[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH INSTITUTE, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XI.[1] Bromination and Dehydrobromination of *cis*-9-Methyl-3-decalone[2]

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The usual treatment of *cis*-9-methyl-3-decalone (Ia) with bromine gave, unexpectedly, a 2-bromo compound in which the position of bromine was definitely established. This is not in accordance with the general rule about bromination of 3-ketosteroids. The 2-bromo and 2,4-dibromo compounds of the *cis*-ketone (Ia) were reacted with a variety of bases to give products of different type depending on the reagent used. The stereochemistry of 9-methyl-*cis*-3-decalols (XVII and XVIII) is discussed.

In the previous papers of this series,[3-5] bromine treatment of *trans*-9-methyl-3-decalone (Ib) was described as giving 2-bromo (IIb) and 2,4-dibromo derivatives (XIVb), which were reacted with various bases and converted to different products. Thus, the monobromo ketone with γ-collidine afforded the Δ^4-3-ketone (III), the rearranged product, while on acetolysis and with the Mattox-Kendall procedure it gave, respectively, the 2-acetoxy ketone (VIb) and the Δ^1-3-ketone (Vb), both the normal products. With γ-collidine or anhydrous sodium acetate, the 2,4-dibromo ketone was converted, respectively, to the $\Delta^{4(10),5(6)}$-dienone or the 2-acetoxy-Δ^1-3-ketone (XVIb), both the rearranged products. The present research was initiated to compare these bromination-dehydrobromination reactions of the *trans*-ketone (Ib) with those of the isomeric *cis*-ketone (Ia).

cis-9-Methyl-3-decalone was prepared by catalytic hydrogenation of the Δ^4-3-ketone (III), essentially as reported previously[6,7] (see Experimental section). The Δ^4-3-ketone was hitherto obtained by the condensation of 2-methylcyclohexan-1-one with 1-diethylamino-3-butanone methiodide in the presence of sodium amide in organic solvent, following the method first reported by duFeu, McQuillin, and Robinson,[7] or by a slight modification thereof. It was found now that when the free Mannich base instead of its methiodide was used with sodium metal in the absence of a solvent, the Δ^4-3-ketone of sufficient purity was obtained in a comparable yield. It provides a more economical and simple procedure for III than the earlier method.

The solid *cis*-ketone (Ia) was reacted with one mole of bromine to give an oily monobromo compound (IIa), which on treatment with γ-collidine, afforded the Δ^4-3-ketone (III) in a comparable yield with that from the *trans*-monobromo ketone (IIb).[3] By the Mattox-Kendall method, the monobromo ketone (IIa) was converted, in a good yield, to the *cis*-Δ^1-3-ketone 2,4-dinitrophenylhydrazone (IVa), showing $\lambda_{\max}^{\mathrm{CHCl_3}}$ 258 mμ (ε 15,000) and 362 mμ (ε 22,600). The hydrazone with pyruvic acid regenerated the known *cis*-Δ^1-3-ketone (Va), identified as the semicarbazone.[8] The location of the double bond in Va was proved by the ultraviolet absorption spectrum, $\lambda_{\max}^{\mathrm{EtOH}}$ 229 mμ (ε 9500), corresponding to the α,β-unsaturated ketone with no substituents.[9]

On heating with anhydrous sodium acetate in glacial acetic acid, the monobromo ketone (IIa) was converted to an acetoxy ketone (VIa) in 80% yield. The acetoxy ketone with alkali afforded, together with the known *cis*-diacid (VIIa),[9] a 2,3-diketone (VIIIa) which gave a positive ferric chloride test (enol form; Xa, XIa, or both), and formed a glyoxime. Perhydrol oxidation of the acetoxyketone and the 2,3-diketone afforded good yields of the *cis*-diacid. As in the case of the *trans*-series (VIIb and VIIIb), these products are presumed to be formed from VIa *via* an intermediate α-ketol (IXa), commonly considered to be unstable. The results clearly indicated the location of the acetoxy group at the 2-position in VIa. The authentic sample of the *cis*-diacid (VIIa) was prepared, as reported previously,[9] by nitric acid oxidation of the *cis*-ketone (Ia), which was much more difficult than the similar oxidation of the *trans*-ketone (Ib).

The above reactions of the *cis*-monobromo ketone (IIa) with bases are completely in parallel with the corresponding reactions reported for the *trans*-isomer (IIb).[3] On analogy with the assignment of the 2-bromo structure (IIb) for the *trans*-monobromo ketone, it may be reasonably assumed that

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[1] Paper X, Yanagita and Futaki, *J. Org. Chem.*, **21**, 949 (1956).

[2] This work was supported in part by a grant in aid for Scientific Research from the Ministry of Education of Japan.

[3] Yanagita and Tahara, *J. Org. Chem.*, **18**, 792 (1953).

[4] Yanagita, Yamakawa, Tahara, and Ogura, *J. Org. Chem.*, **20**, 1767 (1955).

