

Investigations on Xanthoperol and its Precursor

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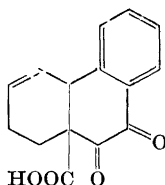
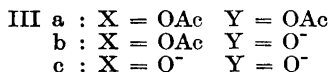
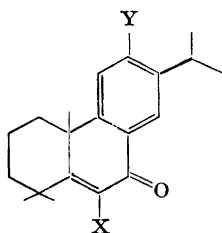
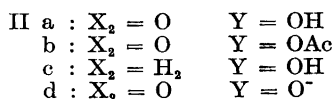
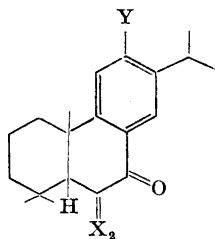
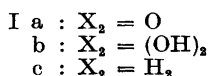
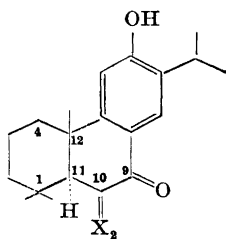
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The 11-epimer of xanthoperol has been found as a precursor. The natural 11 α -configuration (Ia) has been assigned to the precursor and the 11 β -configuration (IIa) to xanthoperol. The epimerisation is effected by heating in alkaline solution. The stability of the *cis*- and *trans*-forms of the A/B ring junction is discussed.

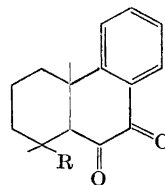
Xanthoperol has been acetylated to a diacetate, the alkaline hydrolysis of which has been studied.

Previous attempts to isolate the precursor of xanthoperol have been unfruitful. It has now been possible, by repeated chromatography, to obtain a small amount of a yellow compound, C₂₀H₂₆O₃, m.p. 207–210°, from the fractions containing the precursor. After boiling in sodium hydroxide solution, the yellow compound gives spectra in infrared and ultraviolet which are almost identical with the spectra of xanthoperol. The extinction values for the ultraviolet spectra are slightly lower owing to a small amount of 9-ketoferruginol which has nearly the same solubility as the compound. The compound is therefore the precursor sought. The precursor has ultraviolet spectra with the same shape as those of xanthoperol¹, with maxima at 249 and 341 m μ in neutral and 269 and 405 m μ in alkaline solution. The infrared spectrum has peaks at 3 160, 1 725 and 1 645 cm⁻¹, thus indicating the presence of a hydroxyl group and two keto groups, which latter nicely correspond to an α -diketo group conjugated with a benzene ring. The precursor has therefore the same functional groups in the same chromophore as xanthoperol and the change under the conditions employed can only be explained as an epimerisation.

Nuclear magnetic resonance investigations² have shown that xanthoperol has the structure of 9,10-diketoferruginol, but it is assumed that the configuration at C-11 is inverted (IIa). The inference has been drawn from the closer relationship of the nmr spectra of xanthoperol to its mono-keto reduction product than to that of 9-ketoferruginol (Ic), from which the mono-keto product differs only in the configuration at C-11, since the centre at C-12 cannot have been influenced under the conditions employed during the rapid reduction of xanthoperol. Inversion at C-12 requires more powerful reagents



IV



V

($AlCl_3$)^{3,4}. This leaves structure IIc for the reduction product * and leads to the above assumption.

Apart from some recently investigated compounds^{5,6}, the natural diterpenes with an angular methyl group at C-12 have the same configuration at the rings A/B, which are *trans*-locked with the methyl group at C-12 in β -orientation^{7,8}. All the diterpenes hitherto found in *Juniperus communis* L.^{9,10} have this configuration and it seems therefore obvious that it should be assigned to the precursor isolated. From the foregoing it can be seen that the precursor is the less stable epimer. It has previously been found^{11,12} that the A/B ring *cis* juncture is more stable than the *trans* juncture in octahydrophenanthrenes with an angular methyl group at C-12. It seems reasonable to assume that 9-keto-11 β -ferruginol (IIc) is more stable than the epimer (Ic) since it is formed under conditions that probably lead to the more stable epimer, and the *cis*-form would therefore be more stable in the 9-keto compounds also. The extension of the stability relationships to the 9,10-diketones cannot be presumed without fuller investigation but does not seem unreasonable in the light of the fact that the configuration for a *cis-syn-trans* perhydrophenanthrene with the keto group next to the *cis*-head is not inverted under the conditions normally employed for conversion¹³. The present evidence therefore strongly suggests that the precursor has the *trans*-form (Ia) and

* Wenkert and Chamberlin¹¹ have independently proposed this structure for the compound.

xanthoperol the *cis*-form (IIa). For it would seem very strange to assign the unnatural *cis*-form to the precursor and the natural *trans*-form to the artefact xanthoperol.

