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Synthesis of 4*a*-Formyl-1,2,3,4,4*a*,10-hexahydrophenanthrene. A New Method for Angular Formylation

The abnormal Reimer–Tiemann reaction[1] for alicyclic phenols has been utilized for the reaction introducing an angular dihalogenomethyl group which may be converted into a methyl group.[2] Now, we wish to report that an angular dibromomethyl group introduced into 1,1-dimethyl-1,2,3,4-tetrahydrophenanthren-9-ol (I) by the reaction can be converted into an angular formyl group.

The dropwise addition of bromoform to a solution of I in 15% aqueous sodium hydroxide at about 80° gave 4*a*-dibromomethyl-1,1-dimethyl-1,2,3,4,4*a*,9-hexahydro-9-oxo-phenanthrene (II),[3] mp 146—148°, IR ν_{max}^{KBr} 1655 cm^{-1}, UV $\lambda_{max}^{ethanol}$ mμ (ε): 236 (899), 256 (4910), NMR ($CDCl_3$) τ: 3.29 (1H, singlet), 3.50 (1H, singlet). The catalytic reduction of II over 10% palladium-carbon in ethanol at room temperature gave the bromoxycyclopropyl ketone (III),[4] mp 128—130°, $C_{17}H_{19}OBr$, IR ν_{max}^{KBr} 1672 cm^{-1}, NMR ($CDCl_3$) τ: 6.32 (1H, singlet, $\underline{H}\triangle Br$), 7.17 (2H, singlet, C-10 CH_2), in 70% yield. The following data are entirely consistent with the presence of a cyclopropane ring in III. Reduction of III with sodium borohydride in boiling methanol produced the alcohol (IV), mp 134°, $C_{17}H_{21}OBr$, IR ν_{max}^{KBr} 3400 cm^{-1}, NMR ($CDCl_3$) τ: 6.14 (1H, singlet, $\underline{H}\triangle Br$), in a good yield. Hydrogenolysis of the bromine atom on the cyclopropane ring of IV with sodium in boiling propanol gave the cyclopropane alcohol (V), an oil, whose NMR spectrum showed a pair of doublets centered at 9.32 τ and 9.06 τ (J=3.5 cps) which were assigned to characteristic signals of geminal cyclopropyl protons.

The treatment of IV with ethanolic hydrogen chloride afforded quantitatively the bromocyclopropyl olefin (VI), mp 83.0—83.5°, $C_{17}H_{19}Br$, NMR ($CDCl_3$) τ: 6.37 (1H, singelt, $\underline{H}\triangle Br$), 4.00 (1H, doublet, J=13 cps), 3.29 (1H, doublet, J=13 cps). This olefin VI was catalytically hydrogenated and subsequently treated with sodium in boiling propanol to give an oily hydrocarbon (VII), NMR ($CDCl_3$) τ: 9.23; 9.08 (1H; 1H, doublet; doublet, J=5 cps; 5 cps, $H\triangle H$). The same hydrocarbon was obtained by the prolonged treatment of IV with sodium in propanol.

In order to convert the cyclopropyl bromide into the aldehyde group,[5a] a successful route implies the solvolysis of cyclopropyl bromide and a ring opening with a double-bond migration. Hydrolysis of the bromocyclopropyl olefin (VI) in aqueous dioxan containing potassium iodide and potassium carbonate at 110° gave the aldehyde (VIII), mp 90.5—91.5°, $C_{17}H_{20}O$, IR ν_{max}^{KBr} cm^{-1}: 2800, 2700, 1725, 1670, NMR ($CDCl_3$) τ: 6.48 (2H, doublet, J=4.5 cps, C-9 CH_2), 3.83 (1H, triplet, J=4.5 cps, >C=C<$\underline{H}$), 0.72 (1H, long ranged coupled doublet, J<1 cps, ⋗C-C$\underline{H}$O) in about 20% yield. Acetolysis of VI in acetic acid in the presence of silver acetate gave in an excellent yield the acetoxy-cyclopropyl olefin (IX), mp 87.5—89.0°, $C_{19}H_{22}O_2$, IR ν_{max}^{KBr} 1738 cm^{-1}, NMR ($CDCl_3$) τ: 8.35 (3H, singlet, $C\underline{H}_3CO-O\overset{H}{\triangle}$), 5.72 (1H,

