Papergram mobilities[6] relative to 16α-hydroxy-9α-fluorohydrocortisone include: System I, 0.35; System II, 0.48; System III, 0.42. The steroid reduces alkaline Tetrazolium Blue reagent and gives a yellow fluorescent reaction with isonicotinic acid hydrazide[7] on papergrams. A normal Porter-Silber chromogen[8] with λ_{max} 413 mμ ($E^{1\%}_{1cm}$. 395) *vs.* λ_{max} 414 mμ. ($E^{1\%}_{1cm}$. 374) *for 9α-fluorohydrocortisone is found. Maximum* color development with alkaline Tetrazolium Blue[9] occurred at 30 min., with λ_{max} 520 mμ ($E^{1\%}_{1cm}$. 580) *vs.* λ_{max} 525 mμ ($E^{1\%}_{1cm}$. 654) for 9α-fluorohydrocortisone, also maximum at 30 min.

Spectra in 0.066*N* ethanolic potassium hydroxide at room temperature (22°) showed a slow shift from λ_{max} 233 mμ ($E^{1\%}_{1cm}$. 312) at 3 min. to λ_{max} 235 mμ ($E^{1\%}_{1cm}$. 226), 380 mμ (28) at 24 hr. At 60° the spectra changed from λ_{max} 232 mμ ($E^{1\%}_{1cm}$. 308) at 3 min., λ_{max} 236 mμ (172) at 1 hr., λ_{max} 239 mμ (132), 378 mμ (62) at 2 hr., to λ_{max} 248 mμ (142), 378 mμ (91) at 3 hr., typical of spectral changes associated with the 6β-hydroxy-Δ⁴-3-ketone chromophore.[8]

The fractions eluted about hold-back volume 3.2 were reduced in volume under vacuum, analyzing by paper chromatography as a single major reducing component of R_f 0.06 in System II. Crystallization of the material from acetone–chloroform–ethyl acetate (1:1:2) yielded 7.1 mg. of crystals, whose infrared absorption spectra indicated the same general structural features to be present as were present in the spectra of II. No further characterization was made of this component.

21-Acetoxy-9α-fluoro-6β,11β,17α,21-tetrahydroxy-4-pregnene-3,20-dione IV. Ten grams of 9α-fluorohydrocortisone 21-acetate (Ia) was added to a solution of 75 ml. of dioxane, 10 ml. of trimethyl orthoformate, and 0.5 ml. of absolute methanol. To this suspension was added 10 ml. of dioxane containing 0.5 ml. of concd. sulfuric acid. After 10 min. a clear solution resulted. After 20 min. at room temperature pyridine was added dropwise until the deep red color of the solution was discharged (total pyridine used, about 1 ml.). The reaction mixture was poured into water, giving an oily material which was extracted into ether. the ether extract washed with saline, and then dried. The ether volume was increased to 200 ml. and 120 ml. of 0.31*N* monoperphthalic acid in ether was added. The reaction mixture was then stored in the dark for 15 hr., at which time the precipitated crystalline product was filtered and washed with ether (4.4 g. weight). Recrystallization from ethyl acetate yielded 1.635 g. of pure IV, m.p. 248–252° dec. (capillary); $[\alpha]^{25}_D$ + 70° (pyridine); λ_{max} 232 mμ (ε 14,000); λ^{KBr}_{max} 2.87, 5.72 (Sh), 5.87, 5.92 (Sh), 5.97, 8.06, 10.04, and 10.61 μ.

Anal. Calcd. for $C_{23}H_{31}O_7F$: C, 63.00; H, 7.13; F, 4.33. Found: C, 62.46; H, 7.26; F. 4.44.

The mother liquors on standing deposited an additional 0.60 g. of crude product, which was recrystallized from ethyl acetate/heptane, 0.24 g., m.p. 234–239° (capillary).

9α-Fluoro-6β,11β,17α,21-tetrahydroxy-4-pregnene-3,20-dione (II). A solution of 600 mg. of the 21-acetate IV in 100 ml. of absolute methanol was prepared under a nitrogen atmosphere. To this solution was added 3.0 ml. of a 10% aqueous potassium carbonate solution. After 1 hr. (under nitrogen) the reaction mixture was neutralized with acetic acid, most of the methanol removed under vacuum, and the reaction concentrate was poured into water. The solids recovered by filtration were recrystallized several times from ethyl acetate–heptane, yielding 145 mg. of plates, m.p. 214–244° (capillary), which after drying in vacuum melted at 235–239° dec. (capillary), 223–225° dec. (Kofler block); $[\alpha]^{25}_D$ + 57.7° (pyridine); λ_{max} 232 mμ (ε 15,000).