It has previously¹⁴ been assumed that the precursor would have the same chromophore as 9-ketoferruginol. The ultraviolet spectra of the fractions containing the precursor still gave an appreciable reduction of the intensity at 280 m μ after hydrolysis but, in addition, it was found that a previously overlooked inflexion at 330 m μ had disappeared. The present evidence does not rule out the possibility of the existence of other precursors.

The ultraviolet and infrared spectra of the diketoferruginol epimers need some comment. The 10-keto group in the *trans*-form is evidently less conjugated with the 9-keto group owing to a larger angle between the keto groups¹⁵. The 9-keto group, on the other hand, is more strongly conjugated with the aromatic ring than the corresponding group in the *cis*-form. The cross-conjugation is therefore much stronger in the *cis*-form, as is clearly seen from the ultraviolet spectra. When the precursor is left to stand in alkaline solution at room temperature, the intensity of the maximum at 405 m μ slowly diminishes. This fall in intensity could be explained by the formation of a hydrate of the 10-keto group (I b). The same behaviour has been observed in several α -diketones¹⁶⁻¹⁸. (In methanol solution the compound IV¹⁸ has about the same spectrum as acetophenone.) Unfortunately, the ultraviolet spectra in this connection were taken only between 355 and 500 m μ and lack of material prevented further investigation.

Several papers have recently been published in which α -diketo compounds with the general structure V are described. Wenkert and Jackson⁴ have found that chromic acid oxidation of the corresponding hydrocarbons can be used as a method for determining the A/B ring junction, since only *cis*-compounds give α -diketones. Ghatak¹⁹ has arrived at the same conclusion in a study of desoxypodocarpic acid isomers and the method has also been used by Saha *et al.*¹² The diketones readily give the enol acetate upon refluxing with acetic anhydride and sodium acetate^{4,19}. This acetylation procedure was therefore applied to xanthoperol. In the crude product after 1 hour's boiling the infrared spectrum showed that the phenolic OH band had disappeared. In the region 1 800—1 630 cm⁻¹ there were four bands at 1 765, 1 724, 1 685, and 1 667 cm⁻¹. When these bands were compared with the bands for xanthoperol monoacetate (IIb), the band at 1 685 could be assigned to the keto group at C-9 in the diketo compound and the band at 1 724 to the keto group at C-10. The band at 1 667 could be assigned only to the keto group at C-9 in a diacetate IIIa and the slightly broadened band at 1 765 therefore belonged to the unresolved phenol and enol acetate bands. Thus, it was found that the acetylation had only been partial and it was therefore continued for 20 h. The crude product now gave only two bands, at 1 765 and 1 665 cm⁻¹, in the afore-mentioned region and the expected diacetate was obtained as prisms, m.p. 158—159°, by crystallisation from aqueous ethanol.

On acidic hydrolysis, the diacetate afforded only mixtures but alkaline hydrolysis yielded interesting results. Short hydrolysis for 1 min with 0.5 N NaOH at room temperature gave a crude product with an infrared spectrum having bands at 3 330, 1 770 and 1 642 cm⁻¹, a side band at 1 747 and an

inflexion at $1\ 670\text{ cm}^{-1}$. The spectrum can be nicely explained if it is assumed that the phenol acetate is rapidly hydrolysed, leaving behind the enol acetate with a small amount of diacetate. It has previously been observed that the phenol acetates of 9-ketoferruginol and xanthoperol are rapidly hydrolysed in alkaline solutions. One minute after the solution has been made alkaline, the ultraviolet spectrum of xanthoperol diacetate was of the same shape and intensity as the spectrum of 9-keto- Δ^{10} -dehydroferruginol in alkaline solution¹⁰, thus supporting the conclusion above. The spectrum slowly changes, with isosbestic points at 400, 320 and 268 μ , to the spectrum of xanthoperol in alkaline solution. The change in the spectra shows that only two absorbing substances are taking part in the alkaline hydrolysis and this can be explained by the reaction sequence IIIa—IIIb—IIIc—IIId, where the absorbing substances are IIIb and IIId. After the rapid hydrolysis of the phenol acetate group, the enol acetate group is slowly hydrolysed with the immediate formation of xanthoperol. The hydrolysed diacetate has been isolated and an infrared spectrum of the crude product gives the bands for xanthoperol. Pure xanthoperol has been crystallised from the crude product. The results obtained thus strongly support the structure IIa for xanthoperol.