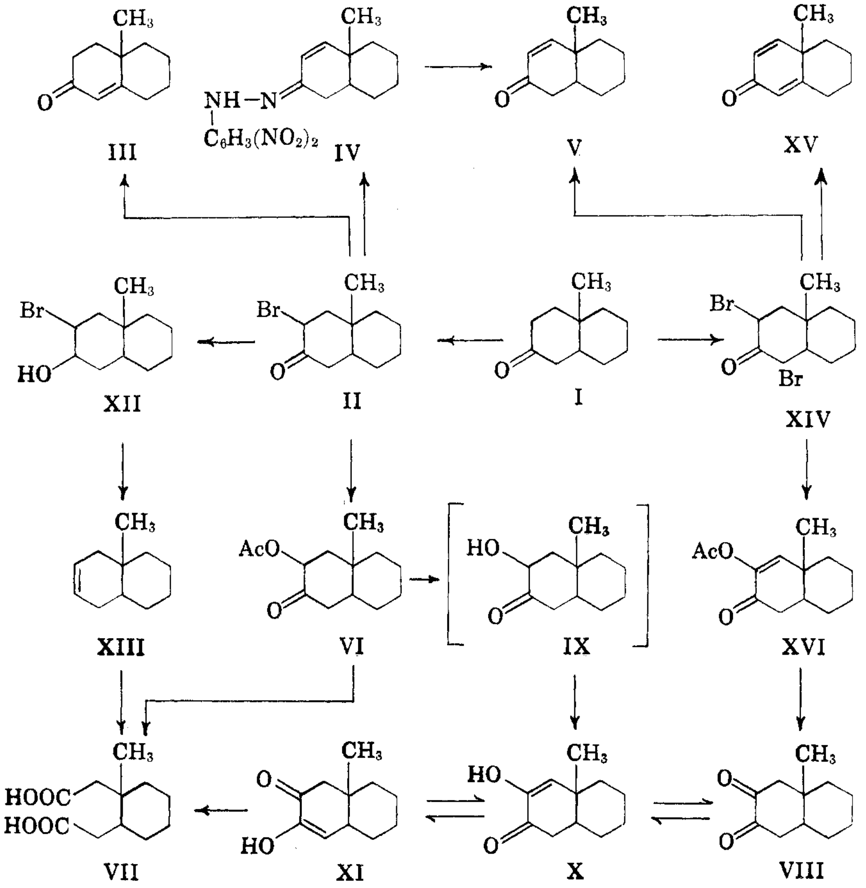
[5] Yanagita and Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

[6] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

[7] DuFeu, McQuillin, and Robinson, *J. Chem. Soc.*, 53 (1937): *cf.* Dauben, Rogan, and Blanz, Jr., *J. Am. Chem. Soc.*, **76**, 6384 (1954).

[8] Burnop and Linstead, *J. Chem. Soc.*, 720 (1940).

[9] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 190.



Series a, *cis*-configuration at the ring juncture
Series b, *trans*-configuration at the ring juncture

the *cis*-isomer also possesses the 2-bromo structure (IIa). It is desirable, however, to confirm this structure for the reason described below. The proof of the position of the bromine atom in IIa was obtained by using the same sequence of reactions (II → XII → XIII → VII) as that reported for IIb.[5] Sodium borohydride reduction of the *cis*-monobromo ketone (IIa) gave rise to a possible epimeric mixture of bromohydrins (XIIa). Without attempting to separate the epimers, the liquid product was treated with zinc dust and acetic acid to produce, together with the *cis*-ketone (Ia), an olefin (XIIIa), which exhibited a weak but sharp absorption band at 1655 cm.$^{-1}$, corresponding to a *cis*-disubstituted ethylene.[5] Contrary to the *trans*-olefin (XIIIb),[5] the *cis*-isomer is found to be quite resistant toward permanganate in acetone solution. Permanganate oxidation of this olefin was carried out with comparable ease in sodium carbonate solution to afford the *cis*-diacid (VIIa), giving conclusive evidence for the 2-bromo structure (IIa).

The above observation that substitution of bromine in the *cis*-3-decalone ring occurs preferentially at the 2- position seems remarkable, since it is not in accord with the general conclusion concerning bromination of 3-ketosteroids, in which the normal series (A/B rings *cis*) always affords the 4-bromo product whereas the allo series gives the 2-bromo compound.[10] If the theory that, on bromination of ketones, bromine first adds to the double bond of the enolic form of the ketones,[11,12] is applied to the present case, it may be seen that in *cis*-9-methyl-3-decalone (Ia), the Δ^2-enol is more favorable than the Δ^3-enol. This deduction is the reverse of the argument suggested by Taylor[13] that *cis*-Δ^1-octalin is more stable than the *cis*-Δ^2-octalin as observed with the enolic forms of the 3-ketosteroids of normal series.

Treatment of the *cis*-ketone (Ia) with two moles of bromine gave a dibromo compound (XIVa), which was isolated in a liquid or a solid form depending on the temperature at which the reaction took place. The former was used for reaction with bases described below, and the latter, showing rather different chemical properties, will be reported in a separate paper.

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(10) Shoppee and Shoppee in Rodd's *Chemistry of Carbon Compounds*, Elsevier Publishing Co., New York-Amsterdam, 1953, Vol. II, Part B, p. 832.

(11) Wheland, *Advanced Organic Chemistry*, 2nd Ed., John Wiley & Sons, Inc., New York, 1949, p. 587.

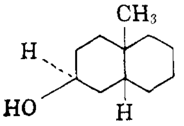
(12) Strain in Gilman's *Organic Chemistry, an Advanced Treatise*, 1st Ed., John Wiley & Sons, Inc., New York, 1938, p. 1273.

(13) Taylor, *Chemistry & Industry*, 250 (1954).

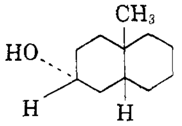
It was reported by Gunstone and Heggie[14] that dibromination-dehydrobromination (γ-collidine) of 9-methyl-3-decalone (I) gave rise to a low yield of the cross-conjugated dienone (XV), which was not isolated as a solid derivative but was converted in low yield to the tetralol by dienone-phenol rearrangement. Their starting material (I), prepared from the Δ^4-3-ketone (III) by catalytic hydrogenation, was apparently a mixture of stereoisomeric ketones,[6] as considered by these authors. From the earlier observation[3] that the 2,4-dibromo derivative (XIVb) of the *trans*-ketone (Ib) on collidine treatment afforded only the linearly conjugated dienone, it may be predicted that a similar treatment of the pure *cis*-dibromo ketone (XIVa) will lead to the cross-conjugated dienone (XV). This prediction was confirmed, but the product (XV) of poor purity was obtained only in a low yield, and was characterized as the 2,4-dinitrophenylhydrazone. It is notable that, in addition to the dienone, the Δ^1-3-ketone (Va) as lower-boiling fraction was isolated also in a low yield. As described above, this monoenone was not detected in the reaction of the *cis*-monobromo ketone (IIa) with hot collidine.

