case would correspond to the 5β-cyano group being axial with respect to ring A (IX) or axial with respect to ring B (X).] But whatever

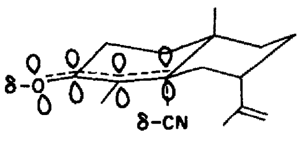
[5] Cf. G. Stork and S. D. Darling, *J. Amer. Chem. Soc.* **82**, 1512 (1960).

[6] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6377 (1956); D. W. Theobald, *Tetrahedron* **19**, 2261 (1963).

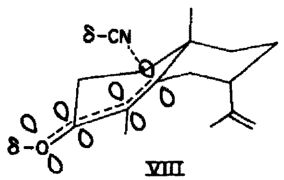
[7] W. Nagata, S. Hirai, H. Itakazi and K. Takeda, *J. Org. Chem.* **26**, 2413 (1961); *Liebigs Ann.* **641**, 184, 196 (1961).

[8] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (2nd Edition) p. 216, Methuen (1958).

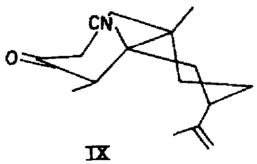
[9] F. J. McQuillin, *J. Chem. Soc.* 528 (1955); R. Howe and F. J. McQuillin, *Ibid.* 2423 (1955); 2671 (1956).



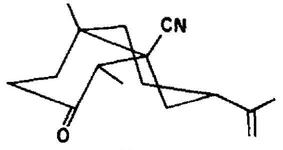
VII



VIII



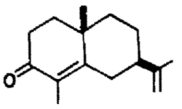
IX



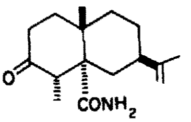
X

the thermodynamic stability of the final product, the transition state for a 5β-attack of cyanide ion resembles VIII and this is energetically unfavourable for the reasons already mentioned. Once bond formation is complete, that is, once the transition state has been passed, the product is free to assume the more stable conformation (X), and undoubtedly a 5β-cyano-derivative of the ketone (II) if it could be prepared, would exist in this conformation.[6] There therefore seems no wholly acceptable transition state for the reaction between cyanide ion and the ketone (II). And this it is suggested explains the failure of this ketone to react.

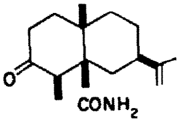
There is no difficulty on the other hand in forming acceptable transition states for



XI



XII



XIII

the reactions between cyanide ion and (+)-carvone (IV), testosterone (V), or the octalone (VI). And this should also be true of the ketone (XI), where the 7-isopropenyl group is β and equatorial. This ketone in fact reacts readily with cyanide ion under the usual conditions to give a mixture of the two amides (XII and XIII) in high yield. No trace of the corresponding nitriles which are presumably the initial products could be detected, and no conditions could be found to yield these nitriles.[7] Some similar results obtained in the reaction of cyanide ion with the octalone (VI) has led to the suggestion that the proximity of the carbonyl group at $C_{(3)}$ assists the hydrolysis of the initially introduced cyano-group in the way shown in Fig. 2.[4]

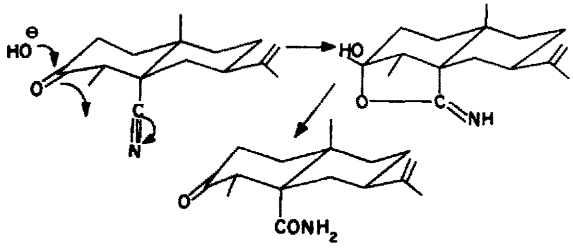
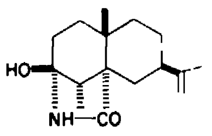
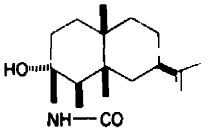


