tained in 2.5% yield with m.p. 156–157°. No depression of the melting points of the two glycols was observed on admixture. The infrared spectra of the two *α-cis*-glycols were identical.

dl-anti-trans-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,-9,9 - tetramethylphenanthro[2,3][1,3]dioxol - 3(2H)one.—A solution of 7.59 g. (0.029 mole) of IVc in 760 ml. of acetone (dried over potassium carbonate) was shaken vigorously with 38 g. of anhydrous copper sulfate for 48 hr. The salt was filtered off and the filtrate shaken with 20 g. of anhydrous potassium carbonate for 0.5 hour. The filtered solution was evaporated at the water-pump. After heating at 50° under oil-pump vacuum, the residue (8.77 g.) solidified. Recrystallization from benzene–low boiling petroleum ether gave 7.86 g. (90% yield) of acetonide, m.p. 151–153° as short needles. From the mother liquors, 0.34 g. of acetonide, m.p. 146–150°, was obtained, making the overall yield 94%. Several crystallizations from benzene–low boiling petroleum ether gave material melting at 155.0–155.8°, λ_{max}^{alc} 289 mμ (ε 25,609).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.13; H, 8.63.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

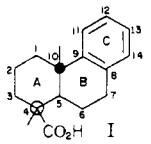
Rearrangements and Oxidations of Tricarbocyclic Diterpenes[1]

BY ERNEST WENKERT AND BILL G. JACKSON

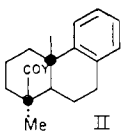
RECEIVED JUNE 3, 1957

A deisopropylation product of dehydroabietonitrile is described. Its stereochemistry is elucidated and its link with podocarponitrile established. The biogenetic consequences in the tricarbocyclic diterpene field are discussed. Possible mechanisms of chromic acid oxidation of ketones are portrayed in the light of certain steric effects observed in these investigations.

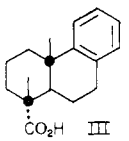
In connection with investigations on the synthesis of tricarbocyclic diterpenes,[2] especially resin acids, it became of importance to acquire the two C-4 epimers of compound I. The isomer (II, Y = OH) derivable from podocarpic acid has been produced most recently,[3] while no compound with the stereochemistry of III is known. However, a compound I with unspecified configuration has been obtained from dehydroabietic acid by acid-catalyzed removal of its isopropyl group.[4] Because of the possibility of arriving at structure III from this source, this reaction was reinvestigated.



I

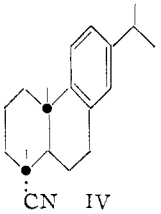


II

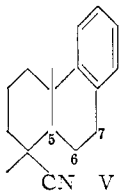


III

Deisopropylation of dehydroabietonitrile (IV) under the stimulus of aluminum chloride in benzene solution led to a mixture of products from which a crystalline $C_{17}H_{21}N$ compound, present in the largest amount (39%), could be isolated readily. Its 4.50μ nitrile band in the infrared and its 265 mμ (log ε 2.95), 272 mμ (log ε 2.93) ultraviolet absorption maxima, characteristic of a tetralin chromophore[2,4] in contrast to the 268 mμ (log ε 2.84), 272 mμ (log ε 2.86) maxima of the starting material IV, suggested that it was a stereoisomer of V. Basic hydrolysis converted V into a carboxylic acid whose melting point, 159–160°, compared favorably with that reported (159–160°) for the deisopropylation product of dehydroabietic acid.[4]



IV



V

Chromic acid oxidation of the nitrile V yielded three crystalline products, two ketones and one acid. One of the two neutral products was a $C_{17}H_{19}ON$ monoketone whose carbonyl group was conjugated with the benzene ring, as indicated by its 5.94 μ infrared band and its typical α-tetralone absorption at 250 mμ (log ε 4.03). The second compound, a yellow $C_{17}H_{17}O_2N$ substance, had all the spectral properties characteristic of an α-diketone. Hence the oxidation had led to a 7-ketone and a 6,7-diketone.[5]

Despite repeated recrystallizations, the diketone refused to yield a sharp melting point, a fact of no small concern until it was discovered that for this compound a melting point was a poor criterion of purity. It appeared that below the apparent melting point the yellow diketone slowly changed to a white substance, presumably the enol, and the mixture gave a wide melting range. However, the crystallinity and constant specific rotation of the diketone were good tests of its homogeneity. Tautomerization to the enol, an unstable compound which on standing was transformed slowly to a gummy yellow material, was a consequence not only of mild pyrolysis but also of alumina chromatography. The initial diketone gave a quinoxaline which was different from the derivative formed by the enol or the diketone resulting from the latter. Thus the original diketone must have had the same configuration at C-5 as its desoxy precursor V, while ketonization of its enol had led to a C-5 epimer.

