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INVESTIGATIONS ON THE SYNTHESIS OF OESTRONE[*]

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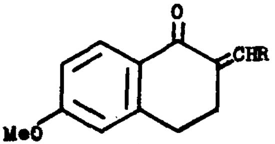
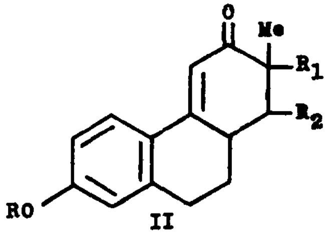
The recent publication of a dissertation abstract[1] prompts us to place on record the work done on similar lines in our laboratory.



I

- a, R = CO_2H
- b, R = CO_2Me
- c, R = CH_2CO_2Me
- d, R = $(CH_2)_2.CO_2Me$



II

- a, R = Me, R_1 = CN, R_2 = CO_2Me
- b, R = Me, R_1 = CN, R_2 = CO_2H
- c, R = Me, R_1 = CN, R_2 = $(CH_2)_2.CO_2Me$
- d, R = Me, R_1 = CN, R_2 = $(CH_2)_2.CO_2H$
- e, R = R_1 = H, R_2 = CO_2H
- f, R = Me, R_1 = H, R_2 = CO_2Me
- g, R = Me, R_1 = H, R_2 = CO_2H
- h, R = Me, R_1 = CN, R_2 = CH_2COOMe

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[*] All melting points are uncorrected. Presented at the Council of Scientific & Industrial Research Convention held at Aligarh, India, in December 1965.

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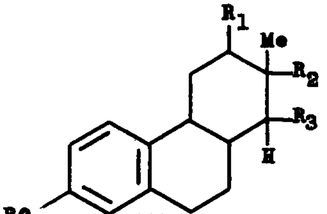
6-Methoxytetralone was condensed[2] with glyoxalic acid in presence of aqueous alcoholic sodium hydroxide to furnish 1-keto-6-methoxy-2-tetralideneacetic acid (Ia) (62%), m.p. 176-178° (vac.). The methyl ester (Ib), m.p. 86-88°; UV λ_{max}^{EtOH} 244 mμ ϵ 10,230, 320 mμ ϵ 14,130; IR $\nu_{max}^{CHCl_3}$ 1724 cm^{-1}, 1669 cm^{-1}, 1639 cm^{-1}, 1613 cm^{-1}, on condensation with α-methylacetoacetonitrile in presence of potassium *t*-butoxide in *t*-butanol gave a mixture (49%) of two isomeric tricyclic cyano-keto-esters (IIa), m.p. 202-204° and m.p. 206-208°, in the ratio 4:1 respectively; UV λ_{max}^{EtOH} 249 mμ ϵ 11,750, 341 mμ ϵ 43,650; IR $\nu_{max}^{CHCl_3}$ 2273 cm^{-1}, 1739 cm^{-1}, 1667 cm^{-1}, 1639 cm^{-1}, 1613 cm^{-1}, with considerable difference in the finger-print region of the two spectra. Condensation of the unsaturated keto-acid (Ia) with the same β-keto-nitrile in an aqueous alkaline medium afforded in relatively higher yield a mixture of isomers of the cyano-keto-acid (IIb) corresponding to the isomers of IIa in 10:1 ratio. The preponderant isomer of IIb, m.p. 222-224° (vac.); UV λ_{max}^{EtOH} 244 mμ ϵ 9,445, 336 mμ ϵ 51,850; IR ν_{max}^{KBr} 3460 cm^{-1}, 2273 cm^{-1}, 1712 cm^{-1}, 1669 cm^{-1}, 1639 cm^{-1}, 1613 cm^{-1} could be prepared in one step from 6-methoxytetralone by treating the bicyclic keto-acid (Ia), formed in the Claisen condensation, *in situ* with the β-keto-nitrile.