FIG. 2

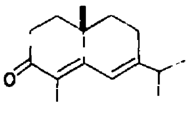
The IR spectra of these two compounds both in chloroform solution and as Nujol mulls show that they exist almost entirely in the hydroxy-lactam forms (XIV and XV).[4,7] Thus these spectra show: for (XIV), ν_{max} 3600 (free OH), 3450 (free NH), 3330 (bonded NH), 1695 (lactam C=O) cm^{-1}; and for (XV), ν_{max} 3600 (free OH), 3450 (free NH), 3350 (bonded NH), 1700 (lactam C=O) cm^{-1}. Further, neither spectrum shows the strong band in the region 1590–1620 cm^{-1} which is associated with primary amides, and which would be expected to be present if these compounds have the structures XII and XIII.[8]



XIV



XV

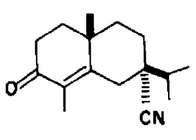


XVI

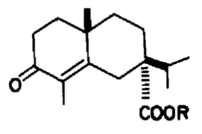
The fact that these compounds exist in the hydroxylactam forms (XIV and XV) complicates any attempt to establish the stereochemistry of the ring fusions by optical rotatory dispersion, for the existence of a Cotton effect depends upon the presence of the free carbonyl group at position 3. In fact the rotatory dispersion curves for these compounds are plain curves, a result which confirms the hydroxy-lactam structures (XIV and XV) proposed on the basis of the IR spectra. However, it seems reasonable to suppose that the major product from the reaction of cyanide ion with the ketone (XI), that with m.p. 221–222°, is the *trans*-amide (XII or XIV), while the minor product, m.p. 145–146°, is the *cis*-amide (XIII or XV). The precedents for this assignment can be found in the results of the reactions of cyanide ion with similar systems,[3,4,7] where the *trans*-isomer is known to predominate. And some direct support for such an assignment is obtained from a comparison of the plain rotatory dispersion curves of these compounds with the plain curves measured for the corresponding compounds derived from cholest-4-en-3-one in which the ring fusions are known.[7]

What is most significant in the present context however, is that these results with the ketone (XI) confirm the view that is it the α-orientation of the 7-isopropenyl group which prevents reaction of cyanide ion with the ketone (II).

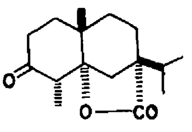
The reaction of cyanide ion with the ketone (XVI) takes place by attack on the less-hindered α-face of the molecule to give (+)-7α-cyano-eudesm-4-en-3-one (XVII). No amide was detected in the reaction product, reflecting perhaps the fact that in this case the carbonyl group at C$_{(3)}$ is in no position to assist the hydrolysis of the cyano-group. Moreover extensive chromatography failed to result in the isolation of the corresponding 7β-cyano-compound. The structure XVII follows from several



XVII



XVIII R=H; R=Me



XIX

observations. The UV spectrum (λ_{max} 251·5 mμ, $\varepsilon = 13700$) indicates the $\alpha\beta$-unsaturated ketone chromophore shown. Hydrolysis with sodium hydroxide gives the gummy acid (XVIII; R=H), characterized as its methyl ester (XVIII; R = Me). The acid (XVIII; R = H) on treatment with boron trifluoride etherate at 20° lactonizes smoothly to give the keto-lactone (XIX), m.p. 68–70°. The formation of such a compound is only likely if the acid (XVIII; R = H) and so the nitrile (XVII) have the structures and stereochemistry shown, the 7-cyano-group being α-oriented. The lactone (XIX), not unexpectedly, is very sensitive to aqueous acids and bases, and can not be obtained by acidifying an aqueous solution of the sodium salt of the acid (XVIII; R = H).

EXPERIMENTAL

M.ps are uncorrected. Specific rotations were determined for $CHCl_3$ solutions at room temp. UV spectra were measured for EtOH solutions on a Unicam SP 700. IR spectra were measured with Perkin–Elmer spectrophotometers PE-21 and Infracord 137 with NaCl prisms.

Alumina used for chromatography refers to Peter Spence's Grade H, deactivated with 5% of 10% acetic acid. Neutral alumina was prepared by treating Grade H with ethyl acetate for 7 days at room temp and then activating at 200° for 24 hr. Petroleum ether refers to the fraction, b.p. 60–80°, unless otherwise stated.