Most recently the first 6,7-diketonic diterpene, xanthoperol (VI), was isolated from a natural

(1) Presented to the Symposium of the Chemical Society on "Recent Advances in the Chemistry of Terpenoid Compounds," Glasgow, Scotland, July 11–12, 1957.

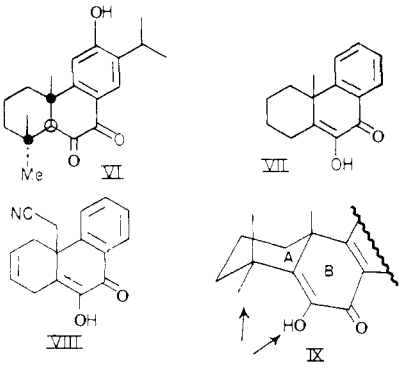
(2) E. Wenkert and T. E. Stevens, THIS JOURNAL, **78**, 2318, 5627 (1956).

(3) E. Wenkert and B. G. Jackson, *ibid.*, **80**, 217 (1958).

(4) W. E. Parham, E. L. Wheeler and R. M. Dodson, *ibid.*, **77**, 1166 (1955).

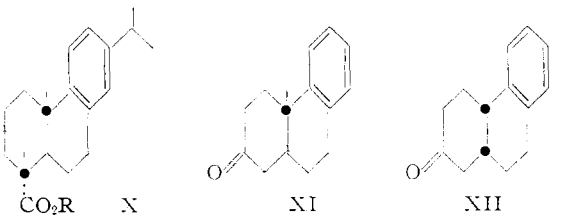
(5) The structure and chemistry of the acid oxidation product will be reported at a later date.

source[6] and was reported to possess unusual properties similar to the diketone under present consideration. Xanthoperol's existence in ketonic form in contrast to the enolic structure of similarly constituted compounds VII[4] and VIII[7] was commented on but not explained. It seems that the two substituents at C-4 must be responsible for the complete suppression of enolization in the 6,7-diketones. Indeed, inspection of a conformational picture (IX) of the enol IX (xanthoperol being used as the model) reveals strongly unfavorable nonbonded interaction between the equatorial C-4 methyl group and the C-6 hydroxyl linkage (arrows in IX). This steric effect of two *peri* substituents must be close in magnitude to a 1,3-diaxial interaction.