Reaction of the *cis*-2,4-dibromo ketone (XIVa) with anhydrous sodium acetate in glacial acetic acid proceeded similarly to that reported for the *trans*-isomer (XIVb),[2] and gave the 2-acetoxy-Δ^1-3-ketone (XVIa) and the above 2,3-diketone (VIIIa). The former product showed the ultraviolet absorption spectrum, $\lambda_{\max}^{\mathrm{MeOH}}$ 239 mμ (ϵ 2300), corresponding to the Δ^1-enol acetate (XVIa) rather than the Δ^4-enol acetate (the acetate of XIa).[15] The 2-acetoxy-Δ^1-3-ketone was readily converted with alkali to the 2,3-diketone (VIIIa) and the diacid (VIIa), giving conclusive evidence for the structure (XVIa). From the foregoing results of reaction with bases, the *cis*-dibromo ketone may possibly be assigned the 2,4-dibromo structure (XIVa). However, the possibility that this dibromo ketone possesses the 2,2-dibromo structure cannot be completely ruled out, in view of the reported rearrangement of 6-bromo-2,4,4-trimethyl-Δ^5-cyclohexen-1-one to the cross-conjugated dienone.[16]

During this investigation, a search was made for preparing the stereoisomers of 9-methyl-*cis*-3-decalol. Hussey, Liao, and Baker[17] claimed that *trans*-9-methyl-*cis*-3-decalol (XVIII)[18] was obtained in a low yield (32%) by the hydrogenation of *cis*-9-methyl-3-decalone (Ia) over platinum dioxide under slight pressure. The evidence for this configurational assignment was based on the nonidentity with "*cis*-9-methyl-*cis*-3-decalol" reported by these authors. However, since the latter decalol was shown to be *trans*-fused,[19] this argument is invalid and the configuration of the hydroxyl group in the hydrogenation product still remains unknown.



XVII



XVIII

It was found that *cis*-9-methyl-3-decalone (Ia) was quite resistant to hydrogenation with platinum dioxide at ordinary temperature and pressure. Lithium aluminum hydride reduction of the *cis*-ketone gave a quantitative yield of a solid alcohol, which is presumed to be identical with the compound obtained by Hussey, Liao, and Baker,[17] from the identity of the melting points of the alcohol itself and its derivatives, and from their method of preparation.

Reduction of the *cis*-ketone (Ia) with sodium and ethanol, which proceeded much less readily than that of the *trans*-ketone (Ib),[5] gave an oily alcohol in low yield. The use of amyl alcohol in place of ethanol markedly improved the results. Of the derivatives from this oil and the customary alcohol reagents, only a 3,5-dinitrobenzoate—α-naphthylamine complex and an anthraquinone-β-carboxylate were obtained crystalline. These derivatives were different from the corresponding derivatives of the solid alcohol. From the mode of their formations, we tentatively assign to the solid and liquid alcohols, respectively, the *cis*- and *trans*-configurations of hydroxyl-to-methyl group (XVII and XVIII), in which the hydroxyl group in the latter is more equatorial.[20] The use of the infrared absorption spectra (Fig. 1) for the elucidation of the configuration of these 9-methyl-3-decalols was unfruitful. Neither the C—O frequencies nor the structure of the 1240 cm.$^{-1}$ acetate band, which are known to serve for configurational assignment of the hydroxyl group in 3-decalols with no angular methyl groups and analogous steroids,[21] gave any insight into the configuration of the hydroxyl group in our alcohols.

In conclusion, we should like to describe the relative reactivities of some pairs of the *cis*- and *trans*-series of the compounds cited above. Previously, it was reported[22] that on reaction with a stereoisomeric mixture of 4,9-dimethyl-3-decalones,

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[14] Gunstone and Heggie, *J. Chem. Soc.*, 1437 (1952).

[15] Reference 9, p. 195.

[16] Yanagita and Inayama, *J. Org. Chem.*, **19**, 1724 (1954).

[17] Hussey, Liao, and Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953).

[18] For an explanation of this nomenclature, see footnote 3 in reference 18.

[19] Dauben, Tweit, and MacLean, *J. Am. Chem. Soc.*, **77**, 48 (1955): Dreiding and Tomasewski, *J. Am. Chem. Soc.*, **77**, 168 (1955).

[20] Dauben, Tweit, and Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

[21] Braude and Waight in Klyne's *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. I, p. 166.

[22] Yanagita and Futaki, *J. Org. Chem.*, **21**, 949 (1956).

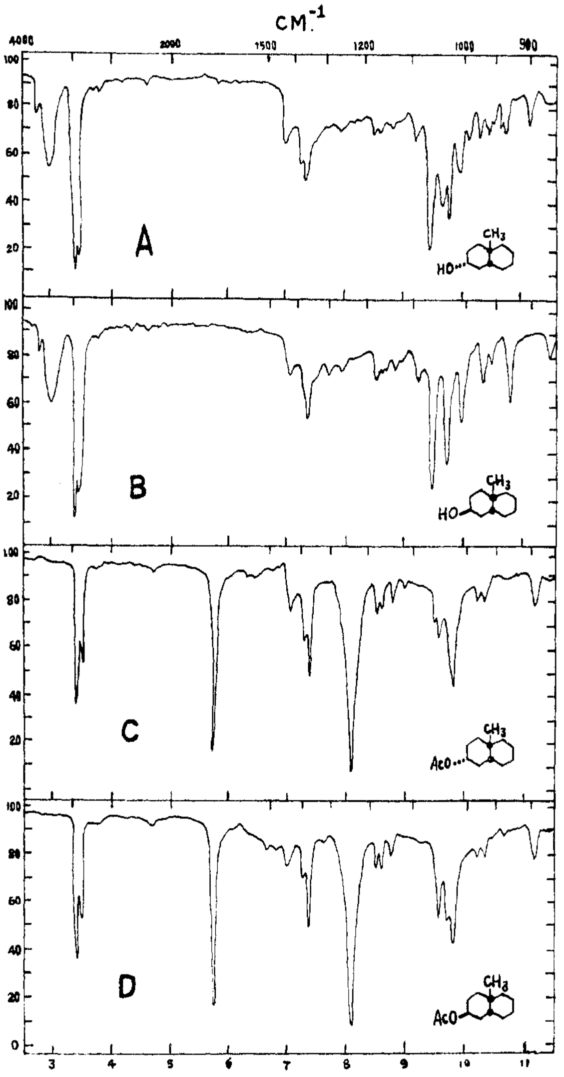

FIG. 1.—INFRARED ABSORPTION SPECTRA (in Carbon Disulfide Solution): A, *trans*-9-Methyl-*cis*-3-Decalol (XVIII); B, *cis*-9-Methyl-*cis*-3-Decalol (XVII); C, the Acetate of XVIII; D, the Acetate of XVII.

