Attempted isomerization of 6-exo-methylene-4α-methyl-17α,20,20,21-bismethylenedioxyallopregnane-3,11-dione. Only starting material was recovered on attempted isomerization of 10 mg. of VII with 1 drop of 60% aqueous perchloric acid in 2 ml. of chloroform at room temperature overnight, or with 20 mg. of *p*-toluenesulfonic acid and 2 cc. of chloroform at reflux for 2 hr.

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Structure of Rhein[1]

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AND TOSHIRO MATSUOKA

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Rhein, a constituent of rhubarb,[2-5] has been known to have the structure of 1,8-dihydroxyanthraquinone-3-carboxylic acid (I).[6]

It was reported recently by Hörhammer, *et al.*[7] that rhein was converted by treatment with acid into another substance which reverted again to rhein on alkaline treatment in the presence of air. They considered from this finding that the previously described rhein (I) must be a dehydrodianthrone compound (II) and the product of the acid treatment has structure I which had been recognized as rhein. Thus they named the former compound (II) "dirhein" and the latter (I) "monorhein."

The German researchers described that rhein (their "dirhein," m.p. 316–319°) obtained from *Rheum palmatum* was dissolved in potassium hydroxide solution, mixed with methanol, and refluxed with an excess of hydrochloric acid for two hours. By subsequent sublimation and recrystallization of the reaction products, they obtained "monorhein" and "monorheinanthranol," the structures of which were derived from the data of infrared spectrum and paper chromatography.

We have found rhein to be unsusceptible to boiling hydrochloric acid in the absence of methanol. Therefore "monorhein" was thought to be rhein methyl ester. The infrared spectrum of "monorhein" was also suggestive of the presence of an ester group. With this view, a re-examination of the structure of rhein was made in this laboratory.

Repetition of the experiment reported by Hörhammer, *et al.* was conducted with rhein, m.p. 318–319°, which was isolated from the fresh rhizome of *Rheum coreanum* Nakai and shown to be identical with "dirhein" by comparison of their ultraviolet and infrared spectra and melting points. Following their conditions exactly, rhein was treated with hydrochloric acid and methanol, and a mixture of two substances was obtained which gave R_f values of 0.32 and 0.84 on the paper chromatogram. If these substances are "monorhein" and "monorheinanthranol," the mixture should be extractable by aqueous sodium bicarbonate. The present experiment showed, however, that the mixture was largely insoluble in bicarbonate solution, and from this insoluble portion there were obtained orange crystals melting at 174° (R_f 0.84). The elemental analysis suggested the product to be rhein methyl ester and its melting point was in agreement with that reported by Robinson.[8] Rhein methyl ester was then prepared from rhein by the action of diazomethane and compared with the above product in mixed melting point, infrared and ultraviolet spectra, paper chromatography, and other properties. This comparison proved the identity of the two compounds. Furthermore, the ultraviolet and infrared spectra were indistinguishable from those of "monorhein." "Monorhein" was thus verified to be rhein methyl ester. From the alkaline layer of the above extraction was recovered a small amount of rhein (R_f 0.32) which was characterized by melting point and infrared spectrum.

Rhein was further converted into its ethyl ester,[8,9] diacetyl ethyl ester,[8] and diacetate.[3,4,8,10,11] Oxidation of aloe-emodin triacetate[10] with chromium trioxide also furnished rhein diacetate.[3,4,8,10,11] Elemental analyses, melting points, and infrared spectra of these derivatives provided additional evidence for the structure of rhein (I). The fact that rhein diacetate was produced from aloe-emodin triacetate. This fact constitutes further proof that bimolecular structure (II) is untenable.

The German authors have given four reasons for the "monorhein-dirhein" hypothesis: 1) conversion of rhein to monorhein and monorheinanthranol by oxidative and reductive cleavages, 2) formation of dirhein by dimerization of monorhein, 3) absence, in the infrared spectrum of dirhein, of a band corresponding to the nonchelated carbonyl group which is observed in the spectrum

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(1) This work was briefly reported in a preliminary communication, *Chem. Pharm. Bull.* (Tokyo), **6**, 566 (1960).