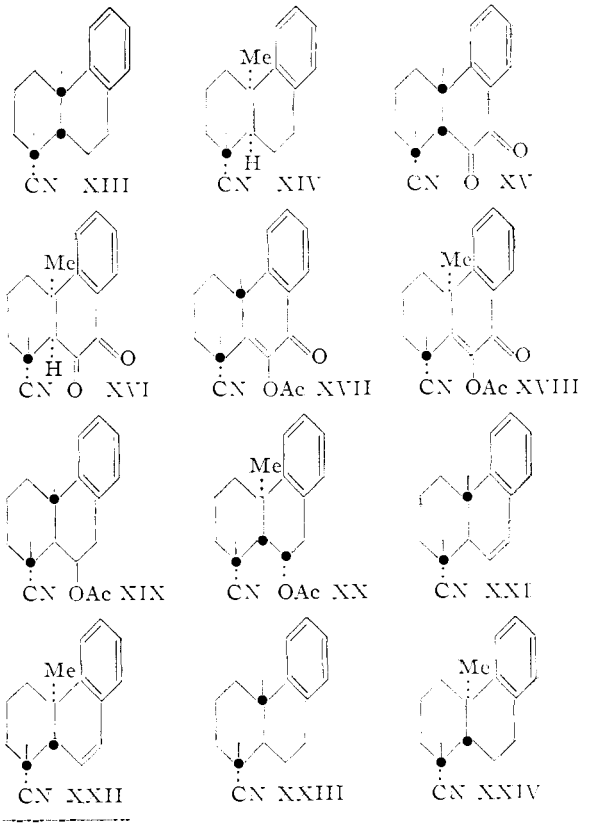


The formation of an α-diketone in the chromic acid oxidation of V was a unique result. Previous oxidations of hydrophenanthrenes have led to monoketones,[8] while under drastic conditions acids have been obtained.[9] In order to ascertain whether there was any stereochemical significance to this contrast of reactivity, six different hydrophenanthrenes were oxidized under standardized conditions identical with those used for the oxidation of V. The compounds chosen were dehydroabietic acid (X, R = H), its methyl ester (X, R = Me) and nitrile IV, methyl desoxypodocarpate[3] (II, Y = OMe) and the hydrophenanthrones[2] XI and XII. All compounds yielded 7-keto derivatives, while the last two also gave acidic compounds.[5] The fact that all A/B *trans* 4,4-disubstituted hydrophenanthrenes led to monoketonic products, in contradistinction to the oxidative behavior of V, hinted strongly at the possibility of the presence of an unnatural, hence *cis*, A/B ring juncture in the deisopropylation product and brought the question of the over-all stereochemistry of V to the fore.

If for the moment it be assumed that V possesses an A/B *cis* ring skeleton, the compound can be assigned one of two structures: XIII or XIV. The diketonic oxidation product of V, hence XV or



XVI, offered itself as an excellent intermediate for chemical reactions designed to differentiate between the two structural formulations. It could be converted readily into an enol acetate (XVII or XVIII) which on catalytic hydrogenation led mainly to a 6-acetoxy product. Since for obvious steric reasons hydrogenation of a Δ^{5-6}-linkage in the presence of an axial angular methyl group and an axial C-4 substituent results in an A/B *trans* system,[10] the reduction product had to be either XIX or XX. Mild pyrolysis produced a styrene (XXI or XXII)[11] which was hydrogenable to a dihydro derivative (XXIII or XXIV). The latter was non-identical and isomeric with the nitrile V, thus presenting unambiguous proof of the A/B *cis* nature of the deisopropylation product (XIII or XIV).



(6) J. B.-S. Bredenberg and J. Gripenberg, *Acta Chim. Scand.*, **10**, 1511 (1956).

(7) M. Gates, THIS JOURNAL, **72**, 228 (1950), and preceding papers.

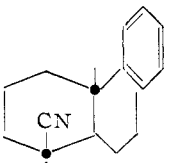
(8) Among others *cf.* (a) A. Brossi, H. Gutmann and O. Jeger, *Helv. Chim. Acta*, **33**, 1730 (1950); (b) D. Arigoni, J. Kalvoda, H. Heusser, O. Jeger and L. Ruzicka, *ibid.*, **38**, 1857 (1955); (c) K. Schaffner, R. Viterbo, D. Arigoni and O. Jeger, *ibid.*, **39**, 174 (1956); (d) P. F. Ritchie, T. F. Sanderson and L. F. McBurney, THIS JOURNAL, **75**, 2610 (1953); (e) R. A. Barnes and M. T. Beachem, *ibid.*, **77**, 5388 (1955).

(9) (a) E. S. Hansen and H. H. Zeiss, *ibid.*, **77**, 1643 (1955); (b) H. H. Zeiss and M. Tsutsui, *ibid.*, **77**, 6707 (1955).

(10) *Cf.* (a) R. B. Woodward, A. A. Patchett, D. H. R. Barton D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957); (b) G. Stork and J. W. Schulenberg, THIS JOURNAL, **78**, 250 (1956).

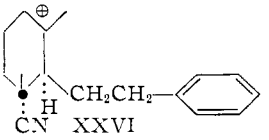
(11) The *cisoid* nature of pyrolytic elimination of acetic acid precluded the formation of a Δ^5-compound as the initial product. A subsequent reversible thermal or acid-catalyzd isomerization of the Δ^6-product to the latter during the pyrolysis experiment was also excluded because of the non-occurrence of such equilibration in even more favorable systems (private communication from Dr. C. H. DePuy). Thus the *trans* structure of the styrene (XXI or XXII) remained assured.

The oxidation–reduction cycle, to which the deisopropylation product had been exposed, had led now to an isomer whose stereochemistry was ripe for exposure by the expedient of comparison with the degradation product of a naturally occurring substance. Since the nitrile had to be either deisopropyldehydroabietonitrile (XXIII) or the enantiomer of desoxypodocarponitrile (XXIV), the desoxygenated derivative of podocarpic acid was prepared. Desoxypodocarpic acid[3] (II, Y = OH) was converted to the acid chloride (II, Y = Cl) with thionyl chloride, and while the product was inert toward aqueous ammonia solution, it could be transformed into a mixture of desoxypodocarpamide (II, Y = NH_2) and desoxypodocarponitrile (XXV) by the action of sodamide in liquid ammonia.[12] Thionyl chloride treatment of the amide yielded the same nitrile. Compound XXV had the identical melting point, infrared spectrum and magnitude, but opposite sign, of specific rotation with the nitrile XXIII-XXIV, thus limiting the latter to structure XXIV. This established stereoformula XIV for the major deisopropylation product of dehydroabietonitrile and structures XVI, XVIII, XX and XXII for its various degradation products.