diethyl oxalate selectively attacked one isomer with a *trans*-configuration at the ring juncture. Similar stereospecificity was observed, as shown above, in nitric acid oxidation and sodium-alcohol reduction of 9-methyl-3-decalones (Ia and Ib) and in permanganate oxidation of 9-methyl-Δ^2-octalins (XIIIa and XIIIb), in which the *trans-* isomer is always more reactive than the *cis-* isomer.

EXPERIMENTAL[23]

3-Keto-9-methyl-Δ^4-octahydronaphthalene (III). This was prepared by an effective variation of the method reported first by duFeu, McQuillin, and Robinson.[7] To a solution of 5.3 g. of 2-methylcyclohexan-1-one and 2.5 g. of 1-diethylaminobutan-3-one[24] in the presence of a small amount of hydroquinone was added, in small pieces, 0.1 g. of sodium metal at room temperature. After the sodium dissolved, the mixture was slowly heated to 135° in an oil bath, and this temperature was maintained for 3 hr. The dark brown solution was cautiously acidified with 10% hydrochloric acid under ice-cooling, and extracted with ether. Washing with water, drying, and evaporation of the ether extract gave an oily residue, which was distilled to give, with a considerable forerun (b.p. 65–70° at 30 mm.) containing the starting material, 1.0 g. (35%) of the Δ^4-3-ketone (III), b.p. 102–110° at 2.5 mm. Reported, b.p. 139° at 15 mm.[7]

It formed, in almost quantitative yield, the 2,4-dinitrophenylhydrazone, m.p. 145–150°, which was recrystallized from ethanol to give scarlet plates, m.p. 169°. Reported, m.p. 169°.[7]

Use of 1-N-piperidinobutan-3-one[25] instead of 1-N-diethylaminobutan-3-one gave almost the same result. To a mixture of 10.0 g. of N-piperidinobutanone, 15.0 g. of 2-methylcyclohexanone, and a small amount of hydroquinone, 0.3 g. of sodium metal was added with ice-cooling. The mixture was treated as described above and 3.5 g. (32%) of the Δ^4-3-ketone (III), b.p. 110–120° at 4 mm., was obtained, with recovery of 12.0 g. of the starting materials.

cis-9-Methyl-3-decalone (Ia). This was prepared by catalytic hydrogenation of the above monoenone (III) in the presence of palladium chloride, essentially following the method reported previously.[6,7] The procedure for isolation of the *cis*-ketone (Ia) from the hydrogenation mixture of isomeric ketones was improved. The monoenone (III, 10.0 g.), b.p. 140–150° at 16 mm., was hydrogenated over palladium-charcoal (prepared from 20 cc. of 1% palladium chloride solution and 2.0 g. of charcoal) at ordinary temperature and pressure. In 40 min., 1290 cc. (0.95 mole) of hydrogen was absorbed. After removal of the catalyst and solvent, the residual oil was subjected to steam-distillation. The first distillate (250 cc.) gave a colorless oil which immediately solidified. Filtering, drying, and washing with petroleum ether afforded 5.75 g. (57%) of *cis*-9-methyl-3-decalone (Ia), white prisms, m.p. 46°. An oil from the second distillate (100 cc.) was fractionated to give 3.45 g. of a colorless oil, b.p. 113–128° at 10 mm., which partly solidified on being stored in a refrigerator. Filtering by suction and washing with cold petroleum ether gave an additional 1.40 g. (total 70%) of the *cis*-ketone (Ia), m.p. 47°. Reported, m.p. 46–48°[6] and m.p. 47°.[7] It formed quantitatively the 2,4-dinitrophenylhydrazone, m.p. 152°, which was refluxed in ethanol for several hours and then recrystallized from ethanol to give orange needles, m.p. 173°. Reported, m.p. 174.5–175.5°.[6] The semicarbazone, m.p. 168–175°, obtained in 90% yield, was recrystallized from ethanol to give colorless prisms, m.p. 198–201°. Reported, m.p. 201–202°.[6] A colorless viscous oil,[26] separated from the solid ketone (Ia), amounted to 2.05 g. (20%).

cis-2-Bromo-9-methyl-3-decalone (IIa). To a stirred solution of 2.0 g. of *cis*-9-methyl-3-decalone (Ia), m.p. 46°, in 25 cc. of chloroform was added, dropwise, a solution of 2.0 g. of bromine in 15 cc. of the same solvent under ice-cooling. Bromine was immediately absorbed, and after the addition was completed, the stirring was continued for an additional 40 min. at room temperature. Evaporation of the chloroform under reduced pressure left a yellow oil, which was distilled to yield 2.7 g. (92%) of a pale yellow oil, b.p. 130–144° at 4 mm. When the bromination of Ia was carried out in glacial acetic acid, as described for preparing the *trans-*

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[23] All temperatures are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer model 21 double-beam spectrophotometer by Mr. Shindo of the Sankyo Co. Ltd., Tokyo, to whom the authors are greatly indebted. Microanalyses were by Miss Shibuya, and ultraviolet measurement by Miss Suzuki, both of this School.

[24] Wilds and Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).

[25] Wilds and Werth, *J. Org. Chem.*, **17**, 1149 (1952).

[26] Further separation of this mixture was effected through the hydroxymethylene derivative which will be reported in the near future.

monobromo ketone (IIb) from Ib,[3,5] the yield of IIa was relatively low (67%).