Anal. Calcd. for $C_{21}H_{29}O_6F$: C, 63.62; H, 7.37; F, 4.79. Found: C, 63.54; H, 7.60; F, 4.65.

The identity of the microbiologically derived II with II derived chemically was established by comparison of infrared spectra, sulfuric acid spectra, melting points and papergram mobility, and color test behavior.

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Chloromethylation. A Novel Route to 4-Methylsteroids

JOHN H. FRIED, ANTHONY N. NUTILE, AND GLEN E. ARTH

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Enol acetates of Δ⁴-3-ketosteroids have been utilized to introduce halogen,[1,2] nitro and hydroxyl substituents at C_6 of steroids by an electrophilic process. An extension of this reaction to include carbonium ions could be a useful path to the biologically important C_6 alkylated steroids.

The solvolytic reaction of chloromethyl methyl ether in acetic acid appeared to be a suitable source of an electrophilic fragment, the chloromethyl carbonium ion.[3] A solution of this reagent and 17α,-20,20,21-bismethylenedioxy-3-acetoxy-3,5-pregnadiene-11-one, II, afforded a crystalline product after percolation through alumina. This product was shown to be a mixture by NMR[4] analysis but could not be resolved by recrystallization or chromatography. However, reduction of the crude crystalline product with zinc in acetic acid afforded 4-methylcortisone BMD,[5] V, in *ca.* 11% overall yield. It follows that 4-chloromethylcortisone BMD, III, was one of the components of the chloromethylation mixture. All attempts to isolate this product failed. However, repeated crystallizations from methanol did afford a second component of the mixture IV in addition to hydrogen chloride. A simpler procedure for isolating IV was to reflux the mixture with dilute hydrochloric acid in methanol. This treatment destroyed the 4-chloromethyl-

(1) A. Bowers, L. C. Ibanez, and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 3707 (1959) and references cited.

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(3) The attacking species is represented as $^+CH_2Cl$ as a matter of convenience but could equally well be $CH_3O^+CH_2Cl$ (H) or one of several ion pairs.

(4) NMR spectra were run on a Varian 60MC Spectrometer at a concentration of *ca.* 20 mg. in 0.3 ml. deuterochloroform. $\tau = \gamma/60 + 3.5$ where γ is the observed band position in c.p.s. relative to benzene as external standard. *Cf.* G. V. D. Tiers, *J. Phys. Chem.*, 62, 1151 (1958). We wish to thank B. Arison and Dr. N. R. Trenner for the determination and interpretation of the NMR spectra.

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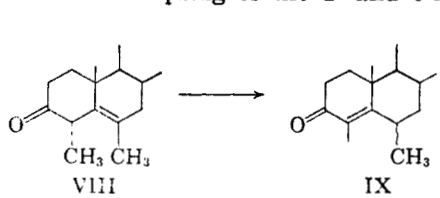
cortisone BMD and afforded IV in pure state. As cortisone BMD was not present in addition to IV, it was assumed that a disproportionation reaction of 4-chloromethylcortisone BMD at least partially accounted for the observed results. Analysis of IV, $C_{26}H_{31}O_6Cl$, indicated the incorporation of two atoms of carbon and one atom of chlorine into cortisone BMD. One of the carbons is present as an exomethylene function, infrared $\lambda_{max}^{CHCl_3}$ 6.20, 11.38 μ, NMR 2 hydrogens τ 4.64.