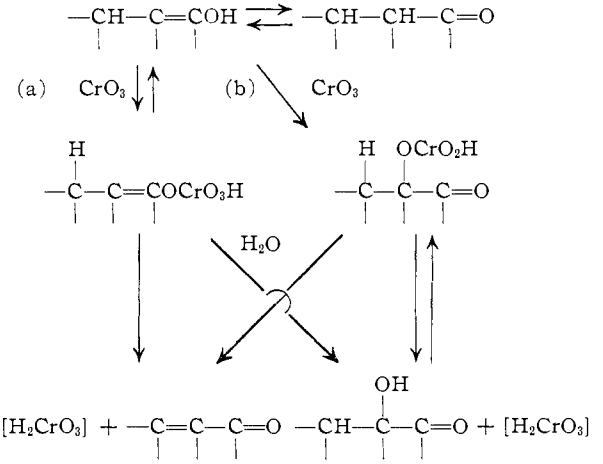
XXV

The deisopropylation process thus consists of two reverse Friedel–Crafts reactions, one a hydrogen replacement of the isopropyl group and the other the cleavage of ring B, and one standard Friedel–Crafts reaction, the reformation of ring B. During the latter the intermediate carbonium ion XXVI has two steric modes of interacting with the benzene ring. Since an aluminum chloride-complexed cyano group undoubtedly is sterically bulkier than the C-4 methyl function, it is not surprising that bond formation occurs on the latter's side of ring A, thus creating an A/B *cis*-podocarpic system.[13,14]



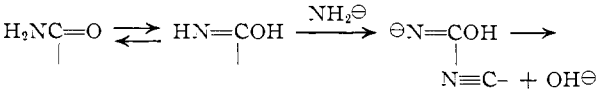
XXVI

Chromic Acid Oxidation of Ketones.—One of the more interesting facets of the above chemical experience is the discovery that chromic acid oxidation can be employed as a powerful diagnostic tool in elucidating the nature of the A/B ring juncture of a monobenzenoid tricarbocyclic diterpene system. Since the dependence of the reaction on the stereochemistry of the substrate is intimately connected with the mechanism of ketone oxidation, prior attention must be paid to the latter. *Formally* two pathways are readily discernible for a 1:1 ketone–chromic acid interaction leading to primary oxidation products, α-ketol or α,β-unsaturated ketone.



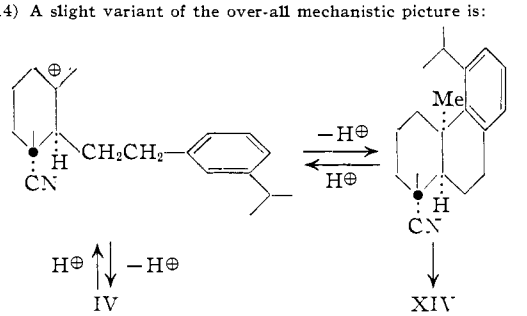
Path a represents chromate attack at the oxygen atom of the reactive species, the enol, by formation of an enol chromate, and either disproportionation of the latter to chromite and unsaturated ketone or nucleophilic attack by solvent on the α-carbon atom with concurrent extrusion of chromite, leading to α-ketol. Path b, on the other hand, implies chromate attack at the enol carbon atom with production of a α-ketochromite which by chromite elimination gives an unsaturated ketone or by solvolysis yields a α-ketol. The nature of the products of most exhaustive ketone oxidations strongly suggests that the ketol, rather than the enone, is the important oxidation product.[15] Its further

(12) The unreactivity of the acid halide toward ammonia and its conversion to nitrile by the strongly nucleophilic amide anion, just as the reductive hydrolysis of methyl ester,[3] are all consequences of the great steric strain inherent in the carboxyl carbon of the podocarpic acid system and show the great reluctance of expansion of the trigonal (sp^2) configuration of that carbon atom to a tetrahedral (sp^3) one as well as apparently the strong driving force toward the least sterically demanding linear (sp) configuration. In the absence of any further data the nitrile formation is represented best as a slow base-catalyzed dehydration of the iminol form of initially produced amide