Reaction of cis-2-bromo-9-methyl-3-decalone (IIa) *with γ-collidine.* A solution of 0.39 g. of the above monobromo ketone (IIa) in 1 cc. of γ-collidine (b.p. 169–170°) was heated to a gentle reflux for 10 min. On cooling, the dark brown mixture was diluted with ether, and the collidine hydrobromide (0.31 g., 96%) was filtered off. The ether solution was worked up in the usual manner.[16] There was obtained 0.11 g. (42%) of a colorless oil, b.p. 103–124° at 4 mm.; λ_{max}^{MeOH} 236 mμ (ε 10,000), chiefly consisting of the Δ^4-3-ketone (III). This fraction formed, in 86% yield, the 2,4-dinitrophenylhydrazone, melting in the range of 98–121°, which was recrystallized from ethanol to give scarlet plates, m.p. 169°, undepressed on admixture with the sample described above.

Mattox-Kendall reaction of cis-2-bromo-9-methyl-3-decalone (IIa). To a solution of 0.10 g. of the *cis*-monobromo ketone (IIa) in 2 cc. of acetic acid was added 0.10 g. of 2,4-dinitrophenylhydrazine and the mixture was heated on a water bath for 5 min. After standing at room temperature for 2 hr., the reaction mixture was poured onto water (5 cc.), and 3-keto-9-methyl-Δ^1-octahydronaphthalene 2,4-dinitrophenylhydrazone (IVa) (0.13 g., 93%) was collected by filtration. Three recrystallizations from ethanol gave red needles, m.p. 153°; $\lambda_{max}^{CHCl_3}$ 258 mμ (ε 15,000) and 362.5 mμ (ε 22,600). On admixture with the same derivatives of the Δ^4-3-ketone (III) and the *trans*-isomer (IVb), m.p. 161–162°,[5] the melting points were depressed to 124–132° and 127–131°, respectively.

Anal. Calcd. for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 58.97; H, 6.05; N, 16.75.

To a suspension of 0.15 g. of the above hydrazone derivative (IVa) in 10 cc. of 50% acetic acid was added 0.5 cc. of freshly prepared pyruvic acid and the mixture was heated for 2 hr. on a water bath. On cooling, the clear yellow solution, separating yellow crystals, was neutralized with anhydrous sodium carbonate and extracted with ether. Washing with 10% aqueous sodium hydroxide, drying, and evaporation of the ether extract yielded a light brown oil, which was fractionated to 0.05 g. (63%) of the *cis*-Δ^1-3-ketone (Va), as a colorless oil, b.p. 95–96° at 3 mm.; λ_{max}^{EtOH} 229 mμ (ε 9500).

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.43; H, 9.81.

It formed quantitatively the semicarbazone, m.p. 200–201° (after recrystallization from dilute ethanol). Reported, m.p. 200–201°.[8]

Anal. Calcd. for $C_{12}H_{19}N_3O$: N, 18.99. Found: N, 19.00.

Reaction of cis-2-bromo-9-methyl-3-decalone (IIa) *with unhydrous sodium acetate. cis-2-Acetoxy-9-methyl-3-decalone* (VIa). A mixture of 0.51 g. of the *cis*-monobromo ketone (IIa) and 0.46 g. of anhydrous sodium acetate in 3.8 cc. of glacial acetic acid was refluxed in an oil bath for 2 hr. with exclusion of moisture. After cooling, the reaction mixture was poured onto 20 cc. of water and worked up as described for the *trans*-monobromo ketone (IIb).[3] As an alkali-soluble product, a minute amount of an oil, showing a violet-brown coloration with ferric chloride, was obtained. Presumably this oil contains the 2,3-diketone (VIIIa) described below, but it could not be characterized as a solid derivative. The oily neutral product was distilled to give 0.375 g. (80%) of *cis*-2-acetoxy ketone (VIa) as a colorless oil, b.p. 120–135° at 5 mm. Redistillation afforded an analytical sample, b.p. 125–130° at 4 mm.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.03; H, 9.02.

Reaction of cis-2-acetoxy-9-methyl-3-decalone (VIa) *with alkali.* The above 2-acetoxy ketone (VIa) was treated with alkali under conditions similar to those reported for the *trans*-isomer (VIb).[3] The *cis*-acetoxy ketone (VIa, 1.0 g.) was added to 17 cc. of 6% methanolic potassium hydroxide solution with cooling, and the mixture was allowed to stand at room temperature for 48 hr. A pale yellow solution was evaporated under reduced pressure, the residue was mixed with a small amount of water, and extracted with ether. Evaporation of the dried ether solution yielded 0.14 g. (14%) of an oil, containing mainly the starting acetoxy ketone.

The alkali solution was acidified and extracted with ether, and the ether solution was shaken with saturated sodium bicarbonate and with water, and dried. Evaporation of the ether left a yellow oil (0.42 g.) which was distilled to give 0.27 g. (33.5%) of *cis-2,3-diketo-9-methyldecalin* (VIIIa), a colorless oil, b.p. 115–116° at 4.5 mm.; λ_{max}^{EtOH} 271 mμ (ε 6500). It gave blue-violet coloration with ferric chloride. This formed, in 86% yield, a *glyoxime*, melting in the range of 170–180°, which was recrystallized from ethanol to give colorless prisms, m.p. 200–201° (dec.), showing red coloration with nickel salt.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.94; H, 8.37; N, 13.23.

The above bicarbonate solution was acidified and extracted with ether. Evaporation of the ether gave 0.32 g. of an oil which mostly solidified. Two recrystallizations from ethyl acetate afforded colorless prisms, m.p. 189–190°, undepressed on admixture with *cis*-1-methylcyclohexane-1,2-diacetic acid (VIIa) described below.