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(3) O. Hesse, *Pharm. J.*, (4), **1**, 325 (1895); O. A. Oesterle and F. Tisza, *Schweiz. Wochschr. Chem. Pharm.*, **46**, 701 (1908); A. Tschirch and K. Heuberger, *Arch. Pharm.*, **240**, 596, 610 (1902); O. Fischer, F. Falco, and H. Gross, *J. prakt. Chem.*, (2), **83**, 208 (1911).

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of monorhein, and 4) thermochromism. In view of the present conclusion it becomes evident that these explanations have been derived from the unfortunate misinterpretation of the experimental results.

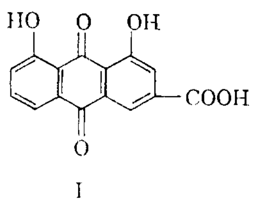
On elemental analysis their samples of "monorhein" and "dirhein" gave incombustible residues, 1.43% and 9.30%, respectively, and the results are inconsistent even with the calculated values of their own. Such difficulties in combustion of rhein have never been experienced by other researchers,[2,4,6] who all obtained the results consistent with structure I, as was also the case with the present study.

The infrared spectral data were reported to be the main ground for the hypothesis. Apparent absence of an absorption corresponding to the nonchelated carbonyl group at around 1680 cm.$^{-1}$ in the spectrum of rhein ("dirhein") must possibly be ascribed to the overlapping of a neighboring strong band of the carboxyl at 1701 cm.$^{-1}$ This interpretation proved to be correct when the infrared spectra of the ammonium salt of rhein and rhein methyl ester ("monorhein") are examined. In those spectra the neighboring carboxyl band shifts respectively to a lower frequency by the salt formation and to a higher frequency by esterification and the carbonyl band (1667 and 1684 cm.$^{-1}$, respectively) appears clearly.

Thermochromism observed with "dirhein" was considered as an evidence for the presence of an aromatic-substituted ethylene linkage. It may be said that sufficient data have not been accumulated to take this phenomenon as a decisive proof for the presence of the linkage.[12]

The above results and discussion lucidly explain the relationship between "monorhein" and "dirhein." Interconversion of the two compounds by respective treatment with acid and alkali is simply a process of esterification and hydrolysis.

The German researchers further indicated the simultaneous occurrence of "monorhein" and "dirhein" in the rhubarb extracts. It is obvious from the present experiment that partial esterification took place probably in their extraction process which involved boiling with methanol and hydrochloric acid. By working up the rhubarb extracts they obtained "dirhein" from the fraction soluble in aqueous sodium bicarbonate, but were unable to isolate "monorhein." Failure of the isolation of "monorhein," now identified as rhein methyl ester, is natural because it is insoluble in sodium bicarbonate solution.



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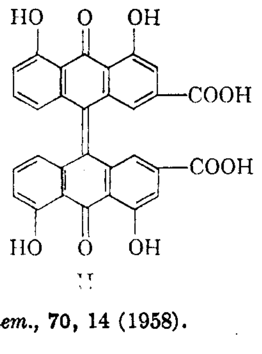

II

Thus, the structure of rhein was reconfirmed to be I and "monorhein" was identified as rhein methyl ester. The hypothesis of "monorhein-dirhein," therefore, is untenable.

EXPERIMENTAL[13]

Rhein. The ethanol extractables of the fresh rhizome of *Rheum coreanum* Nakai were extracted with chloroform and the anthraquinone mixture obtained was shaken with 10% sodium bicarbonate solution. The portion soluble in the alkaline solution furnished orange granules, m.p. 318–319° dec. Infrared ν_{max}^{KBr}: 1701 cm.$^{-1}$ (carboxyl), 1637 cm.$^{-1}$ (chelated carbonyl); ultraviolet $\lambda_{max}^{methanol}$: 229 mμ (ϵ 36,800), 258 mμ (ϵ 20,100), 435 mμ (ϵ 11,100).