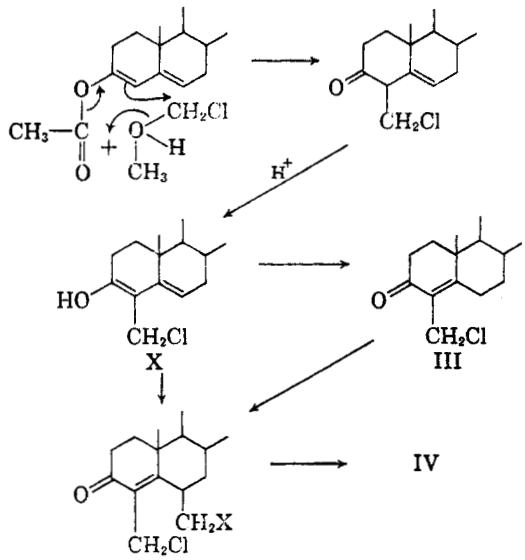
The other carbon and chlorine is present as a chloromethyl group, assigned to C_4 on the basis of NMR spectral data, indicating replacement of the vinyl proton at C_4 by a methylene group, 2 hydrogens τ 5.87, 5.70, 5.40, 5.23 (chloromethyl). Splitting of the chloromethyl function suggests restricted rotation. Molecular models indicate that a 6-*exo*-methylene group but not a 2-*exo*-methylene restricts free rotation of the 4-chloromethyl. The relatively low wave-length peak in the ultraviolet, λ_{max} 253 mμ, may then be ascribed to steric inhibition of resonance. Reduction of IV with Raney nickel afforded the corresponding chlorine-free dienone VI. The shift to higher wavelength in the ultraviolet, λ_{max} 258 mμ, is consistent with a smaller steric factor in the chlorine-free product. Conversion of the chloromethyl to a new methyl group on a carbon bearing no hydrogen is also shown by the NMR spectrum of VI, 2 hydrogens τ 4.71, 5.15 (—C(=CH$_2$)—), 3 hydrogens τ 8.15 (=CCH$_3$).

Reduction of IV with zinc in acetic acid yielded a chlorine-free product VII showing no absorption in the ultraviolet. The presence of an *exo*-methylene group is indicated by infrared peaks at 6.07 and 11.07 μ. In addition to the *exo*-methylene group the NMR spectrum of VII shows formation of a new methyl function on a methine carbon, 2 hydrogens τ 5.10, 5.25 (C=CH$_2$), 3 hydrogens τ 8.98, 9.09, (CH—CH$_3$). This evidence is consistent with removal of chlorine and saturation of the 4,5-double bond in IV. The methyl group in VII is assigned the α and the ring juncture the *trans* configuration since chemical reduction generally yields the more stable product.[6] Attempts to isomerize VII to the conjugated enone IX *via* VIII gave only recovered starting material.[7] Molecular models indicate eclipsing of the 4- and 6-methyls in VIII. This interaction is presumably responsible for the observed result.



VIII IX

The introduction of a chloromethyl at C_4 into the enol acetate II can be considered to proceed *via* the cyclic mechanism depicted:



A similar mechanism proceeding through the 3-enol can be written for cortisone BMD. Further reaction of III with chloromethyl methyl ether or formaldehyde at C_6 *via* the enol X would then lead to a 6-hydroxy or 6-halomethyl derivative which is converted toIV by the loss of the elements of HX.

EXPERIMENTAL[8]

17α,20,20,21-Bismethylenedioxy-3-acetoxy-3,5-pregnadiene-11-one, II. A solution of 4.0 g. of 17α-20,20,21-bismethylenedioxy-4-pregnene-3,11-dione in 85 ml. of benzene was dried by azeotropic distillation. Four hundred milligrams of *p*-toluenesulfonic acid and 23 ml. of isopropenyl acetate were added and the mixture refluxed under nitrogen for 4 hr. The reaction mixture was cooled and worked up.[9] The resultant oil was chromatographed on 130 g. of acid washed alumina (Merck). Elution with 6:4 ether–petroleum ether (b.p. 30–60°) yielded 1.7 g. (40%) of 17α,20,20,21-bismethylenedioxy-3-acetoxy-3,5-pregnediene-11-one. Crystallization from ether afforded a sample, m.p. 172–175°; α_D^{24} −27° (*c* 0.7, $CHCl_3$); ultraviolet $\lambda_{max}^{CH_3OH}$ 234 mμ, ϵ 14,400.

Anal. Calcd. for $C_{28}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.52; H, 7.22.

The compound slowly evolved acetic acid on standing.

4-Methyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, V. A solution of 3.0 g. of cortisone BMD and 30 ml. of chloromethyl methyl ether in 70 ml. of acetic acid was allowed to stand at room temperature overnight. The crude product obtained by standard means[9] was adsorbed

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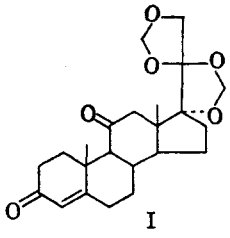
(7) *Cf.* P. F. Beal, M. A. Rebenstorf, and J. E. Pike, *J. Am. Chem. Soc.*, **81**, 1231 (1959).

