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PREPARATION AND PROPERTIES OF 4-OXO-RETINOIC ACID AND ITS METHYLESTER.

A.B. Barua and M.C. Ghosh*
Department of Chemistry, Gauhati University,
Gauhati-14, Assam, India.

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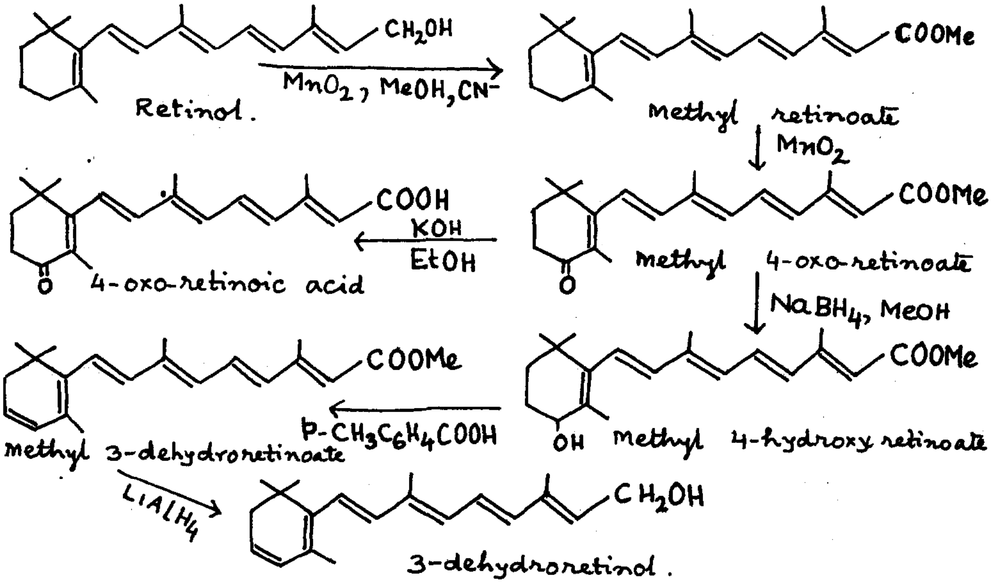
We wish to report the preparation of a new acid congener of retinol viz. 4-oxo-retinoic acid starting from methyl retinoate. The latter was also prepared in a single step by oxidative esterification[1] of retinol. The methyl ester of 4-oxo-retinoic acid was further converted to 3-dehydroretinol by the following scheme (Scheme 1), which is slightly different from the one previously reported[2].

SCHEME I



Following the same procedure outlined in the preparation of methyl retinoate from retinal[3], a methanolic solution of retinol was oxidised to give six products which were separated by chromatography on water deactivated

(5%, v/w) alumina. The main yellow band was found to be methyl retinoate (70-75%) and was crystallised from aqueous methanol to give m.p. 54-55°C. Saponification of methyl retinoate with 10% ethanolic KOH gave retinoic acid which was crystallised from light petroleum to give m.p. 180-181°C. The second band was found to be methyl 5,6-monoepoxyretinoate (3-4%), m.p. 86-87°C, and was characterised by comparison of its properties and by doing a mixed chromatography with a sample prepared from methyl retinoate by the procedure reported earlier[4,5].

Methyl 5,6-monoepoxyretinoate was converted to methyl 5,8-monoepoxyretinoate (furanoid) by treatment with ethanolic HCl (0.05 N) which was subsequently saponified to 5,8-monoepoxyretinoic acid, m.p. 163-164°C (uncorr.); λmax 303, ~320, ~294 nm (light petroleum) and 302 nm (ethanol).

The products obtained by the oxidation of methyl retinoate in light petroleum with MnO_2 (stirred for 24 hrs. in the dark) were chromatographed on water deactivated (5%, v/w) alumina. The first band eluted with light petroleum contained unchanged methyl retinoate, the 2nd. band eluted with 1-2% (v/v) ether contained methyl 5,6-monoepoxyretinoate (6%). The 3rd. band contained an unidentified substance, while the 4th. main band eluted with 4-5% (v/v) ether was characterised as methyl 4-oxo-retinoate (above 60%) which was crystallised from light petroleum at 0°C for three times. The crystals (M^+= 328) had m.p. 93°C (Found : C, 76.55 & H, 8.54%. $C_{21}H_{28}O_3$ requires C, 76.8%, H, 8.61%); λmax 352, 280, ~339 nm. (light petroleum); 355 and 285 nm (ethanol); 360 and 287 nm (chloroform); $E^{1\%}_{1cm.}$ values of 1935, 1717 & 1583 at 352 nm, 355 nm & 360 nm respectively and $SbCl_3$ product λmax at 550 nm. I.r. maxima were present at 970, 1152, 1240, 1608, 1668 (oxo-carbonyl) & 1714 cm^{-1} (ester carbonyl gr.). The NMR spectrum exhibited signals (δ) at 1.2 s for C_1 -, 1.82 s for C_5-, 2.08 s for C_{13}-, 2.38 d (J= 1.0 Hz) for C_9- methyl groups respectively and 3.72 s for $-COOCH_3$ gr.

Saponification of methyl 4-oxo-retinoate with 10% ethanolic KOH gave 4-oxo-retinoic acid. The crystals (from light petroleum at 0°C) melted at 159-161°C (uncorr.) & showed λmax. 352 & 280 nm (light petroleum), 355 & 285 nm. (ethanol), 362 & 287 nm (chloroform) with $E^{1\%}_{1cm.}$ values of 1260, 1147 & 1167 at 352, 355 & 362 nm respectively and $SbCl_3$ product λmax. 540 nm. I.r. spectrum showed bands at 1740, 1667 and 3400 cm^{-1} (broad) which are assigned to -COOH carbonyl, oxo-carbonyl and - COOH hydroxyl groups respectively.

Methyl 4-oxo-retinoate was reduced with $NaBH_4$ in methanol at 0°C to methyl 4-hydroxyretinoate, λmax 345 nm (light petroleum), 348 nm (ethanol) and $SbCl_3$ product λmax. 525 nm.(pink). Dehydration of the ester with p-toluenesulphonic acid gave methyl 3-dehydroretinoate; λmax 365, ~302 nm (light petroleum), 370, ~305 nm (ethanol) and $SbCl_3$ product λmax 643 nm which on saponification gave 3-dehydroretinoic acid, λmax. 365, ~302 nm. (light petroleum), $SbCl_3$ product λmax. 643 nm and m.p. 178-180°C (uncorr.)

Methyl 3-dehydroretinoate was further reduced with $LiAlH_4$ in dry ether at 0°C to give 3-dehydroretinol, λmax. 350, 287 & ~276 nm. (light petroleum) and $SbCl_3$ product λmax. 690 nm which gave anhydrovitamin A_2 on treatment with ethanolic HCl.

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