(13) It might be expected that such stereoselectivity would be even greater in the case of the deisopropylation of dehydroabietic *acid*.[4]

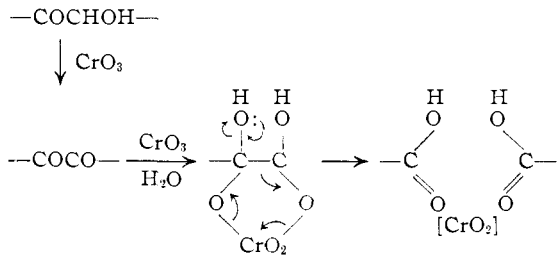
(14) A slight variant of the over-all mechanistic picture is:



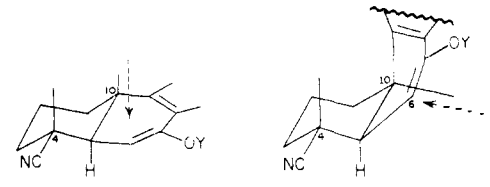
This scheme suggests that ring B opening, proceeding through lower energy states, precedes deisopropylation. Furthermore, it offers an intermediate, the vicinally trisubstituted benzene ring, which because of its high internal strain yields a clue for the ease of the extrusion of the isopropyl group.

(15) Chromic acid oxidation of hydrocinnamyl alcohol systems often leads to conjugated ketones [*cf.* V. Arkley, F. M. Dean, A. Robertson and P. Sidisunthorn, *J. Chem. Soc.*, 2322 (1956); M. J. T. Robinson, *Tetrahedron*, **1**, 49 (1957)]. Benzene ring conjugation in the transition state of the chromite elimination may be the main reason for the

oxidation to penultimate products is dependent on the environment of the hydroxyl group. Thus primary ketols would be transformed to *nor* acids, *via* α-ketoaldehyde and α-ketoacid stages,[16] secondary ketols to α-diketones and subsequently to diacids or two acids,[17] and tertiary ketols to ketones and acids.[18] The following picture should suffice as a *formal* representation of the carbon–carbon cleavage common to all cases



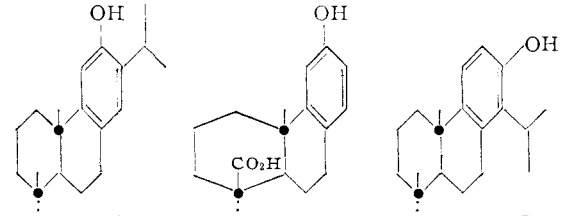
With the above general discussion as background, reasons for the observed differences in the chromic acid oxidation of various diterpenoids are more readily envisioned. In essence, the stability of A/B *trans*-7-keto compounds toward oxidation in contrast to ready diketone formation in an A/B *cis* system requires explanation. In the absence of any discernible gross differences in ease of enolization and of ketol conversion to diketone in the stereoisomers, the dissimilarity in the rate of oxidation must have its origin in the rate-determining step of α-ketol production, *i.e.*, the solvolytic disproportionation of enol chromate, or the α-ketochromite genesis. Regardless of the path of oxidation, it is most reasonable to assume that creation of the new C–O bond in the metamorphosis of ketone to α-ketol should occur by axial attack of reagent upon substrate. This requirement finds ample analogy in the steric course of kinetically controlled bromination[19] and protonation[20] of enols and is based on identical reasons. Inspection of the conformations of the enols or enol chromates of two representative stereoisomers dehydroabietonitrile (XXVII) and its deisopropyl derivative XXVII reveals strong hindrance toward reagent approach at C-6 in the former (*vide* arrow in XXVII) due to the presence of two axial methyl groups at C-4 and 10 but less interference by the 10-methyl substituent in the latter (*vide* arrow in XXVIII).



XXVII XXVIII

Biogenetic Considerations.—The dealkylation of dehydroabietonitrile (*vide supra*) constitutes the first interconversion of the abietic and podocarpic acid types of diterpenes. The facility of the process and the concomitant loss of the aromatic substituent suggest that acid-catalyzed processes may play a role in the phytochemical interrelationship of various tricarbocyclic diterpenes.[21]

The most characteristic representatives of the phenolic diterpenes, all which are part of the conifer family *Podocarpaceae*, are ferruginol (XXIX), podocarpic acid (XXX) and totarol (XXXI). Of these only ferruginol fits the isoprene rule.[21,22] Podocarpic acid is lacking a three-carbon residue to be even considered as a true diterpene, while totarol has its aromatic side-chain in an inappropriate position. However, the present work suggests a simple interrelationship of these compounds.