Anal. Calcd. for $C_{15}H_8O_6$: C, 63.39; H, 2.84. Found: C, 63.40; H, 2.85.

The ammonium salt was prepared by evaporation of a solution of rhein in aqueous ammonia. Infrared ν_{max}^{Nujol}: 1667 cm.$^{-1}$ (free carbonyl).

Treatment of rhein with hydrochloric acid-methanol. Following Hörhammer's description, 100 mg. of rhein, m.p. 318–319° dec., was dissolved in 5 cc. of *N* potassium hydroxide solution, mixed with 95 cc. of methanol and refluxed with 50 cc. of 25% hydrochloric acid for 2 hr. The mixture was concentrated *in vacuo* and the residue was washed with water until the washings became neutral. The yellow powder obtained gave two spots (R_f 0.32 and 0.84) on the paper chromatogram (solvent system: 1-butanol saturated with water; ascending method). The mixture was dissolved in chloroform and extracted with 10% sodium bicarbonate solution. The chloroform layer was washed with water, dried over sodium sulfate, and evaporated. Recrystallization of the crude substance from a mixture of chloroform and methanol afforded 60 mg. of orange granules, m.p. 174°, R_f 0.84. Infrared ν_{max}^{KBr}: 1733 cm.$^{-1}$ (ester), 1684 cm.$^{-1}$ (free carbonyl), 1634 cm.$^{-1}$ (chelated carbonyl); ultraviolet $\lambda_{max}^{methanol}$: 231 mμ (ϵ 44,200), 257 mμ (ϵ 20,600), 430 mμ (ϵ 11,700).

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38; OCH_3, 10.40. Found: C, 64.33; H, 3.37; OCH_3, 10.46.

The physical constants of this product were in good agreement with those reported for rhein methyl ester. The compound was the same as the rhein methyl ester prepared by the method described below. Its melting point and ultraviolet and infrared spectra were identical with those for Hörhammer's "monorhein."

The bicarbonate layer of the above extraction was made acid, and the precipitate was recrystallized from dioxane to yield 20 mg. of rhein, m.p. 315° dec. The R_f value (0.32), mixed melting point determination and infrared spectrum characterized the compound.

Rhein methyl ester. To a solution of 50 mg. of rhein in 50 cc. of dioxane was added 5 cc. of an ethereal solution of diazomethane (prepared from 150 mg. of nitrosomethylurea). After standing for 3 hr. at room temperature, the red solution was concentrated *in vacuo* to dryness and the residue was recrystallized from chloroform-methanol to give 37 mg. of rhein methyl ester, m.p. 175°.

Rhein diacetate from aloe-emodin triacetate. To a solution of 553 mg. of aloe–emodin triacetate in 15 cc. each of acetic acid and acetic anhydride was added drop-wise a solution of 550 mg. of chromium trioxide in 15 cc. of acetic acid and 1 cc. of water at 55° over a period of 30 min. The mixture was then stirred at 65–70° for 3 hr. and poured into lukewarm water. The precipitate was filtered off and recrystallized from dioxane to give 320 mg. of yellow granules, m.p.

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(12) G. Kortüm, *Angew. Chem.*, **70**, 14 (1958).

(13) All melting points are uncorrected.

247–247.5° dec. Infrared ν_{max}^{Nujol}: 1773 cm.$^{-1}$ (ester), 1701 cm.$^{-1}$ (carboxyl), 1689 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_{19}H_{12}O_8$: C, 61.96; H, 3.29. Found: C, 62.17; H, 3.49.

The product was confirmed to be identical with authentic rhein diacetate.