(+)-7β(H)-*Eudesm*-4,11-*dien*-3-*one* (II)

This ketone was prepared by the acid-catalysed dehydration of (−)-5β-hydroxy-4β,7β(H)-eudesm-11-en-3-one as described.[9] It was obtained as an oil, b.p. 125°/0·3 mm; n_D^{20} 1·5330; $[\alpha]_D$ +191° (*c*, 2·1). IR spectrum (natural film): ν_{max} 1670, 1610, 895 cm^{-1}. UV spectrum: λ_{max} 252 mμ (ε = 14000). Lit. records[9]: b.p. 91°/0·1 mm; n_D^{20} 1·5337; $[\alpha]_{5461}$ +210° (*c*, 3·5); λ_{max} 252 mμ (ε = 14100).

(+)-*Eudesm*-4,11-*dien*-3-*one* (XI)

The sample of this ketone used* had b.p. 94–97°/0·1 mm; n_D^{20} 1·5286; $[\alpha]_D$ +104° (*c*, 1·6). IR spectrum (natural film): ν_{max} 1675, 1615, 893 cm^{-1}. UV spectrum: λ_{max} 252 mμ (ε = 14500). Lit. records:[9] b.p. 96–97°/0·2 mm; n_D^{17} 1·5294; $[\alpha]_{5461}$ +115·4°.

The reaction of cyanide ion with the ketone (XI)

A solution of (+)-eudesm-4,11-dien-3-one (XI; 500 mg), KCN (1·1 g) and NH_4Cl (660 mg) in 90% EtOH (15 ml) was heated under reflux for 3 hr. The solid product (550 mg) was recovered by dilution with water and extraction with ether. Careful fractional crystallization from pet. ether–benzene (3:1) gave two products:

(i) (+)-3β-*hydroxy*-4β(H)-*eudesm*-11-*en*-5α-*carboxylic* (5α → 3α)-*lactam* (XIV) as needles (320 mg), m.p. 221–222°; $[\alpha]_D$ +18° (*c*, 2·4). IR spectrum (in $CHCl_3$): ν_{max} 3600, 3450, 3330, 1695, 1645, 895 cm^{-1}. RD in methanol (*c*, 0·5): $[\alpha]_{400}$ +17°, $[\alpha]_{333}$ +34°, $[\alpha]_{286}$ +110°, $[\alpha]_{250}$ +900°, $[\alpha]_{242}$ +1220° (Found: C, 72·8; H, 9·2; N, 5·2. $C_{16}H_{25}NO_2$ requires: C, 73·0; H, 9·5; N, 5·3%).

(ii) (+)-3α-*hydroxy*-4α(H)-*eudesm*-11-*en*-5β-*carboxylic* (5β → 3β)-*lactam* (XV) as needles (90 mg), m.p. 145–146°; $[\alpha]_D$ +12° (*c*, 2·7). IR spectrum (in $CHCl_3$): ν_{max} 3600, 3450, 3350, 1700, 1645, 893 cm^{-1}. RD in MeOH (*c*, 0·5): $[\alpha]_{400}$ +16°, $[\alpha]_{333}$ +18°, $[\alpha]_{286}$ 0°, $[\alpha]_{250}$ −262°, $[\alpha]_{233}$ −820° (Found: C, 72·6; H, 9·4; N, 5·3. $C_{16}H_{25}NO_2$ requires: C, 73·0; H, 9·5; N, 5·3%).

(+)-*Eudesm*-4,6-*dien*-3-*one* (XVI)

Compound II (1·5 g) was treated at 0° with H_2SO_4 (40 ml of 50% v/v), and the mixture kept at 5–10° for 5 hr. Dilution with water and extraction with ether gave an oil which was filtered in pet. ether-benzene (3:1) through alumina (60 g). Compound XVI was obtained as an oil (1·2 g), b.p. 110–115°/0·2 mm, n_D^{20} 1·5635, $[\alpha]_D$ +630° (*c*, 1·0). IR spectrum (natural film): ν_{max} 1665, 1640, 1600,

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* Obtained *via* the semicarbazone, m.p. 213–215°, from a sample of oil of natural origin very kindly supplied by Dr. S. Dev, National Chemical Laboratory, Poona, India.