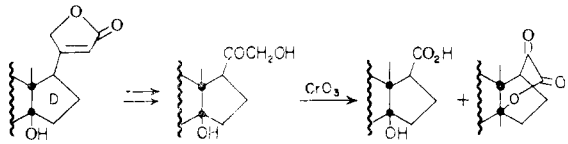
XXIX XXX XXXI

If the common precursor be assumed to be XXXII, *i.e.*, a ferruginol wherein the axial C-4 carbon atom is in an oxidation state higher than methyl, then ferruginol (XXIX) is the reduction product thereof, and its transformation to podocarpic acid (XXX) and totarol (XXXI) proceeds along a path similar to the one already proposed above for the dealkylation of dehydroabietonitrile.

Acknowledgments.—The authors express their most heartfelt thanks to Messrs. W. A. Bappe and R. O. Reinhart for their valuable technical assistance, to Drs. Bible, Hoehn, Ivett and Zeiss for the supply of natural products and to the Institute for Atomic Research, Ames, Iowa, for the use of a Baird infrared spectrophotometer.

preferred formation of enone in these cases. It is of interest that selenium dioxide oxidation of ketones, which may well proceed by a similar mechanistic route, yields mainly enones [*cf.* the conversion of 12-keto steroids to $\Delta^{9,11}$-12-keto derivatives; *e.g.*, E. Schwenk and E. Stahl, *Arch. Biochem.*, **14**, 125 (1947); B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 271 (1948)].

(16) *Cf.* the formation 3,11-diketo-Δ^4-etiocholenic acid from corticosterone, 11-dehydrocorticosterone and Substance T [H. L. Mason, C. S. Myers and E. C. Kendall, *ibid.*, **114**, 613 (1936); H. L. Mason, W. M. Hoehn, B. F. McKenzie and E. C. Kendall, *ibid.*, **120**, 719 (1936); H. L. Mason and W. M. Hoehn, THIS JOURNAL, **60**, 2566 (1938)]. An interesting case of the interruption of the oxidation at the α-ketoacid stage because of competitive rapid ketolactone formation can be found in strophanthidine chemistry [A. Buzas and T. Reichstein, *Helv. Chim. Acta*, **31**, 84 (1948)]



(17) Many such cases can be found in the early investigations on the structure of steroids by Windaus and others [*e.g.*, A. Windaus and G. Stein, *Ber.*, **37**, 3699 (1904), and previous papers]. Similarly, many examples of chromic acid conversion of sapogenins to 2,3-*seco*-dibasic acids are on record [*e.g.*, H. Kiliani and B. Merk, *ibid.*, **34**, 3562 (1901); C. R. Noller, THIS JOURNAL, **59**, 1092 (1937); J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 5375 (1951)].

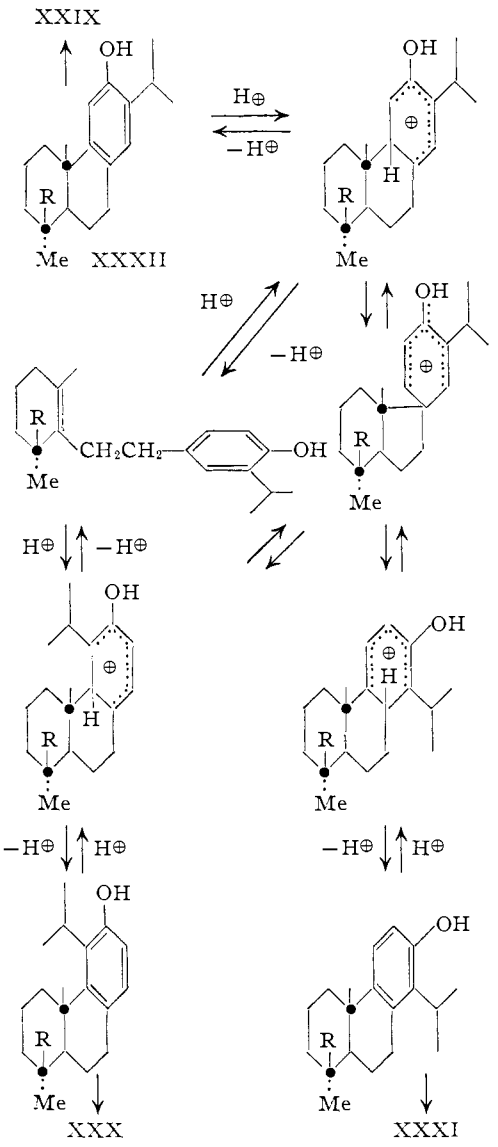
(18) The oxidative removal of the dihydroxyacetone side-chains of corticosteroids can serve as excellent example of this case [*cf.* J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942), and previous papers; L. H. Sarett, *J. Biol. Chem.*, **162**, 601 (1946)].