(8) Melting points were determined on a Kofler Micro hot stage and are corrected. We wish to thank R. Boos and his associates for the microanalyses, A. Kalowsky for the ultraviolet absorption spectra and R. Walker and N. Allen for the infrared spectra (Baird Model B) here reported.

(9) The solution was poured into water and extracted with chloroform. The chloroform layer was washed with aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated *in vacuo*.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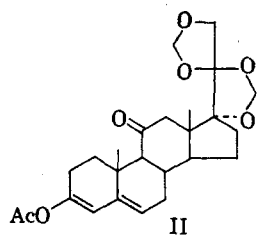
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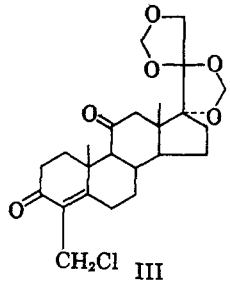
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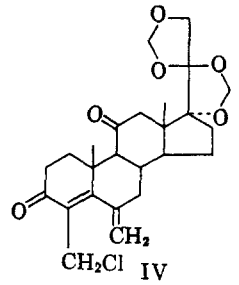
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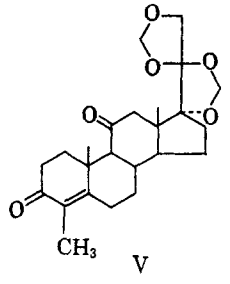
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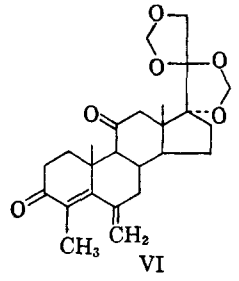
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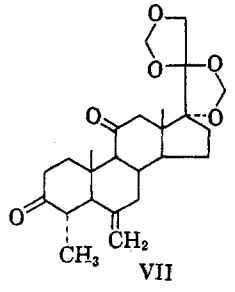
VII

on 100 g. of acid washed alumina and eluted with ether to yield 1.65 g. of a crystalline mixture of compounds (A).

The mixture dissolved in 50 ml. of acetic acid was stirred and treated with 5 g. of zinc dust. The reagent divided into six portions, was added at 25° over a period of 45 min. The suspension was filtered and afforded a crude product that was chromatographed on 40 g. of acid washed alumina. Elution with ether–petroleum ether (b.p. 30–60°) (4:6) afforded 180 mg. of a mixture of saturated compounds (infrared λ_{max}^{Nujol} 5.90 μ; ultraviolet no max) which could not be separated by further chromatography or crystallization. Elution with ether–petroleum ether (8:2) and ether afforded 565 mg. of crystalline fractions. Crystallization from ethyl acetate yielded 320 mg. of 4-methylcortisone BMD, m.p. 268–282°. A sample recrystallized from ethyl acetate, m.p. 273–282°, ultraviolet $\lambda_{max}^{CH_3OH}$ 249 mμ, ϵ 14,300, was not depressed by an authentic sample of 4-methylcortisone BMD.[10] Elution with chloroform yielded 327 mg. of a fraction, m.p. 235–248°. This material was shown to be cortisone BMD by infrared and melting point comparisons.[11] A similar experiment with 1.35 g. of 17α,20,20,21-bismethylenedioxy-3-acetoxy-3,5-pregnadiene-11-one afforded 95 mg. of 4-methylcortisone BMD.

6-Exo-methylene-4-chloromethyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, IV. The crystalline mixture of compounds (A) prepared as above from 5.0 g. of cortisone BMD was refluxed with 5 cc. of 2.5*N* aqueous hydrochloric acid in 125 ml. of methanol for 2 hr. The solution was concentrated *in vacuo*. The crude product[9] was adsorbed on acid washed alumina (Merck) and eluted with ether–petroleum ether (9:1) and ether to yield 0.67 g. of 6-*exo*-methylene-4-chloromethyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, 197–199° dec. after crystallization from methanol.