1) K. Auwers and G. Heil, *Chem. Ber.*, **35**, 4207 (1902).
2) R.B. Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940).
3) M.S. Gibson, *J. Chem. Soc.*, **1961**, **2251**.
4) T.D.J. D'silva and H. Ringold, *Tetrahedron Letters*, **1965**, 4487.
5) *a*) J.A. Landgrebe and L.W. Becker, *J. Am. Chem. Soc.*, **89**, 2505 (1967). *b*) C.H. DePuy, F.W. Breibeit and K.B. DeBruin, *ibid.*, **88**, 3347 (1966).

singlet, $CH_3CO-O\overset{H}{-}$◁, 4.20 (1H, doublet, J=11 cps), 3.12 (1H, doublet, J=11 cps). By the treatment of IX with potassium hydroxide in methanol, the aldehdye (VIII) was obtained in a quantitative yield. The structure of VIII was confirmed as follows. The catalytic reduction of VIII over platinum oxide in glacial acetic acid with warming gave only one saturated aldehyde (X), mp 100—103°, $C_{17}H_{22}O$, IR ν_{max}^{KBr} cm^{-1}: 2840, 2740, 1705. The Wolff-Kischner reduction of X yielded the hydrocarbon (XI), which was identified as A/B *trans*-fused podocarpatriene by comparing its NMR spectrum with that of a sample synthesised by Fetizon.[6]

Fthanolysis of VI with sodium ethoxide in ethanol afforded only the ethoxy-cyclopropyl olefin (XII), an oil, Mass Spectrum *m/e*: 268 (M^+), NMR ($CDCl_3$) τ: 9.26 (3H, triplet, J=6 cps), 7.05 (2H, quartet, J=6 cps), 6.65 (1H, singlet, H⨯OEt). In its NMR spectra, the signals of the methyl protons of acetoxy group of IX and the ethoxy group of XII appeared at an unusually high field (about 0.2—0.3 ppm).[7] Thus, those groups may be oriented to the aromatic ring.

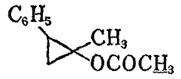
The bromocyclopropyl olefin (VI) did not react with methylamine in ethanol at 190° in a sealed tube, but the keto derivative (III) reacted at 130° with the same reagent and under the same reaction conditions. The isolated products were the iminoketone (XIII), mp 137.5—139.5°, $C_{17}H_{22}O_2$, IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1655 (C=N), (60% yield), the keto-aldehyde (XIV), mp 127—129°, $C_{17}H_{22}O_2$, IR ν_{max}^{KBr} cm^{-1}: 2860; 2710; 1715 (CHO), 1675 (C=O), 3% yield, and the isomeric aldehyde (XV), mp 163—165°, $C_{17}H_{22}O_2$, IR ν_{max}^{KBr} cm^{-1}: 2890; 2770; 1715 (CHO), 1680 (C=O), 6% yield. The iminoketone (XIII) gave the keto-aldehyde (XV).

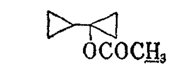
The structures of XIV and XV were confirmed from the following evidences. Oxidation of XIV and XV with chromic acid in acetic acid afforded the keto acid (XVI), mp 228°, $C_{17}H_{20}O_3$, IR ν_{max}^{KBr} cm^{-1}: 3200—2800; 1725 (COOH), 1665 (C=O), and isomeric acid (XVII), mp 233—235°, Mass Spectrum *m/e*; 272 (M^+), IR ν_{max}^{KBr} cm^{-1}: 3400—2400; 1715 (COOH), 1655 (C=O), respectively. Reduction of XVI and XVII with sodium borohydride in boiling ethanol and treatment with dilute hydrochloric acid in methanol respectively gave the γ-lactone (XVIII), mp 144—145°, Mass Spectrum *m/e*: 256 (M^+), IR ν_{max}^{KBr} cm^{-1}: 1775; 1250 (γ-lactone), and the isomeric γ-lactone (XIX), mp 121—122°, Mass Spectrum *m/e*: 256 (M^+), IR ν_{max}^{KBr} cm^{-1}: 1780; 1255 (γ-lactone). The formation of γ-lactone indicate that the aldehyde group in XII and XIII should attach to carbon at C-10*a* and that XIV and XV should be stereoisomers. From the