(19) E. J. Corey, THIS JOURNAL, **76**, 175 (1954).

(20) H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956), and previous papers.

(21) For a discussion of the relation of tetracarbocyclic diterpenes to the tricarbocyclic systems of both the abietane and pimarane types see E. Wenkert, *Chemistry & Industry*, 282 (1955).

(22) L. Ruzicka, *Experientia*, **10**, 357 (1953).



Experimental

5-Isodesoxypodocarponitrile Enantiomer (XIV).—A mixture of 5.00 g. of dehydroabietonitrile, 12.5 g. of anhydrous aluminum chloride and 50 ml. of benzene was refluxed for 6 hr. The mixture then was allowed to cool and was decomposed with ice and concentrated hydrochloric acid. The organic products were extracted with ether, the extracts dried over magnesium sulfate and evaporated. The resulting dark brown gum crystallized slowly. Trituration with petroleum ether and filtration yielded 1.64 g. (39%) of deisopropylated nitrile (XIV), m.p. 107–108°. The analytical sample, m.p. 107–108°, was obtained as colorless needles after two recrystallizations from petroleum ether, $[\alpha]_D$ +16.5° (EtOH); spectra: infrared (CCl_4), CN 4.50(m) μ; ultraviolet (95% ethanol), λ_{max} 266 mμ (ϵ 890) and 273 mμ (ϵ 850).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 85.07; H, 8.79.

A mixture of 1.00 g. of the nitrile, 5 g. of potassium hydroxide, 25 ml. of diethylene glycol and 3 ml. of water was heated at 160° for 21 days. After the reaction mixture had cooled, it was poured into 200 ml. of water and extracted with chloroform. The aqueous phase was then acidified to *p*H 1 with 10% hydrochloric acid and again extracted with chloroform. The latter extracts were dried ($MgSO_4$) and evaporated to dryness. The resulting brown residue was extracted with six 50-ml. portions of hot petroleum ether. On evaporation 0.915 g. (87% yield) of an acid, m.p. 156–158°, was obtained. Three recrystallizations from petroleum ether yielded colorless plates, m.p. 159–160°, $[\alpha]_D$ +8.2° (EtOH); infrared spectrum ($CHBr_3$): OH 2.90(w) μ, 3.28(w) μ; C=O 5.81(m) μ, 5.93(s) μ.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.27; H, 8.75.

An ether solution of *ca.* 200 mg. of diazomethane was added to an ether solution of 75 mg. of the above acid. Two hours later the solvent and the excess of diazomethane were removed under reduced pressure at room temperature. Crystallization of the solid residue from methanol–water gave 65 mg. (82%) of ester, m.p. 70–78°. Four-time recrystallization from methanol–water yielded colorless needles, m.p. 90–90.5°, $[\alpha]_D$ +19.4° (EtOH); infrared spectrum (CCl_4): C=O 5.78(s) μ.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.67; H, 8.94.

General Procedure for Chromic Acid Oxidations.—A solution of chromic oxide in 4:1 acetic acid–water was added to a 10% solution of the appropriate substrate in acetic acid. The weight of chromic acid employed was 1.25 times the weight of substrate and its concentration in the 80% acetic acid solution varied from 5 to 25%. The mixed solutions were left standing at room temperature for 15–18 hr., whereupon the mixture was diluted with a fivefold volume of saturated sodium chloride solution and extracted with chloroform. The combined extracts were washed with 5% sodium hydroxide solution and the acidic products, thus separated, were recovered by acidification of the basic aqueous extracts with 10% hydrochloric acid and extraction by chloroform. The solutions of both the acidic and neutral products were dried over magnesium sulfate and evaporated.