Oxidation of cis-2-acetoxy-9-methyl-3-decalone (VIa) *and cis-2,3-diketo-9-methyldecaline* (VIIIa) *with Perhydrol.* The *cis*-acetoxy ketone (VIa) was oxidized with Perhydrol (H_2O_2) by the procedure similar to that reported for the *trans*- isomer (VIb).[3] To a solution of 0.08 g. of VIa in 2 cc. of 6% methanolic potassium hydroxide was added dropwise 0.4 cc. of 30% Perhydrol. The mixture, which became turbid, was allowed to stand overnight at room temperature. The clear solution was worked up as usual, and there was obtained 65 mg. (85%) of the *cis*-diacid (VIIa), m.p. 170–178°, which was recrystallized from ethyl acetate to give colorless prisms, m.p. and mixed m.p. 188–190°.

The *cis*-2,3-diketone (VIIIa, 35 mg.) was treated with 0.2 cc. of Perhydrol in 1 cc. of methanolic potassium hydroxide solution as described above, but the mixture was allowed to stand for 6 hr. The crude *cis*-diacid, isolated in 90% yield, was recrystallized from ethyl acetate to give colorless prisms, m.p. and mixed m.p. 189–190°.

cis- and trans-1-Methylcyclohexane-1,2-diacetic acids (VIIa and VIIb, respectively). The *cis*-diacid (VIIa) was prepared by a slight modification of the method reported by Linstead, Millidge, and Walpole.[27] A mixture of 0.30 g. of the *cis*-ketone (Ia) and 4 cc. of concentrated nitric acid was heated to reflux for 30 min. After cooling, water (1.5 cc.) was added and the mixture was refluxed for one additional hour. On standing in a refrigerator overnight, 0.15 g. (40%) of the *cis*-diacid (VIIa) precipitated as a colorless solid, m.p. 160–170°. Recrystallization from ethyl acetate gave colorless prisms, m.p. 189–190°. Reported, m.p. 189–190°[10] and m.p. 190–191°.[28]

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.61; H, 8.81.

The optically active *trans*-diacid was reported to have been prepared from 1-*trans*-9-methyl-3-decalone by nitric acid oxidation.[29] The optically inactive *trans*-diacid was obtained from Ib by a slight modification of the reported procedure. The *trans*-ketone (Ib, 0.30 g.) was added dropwise to 4 cc. of concentrated nitric acid (*d* 1.44) under shaking. Slightly exothermic reaction took place under violent evolution of a brown-red gas. On refluxing the

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(27) Linstead, Millidge, and Walpole, *J. Chem. Soc.*, 1140 (1937).

(28) Dreiding and Tomasewski, *J. Org. Chem.*, 19, 241 (1954).

(29) Gautschi, Jeger, Prelog, and Woodward, *Helv. Chim. Acta*, **38**, 296 (1955); Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Am. Chem. Soc.*, **76**, 313 (1954).

mixture in an oil bath for 3 min., the violent reaction subsided. (Under such conditions, oxidation of the *cis*-ketone did not begin.) After addition of 1.5 cc. of water, the mixture was refluxed for further 30 min. There was obtained the *trans*-diacid (0.25 g., 65%), m.p. 190–193°, which was recrystallized from ethyl acetate to give crystals, m.p. 193–195°. Reported, m.p. 195°.[30]

Sodium borohydride reduction of cis-2-bromo-9-methyl-3-decalone (IIa).[31] The *cis*-monobromo ketone (IIa, 1.23 g.) was reduced with 0.20 g. of sodium borohydride in methanol as described for the *trans*-isomer (IIb).[5] The oily product (1.18 g.) was distilled to give a colorless viscous oil (0.95 g.), b.p. 116–123° at 3 mm., which presumably consisted predominantly of epimers of 2-bromo-9-methyl-*cis*-3-decalol (XIIa). It formed no precipitate with Brady's reagent (an alcoholic solution of 2,4-dinitrophenylhydrazine and sulfuric acid).

Zinc reduction of 2-bromo-9-methyl-cis-3-decalol (XIIa).[31] By the procedure reported for the *trans*-bromohydrin (XIIb),[5] 0.95 g. of the *cis*-isomer (XIIa) was reduced with 8.0 g. of zinc dust in 40 cc. of glacial acetic acid. The product, a pale yellow oil (0.62 g.), was distilled giving two fractions; a colorless oil (0.33 g., 57%), b.p. 108–115° at 50 mm., and a colorless oil (0.19 g., 30%), b.p. 121–125° at 12 mm. The lower-boiling fraction, which contained predominantly 9-methyl-Δ^2-octalin (XIIIa), was redistilled to give an oil, b.p. 107–109° at 48 mm. The infrared absorption spectrum possesses a weak but sharp band at 1653 cm.$^{-1}$, corresponding to a *cis*-disubstituted ethylene,[5] and a weak carbonyl band at 1718 cm.$^{-1}$, indicative of contamination with a trace amount of Ia. The higher-boiling fraction gave the crystalline *cis*-ketone (Ia), m.p. and mixed m.p. 48° (after washing with petroleum ether).

Permanganate oxidation of cis-9-methyl-Δ^2-octalin (XIIIa). In contrast to *trans*-9-methyl-Δ^2-octalin (XIIIb),[5] the *cis*-isomer (XIIIa) is quite resistant to permanganate in acetone solution at room temperature. The oxidation was effectively carried out with permanganate in sodium carbonate solution, essentially by the procedure reported previously.[32] To a mixture of 0.10 g. of the *cis*-octalin (XIIIa), 5 cc. of water, and a drop of 5% sodium carbonate, 25 cc. of 1% aqueous potassium permanganate solution was added dropwise under rapid stirring. The addition was completed in 3 hr. The reaction mixture was treated with sulfur dioxide and the separated oil solidified on standing in a refrigerator. The crystals (35 mg., 25%), m.p. 180°, were recrystallized from water to give white nodules, m.p. 189–190°, undepressed on admixture with the *cis*-diacid (VIIa) above described. The mother liquor of the crystals gave an additional 10 mg. (total 32%) of the *cis*-diacid (VIIa).