The non-enolisation of the compound, which was partly responsible for erroneous conclusions¹⁴, has been commented on by Wenkert and Jackson⁴. They have explained it as due to steric compression. The steric conditions are, in our view, not the sole reason for the non-enolisation, but the phenol hydroxyl apparently also has an influence on it. This applies at least to alkaline solutions, in which the phenoxide ion is formed.

Kondo *et al.*²⁰ have recently obtained xanthoperol from the heartwood of *Cryptomeria japonica* D. Don. The bulk of the compound has been obtained after alkaline hydrolysis but a small amount has been isolated by extraction with sodium hydroxide without previous hydrolysis and the authors therefore conclude that xanthoperol is present as such in the tree. In the light of the present results it seems necessary to investigate whether the precursor is rearranged during the isolation procedure that has been used by Kondo *et al.*

EXPERIMENTAL

All m.p.s were determined with a Kofler microscope. The microanalyses were performed by Dr. A. Bernhardt, Mülheim. The infrared spectra were recorded with a Beckman IR-5 instrument, and the ultraviolet spectra with a Beckman DK-2 instrument.

9-Keto-11 β -ferruginol (IIc). Clemmensen-reduced xanthoperol (0.24 g) was acetylated and the acetate oxidised with CrO_3 , as before¹⁴. The oxidised product was hydrolysed and extracted in the usual way. Upon crystallisation from benzene, 15 mg of small prisms were obtained, m. p. $254\text{--}256^\circ$. UV spectrum: ethanol, $\lambda_{\text{max}}\ 235\ \mu$ ($\log\epsilon\ 4.20$), $286\ \mu$ ($\log\epsilon\ 4.12$).

Isolation of the precursor. One hundred grams of the non-steam-volatile portion of the neutral extract from *Juniperus communis* L.⁹ was chromatographed on alumina and small samples from each fraction were taken for investigation of the content of the precursor by taking the ultraviolet spectra before and after hydrolysis. The fractions containing the precursor were chromatographed anew and the spectra were taken as before. The fractions now containing the precursor were combined (0.54 g) and dissolved in 100 ml ether. The solution was extracted four times with 25 ml 2 % NaOH solution. The alkaline solutions were acidified and extracted with ether within 5 min after the extraction with alkaline solution. The ether extracts were combined and worked up as usual, leaving a crystalline

residue. This was crystallised from benzene and yielded 10 mg of small prisms, m. p. 207–210°, easily soluble in ethanol and difficultly soluble in benzene. (Found: C 77.0; H 8.2. Calc. for $C_{20}H_{26}O_5$: C 76.4; H 8.3.) UV spectrum: ethanol, λ_{\max} 249 $m\mu$ (log ϵ 3.73), 341 $m\mu$ (log ϵ 3.94); 0.5 N NaOH in ethanol-water (1:1), 269 $m\mu$ (log ϵ 3.83) 405 $m\mu$ (log ϵ 4.08). IR spectrum: 1 mg/300 mg KBr, principal bands, cm^{-1} , 3 160 (s), 2 940 (s), 2 870 (m), 1 725 (m), 1 645 (s), 1 600 (s), 1 585 (s), 1 560 (s), 1 500 (s), 1 465 (m), 1 380 (m), 1 365 (m), 1 345 (m), 1 310 (s), 1 270 (s), 1 220 (m), 1 170 (m), 1 100 (m), 965 (w), 917 (w), 897 (w), 870 (m), 835 (w). The compound was contaminated with a small amount of 9-ketoferruginol.

Epimerisation of the precursor. The precursor was dissolved in 0.5 N NaOH in water (c 20 mg/l) and ultraviolet spectra were recorded in the range 500–355 $m\mu$. The following extinction values were recorded at the maximum at 405 $m\mu$ at room temperature: a (time after solution, min), 38 (5), 36 (30), 33 (60), 27 (120), and 12 (300). The solution was thereafter heated on a water bath and the following values were recorded: λ_{\max} , a (min), 410, 20 (15), 430, 19 (30), 440, 19.5 (45), and 445, 37 (120). UV spectrum of the epimerised product: ethanol, λ_{\max} 251 $m\mu$ (log ϵ 3.74), 352 $m\mu$ (log ϵ 3.86); 0.5 N NaOH in ethanol-water (1:1), plateau at 260–270 $m\mu$ (log ϵ 3.9), max. 445 $m\mu$ (log ϵ 4.07) and an inflexion at 350 $m\mu$ due to the presence of a small amount of 9-ketoferruginol. IR spectrum: film on KBr, principal bands, cm^{-1} , 3 350 (broad), 2 950 (s), 2 870 (m), 1 718 (m), 1 660 (m), 1 595 (s), 1 565 (s), 1 505 (m), 1 460 (m), 1 370 (m), 1 330 (s), 1 295–1 265 (broad), 1 180 (m), 1 163 (m), 1 149 (m), 920 (w, broad), 865 (w, broad).