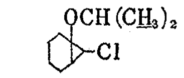
Table I. NMR Data of *cis*- and *trans*-Fused Compounds

Compounds	$C\underline{H}_3$ at C_1		$C\underline{H}_2$ at C_{10}		$C\underline{H}$ at C_9
cis-Aldehyde (XIV)	9.06	8.80	7.35	6.90	—
cis-Carboxylic acid (XVI)	9.08	9.00	7.22	6.83	—
cis-γ-Lactone (XVIII)	9.00	8.58	7.65	7.40	4.92
trans-Aldehyde (XV)	9.07	8.85	7.72	6.86	—
trans-Carboxylic acid (XVII)	9.15	8.90	7.67	6.90	—
trans-γ-Lactone (XIX)	8.95	8.95	8.00	7.30	4.90

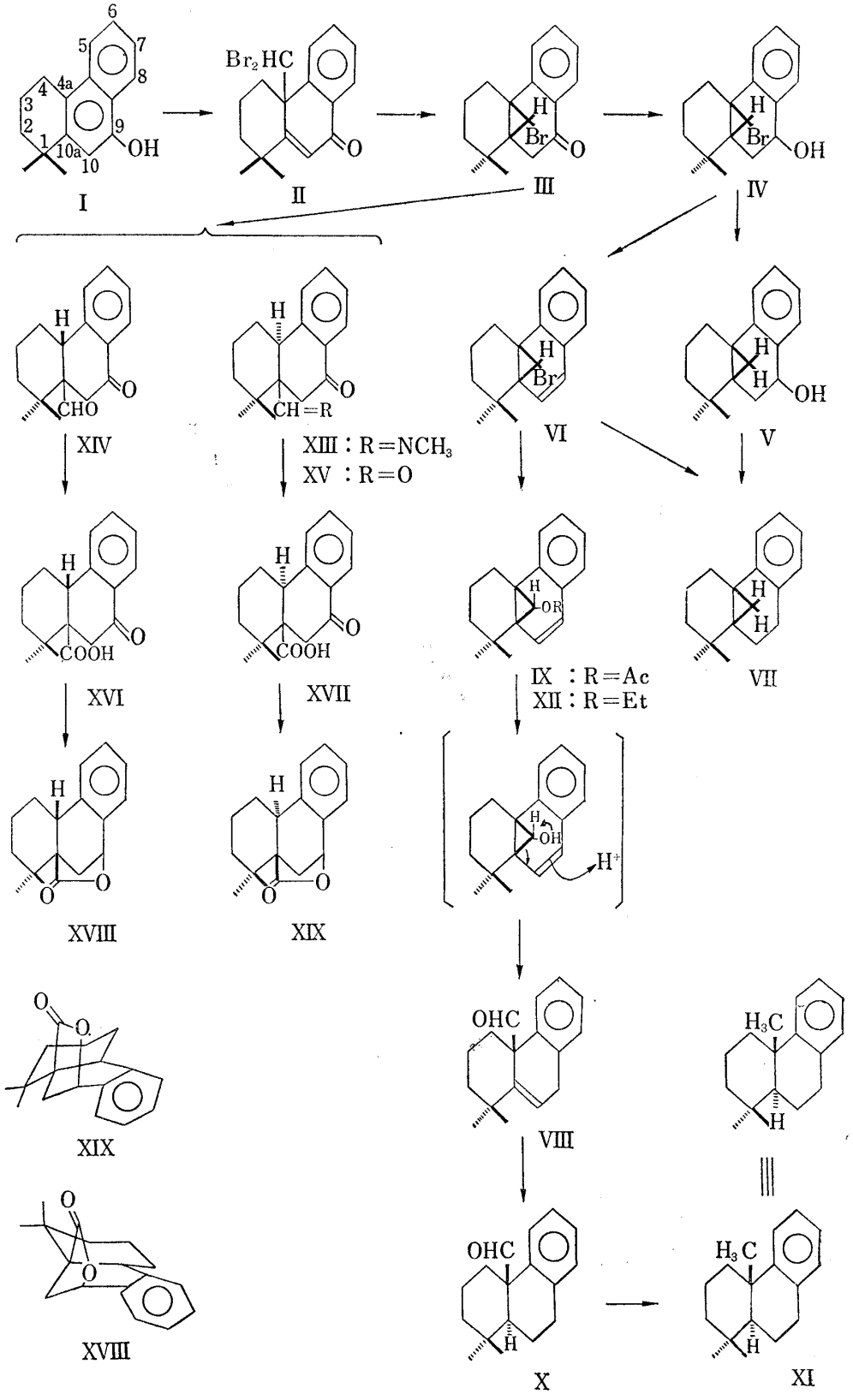
6) M. Fetizon and G.M. Moream, *Bull. Soc. Chim. France*, **1965**, 3481.