The phenanthrene skeleton of II was proved by converting the preponderant isomer of IIb, *via* the phenolic keto-acid (IIe), m.p. 280-282° (vac.), the methoxy keto-ester (IIf), m.p. 143-145°;

UV λ_{max}^{EtOH} 244 mμ ε 10,720, 331 mμ ε 27,540; IR $\nu_{max}^{CHCl_3}$ 1721 cm^{-1}, 1664 cm^{-1}, 1626 cm^{-1}, 1613 cm^{-1}, and the diol (IV), m.p. 173-174°, to the known 1,2-dimethyl-7-methoxyphenanthrene by successive treatment with hydrobromic-acetic acid, potassium carbonate and dimethyl sulphate, lithium-aluminium-hydride in monoglyme and selenium at 330° in a sealed tube. The methyl ester (IIa) of the other isomer of the cyano-keto-acid (IIb) on treatment with hydrobromic-acetic acid followed by methylation and esterification furnished the same unsaturated keto-ester (IIf).



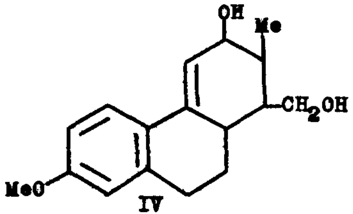
III

a, R = Me, R_1 = OH, R_2 = CN, R_3 = CO_2Me
b, R = Me, R_1 = Cl, R_2 = CN, R_3 = CO_2Me
c, R = Me, R_1 = H, R_2 = CN, R_3 = CO_2Me
d, R = Me, R_1 = H, R_2=CN, R_3 = CO_2H
e, R = R_1 = H, R_2 = R_3 = CO_2H
f, R = Me, R_1 = H, R_2 = R_3 = CO_2Me
g, R = Me, R_1 = H. R_2 = R_3 = CH_2OH
h, R = Me, R_1 = OH, R_2 = H, R_3 = CO_2Me
i, R = Me, R_1 = OH, R_2 = CN, R_3 = $(CH_2)_2COOMe$
j, R = Me, R_1 = H, R_2 = $CONH_2$, R_3 = $(CH_2)_2CO_2Me$
k, R = Me, R_1 = Cl, R_2 = CN, R_3 = $(CH_2)_2CO_2Me$

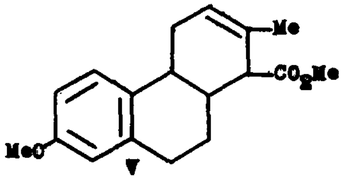
Study of the catalytic hydrogenation, with various catalysts, of the conjugated ketone system present in II, initially with the unsaturated keto-ester (IIf), showed that both the ethylenic linkage and the keto group were invariably simultaneously hydrogenated to yield a mixture of two isomeric IIIh, m.p. 149-150°; UV λ_{max}^{EtOH} 278 mμ ϵ 1,995; IR $\nu_{max}^{CHCl_3}$ 3774 cm^{-1}, 1739 cm^{-1}, 1600 cm^{-1}, 1010 cm^{-1}, and m.p. 109-110°; UV λ_{max}^{EtOH} 277.5 mμ ϵ 2,050; IR $\nu_{max}^{CCl_4}$ 3448 cm^{-1}, 1739 cm^{-1}, 1608 cm^{-1}, 1020 cm^{-1}, almost in equal proportion. Axial and equatorial conformations of the hydroxyl groups of the two isomers of IIIh were proved by their oxidation with Jones' reagent[3] to two keto-esters, m.p. 130-131° and 124-125°, in 75% and 15% yields and by the formation of 3,5-dinitrobenzoates, m.p. 235-237° (vac.) and m.p. 263-264° (vac.), in 20% and 80% yields respectively; formation of two different keto-esters by oxidation showed that the two isomers differed also in their configurations at the ring fusion. The trans-ring fusion and the equatorial hydroxyl in the isomer, m.p. 109-110°, were proved by its obtention from the unsaturated keto-acid (IIg), m.p. 254-256° (vac.), by treatment with sodium-in-liquid ammonia followed by esterification with diazomethane. Consequently, the higher melting isomer has been assigned the cis-ring fusion.