Dibromination-dehydrobromination of cis-9-methyl-3-decalone (Ia). The *cis*-ketone (Ia, 0.60 g.) was brominated with 2 moles of bromine, and the product, without purification, was heated with γ-collidine (3 cc.) at 170° for 70 min., by the procedure reported by Gunstone and Heggie[14] for the 9-methyl-3-decalone (I). Distillation of the oily product afforded a pale yellow oil (120 mg., 20.5%), boiling in the range 98–180° at 3 mm.; λ_{max}^{EtOH} 246 mμ (ε 8100). Redistillation gave two fractions; a colorless oil (0.03 g., 5%), b.p. 95–110° at 3 mm.; λ_{max}^{EtOH} 234 mμ (ε 8000), and a pale yellow oil (0.04 g., 7%), b.p. 130–140° at 3 mm.; λ_{max}^{EtOH} 240 mμ (ε 6000). The lower-boiling fraction formed, in 81% yield, the Δ^1-3-ketone 2,4-dinitrophenylhydrazone (IVa), m.p. 120–131°, which was recrystallized three times from ethanol to give red needles, m.p. and mixed m.p. 152°. The higher-boiling fraction yielded a mixture of 2,4-dinitrophenylhydrazones (0.04 g., 50%), melting in the range of 75–90°, which was chromatographed on alumina (1.5 g.). Elution with 1 cc. of carbon tetrachloride followed by recrystallization from ethanol afforded the derivative of the Δ^1-3-ketone (VIa), m.p. and mixed m.p. 152°. Further elution of the chromatogram with 5 cc. of carbon tetrachloride gave the derivative of *3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene* (XV), m.p. 130°[30] (after crystallization from ethanol). It showed no depression of the melting point on admixture with a sample prepared by the method reported by Woodward and Singh.[33]

In another run, dibromination of the *cis*-ketone (Ia) was conducted in the same solvent at a somewhat higher temperature. Thus, 0.21 g. of Ia in 2 cc. of glacial acetic acid was treated with 0.42 g. of bromine in 2 cc. of the same solvent under ice-cooling, with stirring. After the complete addition of bromine, the yellow solution was slowly warmed to 50°, and this temperature was maintained for 30 min. on a water bath. The water bath was removed, the stirring was continued for 4 hr., and the white precipitate (0.16 g., 39%), m.p. 158–160°, was filtered. The mother liquor, after standing in a refrigerator overnight, was evaporated under reduced pressure to give additional crystals (0.16 g., total 78%), m.p. 158–160° (after washing with petroleum ether). Two recrystallizations from petroleum ether gave colorless needles, m.p. 160–161°.

Anal. Calcd. for $C_{11}H_{16}Br_2O$: C, 40.74; H, 4.98. Found: C, 40.41; H, 5.05.

The solid dibromo ketone differed somewhat from the liquid one in behavior toward bases.

Reaction of cis-2,4-dibromo-9-methyl-3-decalone (XIVa) *with anhydrous sodium acetate.* The dibromo ketone (XIVa), used for acetolysis, was prepared from the *cis*-ketone (Ia, 0.50 g.) with 2 moles of bromine (0.98 g.) in chloroform under the conditions employed for the monobromo ketone (IIa). Acetolysis of the crude dibromo ketone (1.0 g.) was carried out, exactly following the procedure reported for the *trans*-dibromo ketone (XIVb).[3] A neutral product, containing *cis-2-acetoxy-3-keto-9-methyl-Δ^1-octahydronaphthalene* (XVIa), was obtained as a colorless viscous oil (0.50 g., 75%), b.p. 127–143° at 4 mm. Redistillation gave an oil, b.p. 130–135° at 4 mm.; λ_{max}^{MeOH} 239 mμ (ε 2300).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.06; H, 8.22.

The alkali-soluble fraction afforded a small amount of a yellow viscous oil (0.03 g., 5.5%), containing mainly the above 2,3-diketone (VIIIa). It showed dark blue–violet coloration with ferric chloride. The glyoxime, m.p. 195–199°, was obtained in 72% yield, which was recrystallized from methanol to give prisms, m.p. and mixed m.p. 200–201°.

Reaction of cis-2-acetoxy-3-keto-9-methyl-Δ^1-octahydronaphthalene (XVIa) *with alkali.* The acetoxy-Δ^1-3-ketone (XVIa, 0.30 g.) was treated with 6% methanolic potassium hydroxide (5.1 cc.) as described above for the *cis*-2-acetoxy ketone (VIa). The starting material (0.02 g., 7%) was recovered as a neutral fraction. The alkali-soluble fraction afforded a pale yellow oil (0.11 g.) which was distilled to give 0.10 g. (40%) of the 2,3-diketone (VIIIa), as a colorless oil, b.p. 103–104° at 3 mm. It gave blue-violet coloration with ferric chloride and formed a glyoxime, m.p. and mixed m.p. 200–201° (after crystallization from methanol). The bicarbonate-soluble fraction gave an oil (0.12 g., 41%) which mostly solidified. Recrystallization from ethyl acetate afforded the *cis*-diacid (VIIa) as colorless prisms, m.p. and mixed m.p. 189–190°.

Lithium aluminum hydride reduction of cis-9-methyl-3-decalone (Ia). *Formation of cis-9-methyl-cis-3-decalol* (XVII). To a stirred solution of 0.5 g. of the *cis*-ketone (Ia) in 20

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(30) Yanagita and Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955).

(31) This experimentation was carried out by M. Hirakura in our Laboratory.

(32) Linstead, Millidge, and Walpole (ref. 10) reported that dehydration of *cis*-9-methyl-2-decalol afforded an impure 9-methyl-Δ^2-octalin (XIII), b.p. 78–80° at 12 mm., which was oxidized with permanganate in aqueous sodium carbonate to give the *cis*-diacid (VIIa) in about 8% yield.

(33) Woodward and Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

cc. of absolute ether was added, dropwise, a solution of lithium aluminum hydride in 30 cc. of the same solvent with shaking. A slightly exothermic reaction took place to give a white precipitate. The mixture was heated to reflux on a water bath for 3 hr. After processing in the usual manner, 0.50 g. (quantitatively) of *cis*-9-methyl-*cis*-3-decalol (XVII) was obtained as white crystals, m.p. 62–66°. Recrystallization from petroleum ether gave colorless prisms, m.p. 67.5°. The infrared absorption spectrum; 1007 m, 1034 s, 1058 s, 1088 m cm $^{-1}$ (Fig. 1). Hussey, Liao, and Baker gave m.p. 67° for 9-methyl-*cis*-3-decalol prepared from the *cis*-ketone (Ia) by catalytic hydrogenation.[18]

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.15; H, 11.94.