7)

8.01 τ See Ref. 5*b*).


8.10 τ See Ref. 5*a*).


8.90, 8.93 τ (P.D. Gardner. *et al.*, *J. Am. Chem. Soc.*, **87**, 3026)

examination of their models, the β–methyl group at C–1 in A/B *cis*–fused γ–lactone may be coplanar with the lactonic carbonyl group, and a downfield shift should be expected in their NMR signals, while no such shift should be expected in A/B *trans*–fused γ–lactone. The observed large downfield shift in XVIII shows that it has a *cis*–fused A/B ring. Consequently, the A/B ring juncture of XIX is *trans*.



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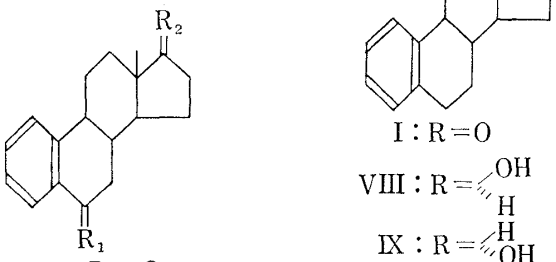
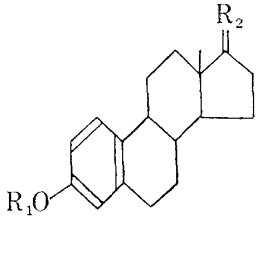
Further Studies on Metabolites of 3-Desoxyestrone in Rabbit Urine

In the preceding publication[1] the authors reported the isolation of 17α-estradiol and 2-hydroxy-3-desoxyestrone[2] as the urinary metabolites of 3-desoxyestrone (I)[3] administered to a rabbit. The present communication deals with the characterization of additional two phenolic and three neutral metabolites separated from the rabbit urine. In a typical run, a single dose of a suspension of I (350 mg) in Tween 80 was orally given to an adult male rabbit weighing about 2.0 kg. The urine collected for 48 hours after the administration was processed in the same manner as described in the previous paper.[1] When the crude extract was chromatographed on alumina, the non-polar metabolites were initially eluted with benzene before the phenolic substances. Thin-layer chromatography indicated that this fraction would consist of three neutral metabolites besides the unchanged steroid. These substances showed the negative reaction with Folin-Ciocalteu reagent and the yellow coloration with *conc.* sulfuric acid.



I : R=O
VIII : R=α-OH
IX : R=β-OH

II : R_1=R_2=O
III : R_1=β-OH, R_2=α-OH
IV : R_1=β-OCOC$_6$H$_5$, R_2=α-OH
V : R_1=β-OCOC$_6$H$_5$, R_2=α-OCOC$_6$H$_5$
VI : R_1=β-OCOC$_6$H$_5$, R_2=O
VII : R_1=β-OH, R_2=O



X : R_1=$CH_2C_6H_5$, R_2=O
XI : R_1=$CH_2C_6H_5$, R_2=β-OH
XII : R_1=$CH_2C_6H_5$, R_2=β-OTs
XIII : R_1=$CH_2C_6H_5$, R_2=β-OAc
XIV : R_1=H, R_2=β-OAc
XV : R_1=H, R_2=O

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2) These metabolites have been designated as A and B, respectively.[1]
3) A.H. Goldkamp, W.M. Hoehn, R.A. Mikulec, E.F. Nutting, and D.L. Cook, *J. Med. Chem.*, **8**, 409 (1965).