Hydrogenation of IIa, m.p. 202-204°, in presence of Pd-$SrCO_3$ catalyst, however, afforded a single hydroxy-cyano-ester (IIIa), m.p. 169-170°; UV λ_{max}^{EtOH} 278 mμ ϵ 1,995, 286 mμ ϵ 1,738; IR $\nu_{max}^{CHCl_3}$ 3774 cm^{-1}, 2273 cm^{-1}, 1730 cm^{-1}, 1613 cm^{-1}, 1015 cm^{-1}, in quantitative yield; formation of the 3,5-dinitrobenzoate (83%), m.p. 241-242° (vac.), and recovery of the unchanged product on treating it with Jones' reagent[3] indicated an equatorial hydroxyl. Catalytic hydrogenation of the other isomer, m.p. 206-208°, gave a different crystalline isomer of IIIa, m.p. 189-190°; UV λ_{max}^{EtOH} 278 mμ ε 1,950, 286 mμ ε 1,778; IR $\nu_{max}^{CHCl_3}$ 3774 cm^{-1}, 3448 cm^{-1}, 2273 cm^{-1}, 1748 cm^{-1}, 1613 cm^{-1}, along with a gum, thin layer chromatography of the latter showing the presence of another isomer.

The hydroxy-cyano-ester (IIIa), m.p. 169-170°, on refluxing with phosphorous oxychloride and pyridine furnished the chloro-cyano-ester (IIIb) (61%), m.p. 152-154°; IR $\nu_{max}^{CCl_4}$ 2273 cm^{-1}, 1748 cm^{-1}, 1613 cm^{-1}. Dechlorination of IIIb with zinc and formic acid afforded the cyano-ester (IIIc) (62%), m.p. 142-143°; UV λ_{max}^{EtOH} 278 mμ ε 1,525, 286 mμ ε 2,171; IR $\nu_{max}^{CHCl_3}$ 2273 cm^{-1}, 1730 cm^{-1}, 1613 cm^{-1}, and the unsaturated ester (V) (14%), m.p. 87-88.5°; UV λ_{max}^{EtOH} 278 mμ ε 1,585, 286 mμ ε 1,995; IR ν_{max}^{nujol} 1739 cm^{-1}, 1650 cm^{-1}, 1613 cm^{-1}, 800 cm^{-1}. Selective saponification of IIIc furnished the cyano-acid (IIId) (83%), m.p. 201-202° (vac.); IR $\nu_{max}^{CHCl_3}$ 3704 cm^{-1}, 3226 cm^{-1}, 2273 cm^{-1}, 1739 cm^{-1}, 1704 cm^{-1}, 1613 cm^{-1}. All attempts to homologate



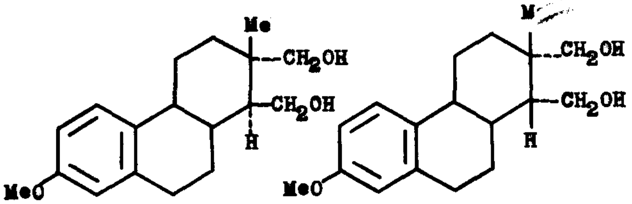
IV



V

the carboxyl group in IIId were unsuccessful.

Two optically active isomers of the diol (IIIg), obtained by the degradation of oestrone, were made available by



G. D. Searle & Co[*]. With a view to finding out whether the configuration of the cyano-ester (IIIc) conformed to that of any one of these isomers, it was converted to the diol (IIIg), m.p. 166-167°, via the phenolic diacid (IIIe), m.p. 198-200° (vac.), and the methoxy-diester (IIIf), m.p. 125-127°, in the usual manner. Comparison of IR spectra in chloroform showed the configuration of the synthetic diol to be different from those of the two isomers.

Failure of homologation experiment with the cyano-acid (IIId) led us to investigate the preparation of higher homologues (Ic and Id) of the bicyclic compound (Ib). Arndt-Eistert reaction with Ia furnished the unsaturated keto-ester (Ic) (8.5%), m.p. 81-83°; UV λ_{max}^{EtOH} 222.5 mμ ϵ 14,640, 284 mμ ϵ 17,400; IR ν_{max}^{nujol} 1718 cm^{-1}, 1667 cm^{-1}, 1613 cm^{-1}. Michael condensation of Ic with α-methylacetoacetonitrile, however, was not successful. The desired tricyclic unsaturated keto-cyano-ester (IIh), m.p. 162-164°, could be prepared by homologating the acid

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(IIb), but in extremely poor yield (4%).