1385, 1370 cm^{-1}. UV spectrum: λ_{max} 301 mμ (ϵ = 26300). Lit. records[9]: n_D^{20} 1·5632; $[\alpha]_{5461}$ +672°, +681°; λ_{max} 301 mμ(log ϵ = 4·44).

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate as crimson plates, m.p. 229–230°. Lit. records:[9] m.p. 230–231°.

(+)-*7α-Cyano-eudesm-4-en-3-one* (XVII)

A solution of XVI (1·0 g), KCN (2·2 g) and NH_4Cl (1·3 g) in 90% EtOH (25 ml) was heated under reflux for 4 hr. Dilution with water and extraction with ether gave an oily product which was absorbed on neutralized alumina (150 g). Elution with pet. ether–benzene (5:2; 150 ml) gave XVII as an oil (400 mg), n_D^{20} 1·5629, $[\alpha]_D$ +155° 155 (*c*, 3·1). IR spectrum (natural film): ν_{max} 2260, 1670, 1645 cm^{-1}. UV spectrum: λ_{max} 251·5 mμ (ϵ = 13700) (Found: C, 78·1; H, 9·1; N, 5·6. $C_{16}H_{23}NO$ requires: C, 78·4; H, 9·4; N, 5·7%).

Further elution with the same solvent (150 ml) gave fractions (110 mg) consisting of a mixture of the cyano-compound (XVII) and starting material (XVI), and yet further elution (200 ml) fractions consisting of pure starting material (380 mg).

(+)-*7α-Carbomethoxy-eudesm-4-en-3-one* (XVIII; R = Me)

A solution of XVII (500 mg) and NaOH (500 mg) in EtOH (5 ml) and water (3 ml) was heated under reflux for 3 hr in a N_2 atm. Dilution with water and extraction with ether gave unchanged starting material (XVII; 160 mg). Acidification of the aqueous phase and extraction with ether gave *the acid* (XVIII; R = H) as a gum (300 mg), $[\alpha]_D$ +154° (*c*, 1·6). IR spectrum (in $CHCl_3$): ν_{max} 1710, 1665, 1640 cm^{-1}. This acid could not be purified sufficiently for satisfactory analysis.

The *methyl ester* (XVIII; R = Me) prepared by methylation with diazomethane was eluted from alumina by pet. ether–benzene (3:1) as an oil, b.p. 125–130°/0·2 mm (bath), n_D^{20} 1·5600, $[\alpha]_D$ +135° (*c*, 2·9). IR spectrum (natural film): ν_{max} 1745, 1665, 1640, 1240 cm^{-1}. UV spectrum: λ_{max} 251 mμ (ϵ = 12900) (Found: C, 73·2; H, 9·3. $C_{17}H_{26}O_3$ requires: C. 73·4; H, 9·4%).

The lactonization of the acid (XVIII; R = H)

A solution of the acid (XVIII; R = H; 300 mg) in anhydrous benzene (10 ml) was treated with BF_3 etherate (1 ml), and the mixture kept at 20° for 30 min. The solvents were removed *in vacuo* leaving a pasty residue which crystallized from pet. ether (b.p. 30–40°) to give (+)-*3-oxo-4β(H)-eudesman-7α-carboxylic* (*7α → 5α*)*-lactone* (XIX) as prisms (230 mg), m.p. 68–70°, [α] +6° (*c*, 3·9). IR spectrum (in Nujol): ν_{max} 1775, 1700 cm^{-1} (Found: C, 72·6; H, 9·0. $C_{16}H_{24}O_3$ requires: C, 72·7; H, 9·1%).

Acknowledgments—The author is grateful to W. J. Bush & Co. Ltd. for a gift of (+)-carvone from which most of the starting materials for these investigations were prepared, and to Professor W. Klyne and Dr. M. Scopes for the rotatory dispersion measurements.