Xanthoperol diacetate (IIIa). Xanthoperol (140 mg) was acetylated with acetic anhydride and sodium acetate according to the procedure of Wenkert and Jackson⁴. The crude product after 1 hour's boiling had the maxima in the infrared: (film on KBr), 1 765 (s), 1 724 (m), 1 685 (s), 1 667 cm^{-1} (s), no hydroxyl band. The acetylation was completed by boiling for 20 h. The crude product was crystallised from aqueous ethanol, yielding 100 mg colourless prisms, m. p. 158–159°. By sublimation of the evaporated mother liquor a further amount (30 mg) of a colourless sublimate was obtained, m. p. 159–160°, identical with the previous crystals. (Found: C 72.0; H 7.5; O 20.3. Calc. for $C_{24}H_{30}O_5$: C 72.3; H 7.6; O 20.1.) UV spectrum: ethanol, λ_{\max} 263 $m\mu$ (log ϵ 4.10), plateau 277 $m\mu$ (log ϵ 4.08). IR spectrum: 1 mg/300 mg KBr, principal bands, cm^{-1} , 2 960 (m), 2 870 (w), 1 765 (s), 1 665 (s), 1 612 (m), 1 565 (w), 1 495 (w), 1 460 (w), 1 420 (w), 1 385 (w), 1 370 (s), 1 320 (m), 1 205 (s), 1 170 (m), 1 155 (m), 1 110 (m), 1 095 (m), 1 035 (s), 932 (m), 903 (w), 885 (w), 865 (w), 795 (w).

Hydrolysis of xanthoperol diacetate. a. Acid hydrolysis. Hydrolysis with 2 N HCl gave ultraviolet and infrared spectra which showed that the hydrolysis was slow and gave a mixture of compounds.

b. Alkaline hydrolysis. 1. The diacetate (7 mg) was dissolved in ethanol (20 ml) and 1 N NaOH (20 ml) was added. The hydrolysis was stopped after 1 min at room temperature by acidification and extraction with ether. An infrared spectrum of the extracted product (film on KBr) showed bands at 3 330 (broad), 1 770 (s), 1 747 (m), 1 670 (inflexion), and 1 642 cm^{-1} (s). Attempts to obtain crystals from the crude product failed.

2. The diacetate (1.3 mg) was dissolved in ethanol (50 ml) and 1 N NaOH (50 ml) was added. A series of ultraviolet spectra were taken at 1, 5, 20, 60, 90, 120, 240, and 1 320 min at room temperature and warming for 10 min on a water bath. The spectra had isosbestic points at 268, 320 and 400 $m\mu$, except the two last-mentioned which did not pass through the two lower points, probably owing to slow deterioration of the alkaline solutions. The first spectrum had λ_{\max} 246 $m\mu$ (log ϵ 4.17, calc. for xanthoperol monoacetate) and 382 $m\mu$ (log ϵ 4.13). At the times given the high-end maximum had the following values: λ_{\max} (a), 382 (38), 382 (37), 387 (35), 395 (33), 400 (33), 405 (34), 410 (34), 415 (35), and 420 (35). At the time when the experiment was interrupted the maxima were at 270 and 420 $m\mu$ in the alkaline solution and 250 and 345 $m\mu$ in the acidified solution.

3. The diacetate (4 mg) was hydrolysed for 2 h on a water bath with 1 N NaOH. After acidification and extraction the crude product gave the infrared spectrum of xanthoperol, and upon crystallisation from light petroleum-benzene, 1 mg of xanthoperol was isolated.

*Xanthoperol monoacetate*¹⁴ (*IIB*). IR spectrum: 1 mg/300 mg KBr, principal bands, cm^{-1} , 2 960 (m), 2 870 (w), 1 780 (s), 1 724 (s), 1 685 (s), 1 610 (s), 1 555 (m), 1 490 (m),

1 460 (m), 1 385 (w), 1 370 (s), 1 320 (m), 1 265 (m), 1 250 (s), 1 190 (s), 1 180 (s), 1 150 (m), 1 120 (w), 1 110 (m), 1 098 (m), 1 050 (m), 1 022 (m), 1 010 (m), 970 (w), 952 (w), 928 (m), 915 (m), 882 (w), 868 (m), 846 (w), 778 (m).

The author is indebted to the late Prof. K. Alder for an ultraviolet spectrum of compound IV.

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