An *acetate*, prepared with acetic anhydride and pyridine, was obtained as a colorless oil, b.p. 130–135° (bath-temperature) at 5 mm. The infrared absorption spectrum is shown in Fig. 1.

The decalol (XVII) formed, in 94% yield, a *3,5-dinitrobenzoate*, m.p. 93–97.5°, which was recrystallized from *n*-hexane to give colorless needles, m.p. 98–99°. The above authors[17] gave m.p. 97.5–98.5°.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.23; H, 5.87; N, 7.88.

A mixture of equimolar amounts of the 3,5-dinitrobenzoate (0.06 g.) and α-naphthylamine (0.03 g.) was dissolved into a few drops of ethanol. Without delay, an *addition compound* (0.08 g., 97%) separated as orange crystals. Recrystallization from petroleum ether gave orange plates, m.p. 101.5–102°.

Anal. Calcd. for $C_{28}H_{29}N_3O_6$: C, 66.78; H, 5.81; N, 8.35. Found: C, 66.42; H, 6.19; N, 8.48.

To a solution of 0.17 g. of the decalol (XVII) in 2 cc. of pyridine and 2 cc. of anhydrous benzene was added 0.30 g. of anthraquinone-β-carboxylic chloride, and was allowed to stand 5 days. The separated solid was filtered and washed with ether, and the filtrate, combined with the ether washing, was worked up by the procedure reported previously.[34] There was obtained a yellow viscous oil (0.19 g.), which upon treatment with petroleum ether gave 0.11 g. (24%) of yellow crystals, m.p. 111–115°. Two recrystallizations from petroleum ether afforded light yellow prisms, m.p. 123–126°.

Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 76.99; H, 6.84.

Attempted hydrogenation of the *cis*-ketone (Ia, 0.05 g.) over platinum dioxide (0.01 g.) in acidic medium under normal pressure was made, but the starting ketone was quantitatively recovered.

trans-9-Methyl-cis-3-decalol (XVIII). This was prepared by reduction of *cis*-9-methyl-3-decalone (Ia, 0.30 g.) with sodium (1.0 g.) and ethanol (30 cc.),[35] exactly following the procedure described earlier for the *trans*-ketone (Ib).[4] There was obtained a yellow oil (0.28 g.), which was chromatographed on alumina (6 g.). Elution with petroleum ether afforded 0.08 g. (27%) of the starting ketone, m.p. and mixed m.p. 46°. Further elutions with petroleum ether-benzene (1:1) (10 cc.) and benzene (10 cc.) gave a pale yellow oil (0.115 g., 37%), giving no precipitate with Brady's reagent. This oil formed quantitatively an oily 3,5-dinitrobenzoate (0.23 g.), which could not be induced to crystallize and was chromatographed on alumina (6 g.). Elutions with petroleum ether (30 cc.) and with benzene (10 cc.) yields, respectively, 105 mg. and 65 mg. (total 74%) of a colorless oil, which, by the procedure described above for the same derivative of XVII, formed quantitatively an α-naphthylamine addition compound, m.p. 95–99°. An oily residue (60 mg.) from elution with benzene-ether (1:1) (50 cc.) gave no crystalline compound with α-naphthylamine. The addition compound was recrystallized from petroleum ether to give orange needles, m.p. 104–105°. On admixture with the addition compound of the *cis,cis*-decalol (XVII), the melting point was slightly depressed to 98–100°.

Anal. Calcd. for $C_{28}H_{29}N_3O_6$: C, 66.78; H, 5.81; N, 8.55. Found: C, 66.60; H, 6.06; N, 8.07.

Reduction of the *cis*-ketone (Ia) with sodium and amyl alcohol gave in a better yield the decalol (XVIII) of higher purity. To a refluxed solution of 0.30 g. of the *cis*-ketone in 30 cc. of amyl alcohol (b.p. 130–135°) in an oil bath was added, in small portions, 1.2 g. of sodium metal during 20 min. After violent reaction subsided, the reflux was continued further for 2 hr. On cooling, the mixture was diluted with ether and washed repeatedly with water. The organic layer was evaporated under reduced pressure, the residual oil was dissolved in ether, and dried over anhydrous sodium sulfate. Evaporation of the ether and subsequent distillation of the residual oil gave 0.24 g. (79%) of the *trans,cis*-decalol (XVIII), as a colorless oil, b.p. 104–107° at 4.5 mm. It could not be induced to crystallization even after redistillation (b.p. 104–106° at 4.5 mm.). The infrared absorption spectrum; 1007 m, 1022 s, 1034 s, 1054 s, 1086 w cm.$^{-1}$ (Fig. 1). This oil formed quantitatively an oily 3,5-dinitrobenzoate, which afforded a quantitative yield of α-naphthylamine addition compound, m.p. and mixed m.p. 104–105° (after recrystallization from petroleum benzine).

An *acetate*, prepared with acetic anhydride and pyridine, was obtained as a colorless oil, b.p. 115–116° at 6 mm. The infrared absorption spectrum is shown in Fig. 1.

By the procedure described above for the *cis,cis*-decalol (XVII), this oil (0.08 g.) was converted to an anthraquinone-β-carboxylate (0.02 g., 10%), light yellow prisms, melting in the range 112–130°. Two recrystallizations from petroleum benzine raised the m.p. to 153–155.5°.

Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 78.37; H, 7.08.

SHINJUKU-KU, TOKYO, JAPAN

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[34] Reichstein, *Helv. Chim. Acta*, 9, 805 (1926).

[35] Correction; reference 4, page 1770, line 4, read "30 cc. of ethanol" instead of "300 cc. of ethanol."