The homologue (Id) (68%), b.p. 198-200°/5 x 10^{-4} m.m; UV λ_{max}^{EtOH} 232 mμ ε 9,987, 305 mμ ε 14,740; IR $\nu_{max}^{CCl_4}$ 1745 cm^{-1}, 1681 cm^{-1}, 1634 cm^{-1}, 1610 cm^{-1}, was prepared by heating 6-methoxytetralone with a methanolic solution of methyl β-aldehydopropionate containing a trace of hydrogen chloride in a sealed tube[4] ; a failure to effect this condensation under basic conditions was earlier reported in literature[5]. Condensation of Id with the β-ketonitrile yielded a mixture of a cyano-keto-ester (IIc), m.p. 133-134°; UV λ_{max}^{EtOH} 234 mμ ε 20,990, 340 mμ ε 24,340; IR ν_{max}^{nujol} 2247 cm^{-1}, 1745 cm^{-1}, 1667 cm^{-1}, 1626 cm^{-1}, 1600 cm^{-1}, and a cyano-keto-acid (IId), m.p. 214-215°; UV λ_{max}^{EtOH} 245 mμ ε 9886, 339 mμ ε 20,280; IR ν_{max}^{nujol} 3425 cm^{-1}, 2252 cm^{-1}, 1733 cm^{-1}, 1667 cm^{-1}, 1639 cm^{-1}, 1613 cm^{-1}; the latter on treatment with diazomethane gave a different isomer of IIc, m.p. 137-138°; UV λ_{max}^{EtOH} 247 mμ ε 10,720, 338 mμ ε 29,510; IR ν_{max}^{nujol} 2268 cm^{-1}, 1754 cm^{-1}, 1681 cm^{-1}, 1626 cm^{-1}, 1600 cm^{-1}. Hydrogenation of IIc, m.p. 133-134°, in presence of Kuhn's catalyst[6] yielded a mixture of a crystalline hydroxy-cyano-ester (III i) (35%), m.p. 79-80°, 114-115° and 141-142° (polymorphs); UV λ_{max}^{EtOH} 279 mμ ε 1,772; IR ν_{max}^{nujol} 3650 cm^{-1}, 2247 cm^{-1}, 1724 cm^{-1}, 1610 cm^{-1} and a gum (60%), UV λ_{max}^{EtOH} 279 mμ ε 1782; IR ν_{max}^{smear}

3626 cm^{-1}, 2268 cm^{-1}, 1730 cm^{-1}, 1726 cm^{-1}, 1613 cm^{-1}. Oxidation of the aforementioned crystalline hydroxy compound with Jones' reagent[3] to give the corresponding keto-cyano-ester (85%), m.p. 119-120°; semicarbazone (90%), m.p. 218-219° (decomp.); UV λ_{max}^{EtOH} 230 mµ ϵ 26,850, 278 mµ ϵ 2,891, and the failure to form a 3,5-dinitrobenzoate indicated an axial hydroxyl. The above semicarbazone on heating with potassium _t_-butoxide in toluene gave the amide-acid (III j), m.p. 209-210°; UV λ_{max}^{EtOH} 279 mµ ϵ 2,550; IR ν_{max}^{nujol} 3571 cm^{-1}, 3425 cm^{-1}, 1704 cm^{-1}, 1634 cm^{-1}, 1613 cm^{-1}, in low yield. Hydrogenation of IIc, m.p. 137-138°, with Kuhn's catalyst[6] afforded another crystalline isomer of the hydroxy-cyano-ester (III i) (90%), m.p. 150-151°; UV λ_{max}^{EtOH} 279 mµ ϵ 1,795; IR ν_{max}^{nujol} 3636 cm^{-1}, 2257 cm^{-1}, 1724 cm^{-1}, 1613 cm^{-1}; the ready formation of a 3,5-dinitrobenzoate (85%), m.p. 191-192°, indicated equatorial hydroxyl. Treatment of III i, m.p. 150-151°, with phosphorous oxychloride and pyridine furnished the chloro-cyano-ester (III k) (56%), m.p. 108-109°; IR ν_{max}^{nujol} 2257 cm^{-1}, 1726 cm^{-1}, 1613 cm^{-1}. Attempts to dechlorinate III k has so far not been successful.

Elemental analyses of all compounds, described in this article, agreed with their respective assigned structures.

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