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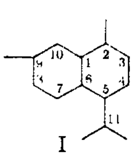
Structures of Carotol and Daucol[1]

L. H. ZALKOW, E. J. EISENBRAUN,[2] AND J. N. SHOOLERY[3]

Received June 3, 1960

Three different carbon skeletons have been proposed for the sesquiterpenic alcohol carotol. Sorm and Urbanek[4] originally proposed formula I; carotol was represented as having a hydroxy group at C_{11} and a double bond at C_1—C_2. These workers[5] later suggested that the hydroxy group was at C_6 and the double bond at C_8—C_9 or C_9—C_{10}. Very recently Sorm and co-workers[6] proposed formula II for carotol on the basis of new degradative experimental work. At the time of the latter report there appeared another publication in which other workers[7] offered evidence in support of formula III.



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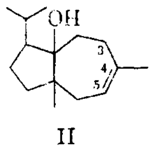

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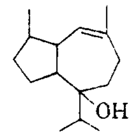
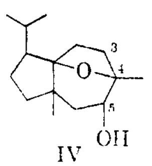
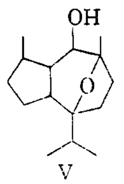


III

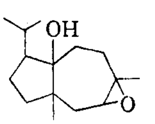
Daucol (carotol oxide), another sesquiterpenic constituent of the oil of *Daucus carota L.*, is also obtained from carotol on oxidation with peracids.[4] Originally daucol was believed to be the epoxide of carotol, but it was recently shown that oxidation of daucol gives a keto ether, $C_{15}H_{24}O_2$, and formula IV was proposed as the structure of daucol.[6]



IV



V



VI

We were in the process of determining the absolute configuration of carotol when the recent conflicting reports appeared. We wish to offer evidence which, together with the recent work of Sorm, *et al.*,[6] shows that structures represented by formulas I and III are untenable and that formula II or its isomer with the double bond at C_3—C_4 represents the correct structure of carotol.

Carotol was isolated from carrot seed oil, as previously described, and converted to daucol by oxidation with peracids.[4] The NMR spectrum of daucol is consistent only with formula IV. Formula V would represent daucol if carotol were correctly represented by formula III.

The two sharp lines at 64 cps (δ = 8.932) and 82 cps (δ = 8.632) in the NMR spectrum of daucol can be assigned to the bridgehead methyl group of IV and the methyl group at the tertiary carbon C_4, respectively, since neither line shows spin coupling to a neighboring proton. The methyl group attached to the five-membered ring of V would show a doublet character similar to that observed for each of the isopropyl methyls at 49 and 63 cps (δ = 9.184 and 8.950). The isopropyl methyl groups possess different chemical shift values in this compound (see reference 8 for discussion of this). Further evidence for IV in preference to V is the four line pattern at 224 cps (δ = 6.265) which arises from the proton attached to the same carbon atom as the hydroxy group in IV. The two protons of the adjacent CH_2 group couple their spins to this proton with different coupling constants, leading to the observed pattern. In the case of V, the single neighboring proton could not split the resonance of the proton in question into more than a doublet.

The acetate of daucol was prepared and its NMR spectrum showed the isopropyl methyls unshifted relative to daucol itself, while the bridgehead methyl and tertiary methyl group at C_4 showed small shifts. The large shift of the multiplet from 224 cps to 296 cps (δ = 5.070), a shift of 1.20 parts per million, is characteristic of the behavior of a proton adjacent to hydroxy upon acetylation of the hydroxy group. Therefore, the hydroxy group of daucol is adjacent to CH_2 and IV represents the correct structure; VI, which corresponds to the epoxide of II, is excluded. With the evidence available it is not possible to say with certainty whether the hydroxy group in IV is at position 5 or 3.

The NMR spectrum of carotol itself showed a flat-topped peak in the olefinic region which is characteristic of an olefinic proton adjacent to a CH_2 group. Treatment of carotol with permanganate at 0° gave the previously reported triol.[4]

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(1) This work was supported in part by Frederick Gardner Cottrell Grant from the Research Corporation and the Research Foundation of Oklahoma State University.

(2) Department of Chemistry and Chemical Engineering, Stanford University, Stanford, Calif.

(3) Varian Associates, Palo Alto, Calif.

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