This material was also prepared from 17α,20,20,21-bismethylenedioxy-3-acetoxy-3,5-pregnadiene-11-one by treatment with chloromethyl methyl ether in acetic acid. Treatment of 15 g. of the enol acetate with 90 ml. of chloromethyl methyl ether and 240 ml. of acetic acid at 25° overnight afforded 4.46 g. of a crystalline mixture which was essentially the same as (A) by infrared comparison after percolation with ether through acid washed alumina (Merck). This material could not be purified by crystallization from methanol but decomposition with formation of hydrochloric acid was observed. A part of this material, 3.5 g., was subsequently chromatographed on 200 g. of acid washed alumina and eluted with ether–petroleum ether (8:2). Repeated crystallization of this material from methanol (with some decomposition) afforded *ca.* 1 g. of 6-*exo*-methylene-4-chloromethyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, m.p. 193–198°. The sample for analysis was recrystallized from methanol, m.p. 200–205°; α_D^{25} +211° (*c* 1, $CHCl_3$); ultraviolet $\lambda_{max}^{CH_3OH}$ 253 mμ, ϵ 11,600; infrared $\lambda_{max}^{CHCl_3}$ 5.85, 5.95, 6.10, 6.20, 11.38 μ.

Anal. Calcd. for $C_{25}H_{31}O_6Cl$: C, 64.84; H, 6.75; Cl, 7.66. Found: C, 64.75; H, 6.85; Cl, 7.40.

6-Exo-methylene-4-methyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, VI. A solution of 150 mg. of IV in 30 ml. of ethanol was stirred with *ca.* 2 g. of Raney nickel[12] (W 3–4) for 2.5 hr. at room temperature. The suspension was filtered and concentrated *in vacuo*. Crystallization from methanol afforded 25 mg. of 6-*exo*-methylene-4-methyl-17α,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione, m.p. 187–195°. Recrystallization from methanol afforded a sample for analysis, m.p. 198–203°; α_D^{23} +243 (*c* 0.6 $CHCl_3$); ultraviolet $\lambda_{max}^{CH_3OH}$ 258 mμ, ϵ 10,400; infrared λ_{max}^{KBr} 5.85, 5.98, sh. 6.10, 6.21, 11.37 μ.

Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.36; H, 7.71.

Chromatography of the mother liquors on 10 g. of acid washed alumina (Merck) and elution with ether–petroleum ether (8:2) afforded 50 mg. of VI, m.p. 185–194°, a total of 75 mg., 54% yield.

6-Exo-methylene-4α-methyl-17α,20,20,21-bismethylenedioxyallopregnane-3,11-dione, VII. A solution of 100 mg. of IV in 10 ml. of acetic acid was treated with a total of 2 g. of zinc divided into five portions over a period of 45 min. The solution was filtered diluted with water and extracted with chloroform. The chloroform layer was washed with aqueous sodium bicarbonate solution, dried, and concentrated *in vacuo*. Chromatography on 4 g. of acid washed alumina and elution with ether–petroleum ether (6:4) afforded 52 mg. of crude VII. Three crystallizations from methanol yielded a sample of 6-*exo*-methylene-4α-methyl-17α,20,20,21-bismethylenedioxyallopregnane-3,11-dione, m.p. 217–226°. Physical properties determined on a sample prepared as above were: m.p. 222–229°; infrared λ_{max}^{KBr} 5.85, 6.07, 11.08 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.69; H, 8.33.

(10) Kindly supplied by Dr. R. Hirschmann.

(11) R. E. Beyler, R. M. Moriarty, Frances Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(12) The Raney nickel was about 3 months old and had been stored under ethanol. Freshly prepared Raney nickel causes reduction to a mixture of saturated ketosteroids.

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.

MERCK SHARP & DOHME RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, N. J.

Structure of Rhein[1]

HAYAO NAWA, MASAO UCHIBAYASHI, 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

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

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(4) A. Tschirch and P. A. A. F. Eijken, *Schweiz. Wochschr. Chem. Pharm.*, **42**, 549 (1904).

(5) O. A. Oesterle, *Arch. Pharm.*, **241**, 604 (1903).

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(9) O. A. Oesterle and G. Riat, *Arch. Pharm.*, **247**, 527 (1909).

(10) F. Tutin and H. W. B. Clewer, *J. Chem. Soc.*, **99**, 946 (1911).

(11) F. Tutin, *J. Chem. Soc.*, **103**, 2006 (1913).