The neutral fraction of the oxidation of 5.00 g. of XIV was crystallized from petroleum ether–benzene, giving 1.36 g. of 6,7-diketo-5-isodesoxypodocarponitrile enantiomer (XVI), m.p. 150–167°. An alcoholic solution of the diketone gave a negative ferric chloride test. Four recrystallizations from petroleum ether–benzene yielded bright yellow needles, m.p. 125–164°, $[\alpha]_D$ −267° ($CHCl_3$); spectra: ultraviolet (95% alcohol), λ_{max} 290 mμ (ϵ 5500); infrared ($CHCl_3$), C≡N 4.47(w) μ, C=O 5.80(s) μ, 5.93(s) μ, C=C 6.25(m) μ.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.10; H, 6.43; N, 5.37.

Its colorless quinoxaline derivative was recrystallized from aqueous methanol, m.p. 196–197°, $[\alpha]_D$ −206°.

Anal. Calcd. for $C_{23}H_{21}N$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.22; H, 6.32; N, 12.3.

The filtrates of the neutral fraction were chromatographed on alumina. Elution with petroleum ether afforded 1.10 g. of starting material (XIV), while the 3:1 petroleum ether–ether eluates yielded 1.38 g. of 7-keto-5-isodesoxypodocarponitrile enantiomer, m.p. 154–157°. Three recrystallizations from petroleum ether gave colorless needles, m.p. 156–157°, $[\alpha]_D$ −107° (EtOH); spectra: ultraviolet (95% alcohol), λ_{max} 253 mμ (ϵ 12,600) and 294 mμ (ϵ 2,420); infrared ($CHCl_3$), C≡N 4.47(w) μ, C=O 5.95(s) μ, C=C 6.24(m) μ.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.55; H, 7.58; N, 5.55.

When in some experiments the 6,7-diketone was not separated initially by fractional crystallization but the entire neutral material chromatographed on alumina, the diketonic portion, recovered by methanol elution, could not be crystallized. The gum gave a brown ferric chloride test. Its quinoxaline melted at 157–159°, $[\alpha]_D$ −357°, and depressed the melting point of the previous quinoxaline (138–160°).

Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24. Found: C, 80.96; H, 6.44.

Heating or subliming the crystalline diketone converted it to a semi-crystalline gum, whose quinoxaline derivative melted at 157–159° and showed no depression on admixture with the lower melting quinoxaline above.

Chromic acid oxidation of 200 mg. of dehydroabietonitrile (IV) produced 3 mg. of crude acidic product and the remainder neutral material. Alumina chromatography of the latter and elution with petroleum ether yielded 17 mg. of starting material, whereas the 10:1 petroleum ether–ether

eluate led to 85 mg. of colorless gummy 7-ketodehydroabietonitrile, $[\alpha]D$ +145° (EtOH); spectra: ultraviolet (95% alcohol), λ_{max} 254 mμ (ε 9,950) and 300 mμ (ε 1,510); infrared (CCl_4), C≡N 4.50(w) μ, C=O 5.94(s) μ, C=C 6.23(m) μ. Its 2,4-dinitrophenylhydrazone was obtained as orange needles, m.p. 157–159°.

Oxidation of 200 mg. of methyl dehydroabietate (X, R = Me) yielded only neutral products. Alumina chromatography gave 91 mg. of starting ester in the petroleum ether eluates and 84 mg. of colorless, gummy methyl 7-ketodehydroabietate from 4:1 petroleum ether–ether eluates, $[\alpha]D$ +7.9° (EtOH) (lit. value[7d] +6.6°); spectra: ultraviolet (95% alcohol), λ_{max} 254 mμ (ε 10,800) and 302 mμ (ε 1,770); infrared (CCl_4), C=O 5.79(s) μ, 5.95(s) μ, C=C 6.22(m) μ. Its 2,4-dinitrophenylhydrazone melted at 185–186° (lit.[7d] value 184.5–185.5°).

The oxidation products of 200 mg. of dehydroabietic acid (X, R = H) were treated with ethereal diazomethane solution and after this methylation procedure were worked up as usual. Separation of the components of the mixture led to 15 mg. of methyl ester (X, R = Me) and 85 mg. of its 7-keto derivative. All their physical properties checked with those quoted above.

Oxidation of 200 mg. of methyl desoxypodocarpate (II, Y = OMe) produced no acidic substances. Alumina chromatography and elution with petroleum ether afforded 37 mg. of starting ester, whereas from the 4:1 petroleum ether–ether eluates there was obtained 110 mg. of methyl 7-ketodesoxypodocarpate, m.p. 147–153°. Four recrystallizations from methanol–water produced colorless needles, m.p. 152–153°, $[\alpha]D$ +84.5° (EtOH); spectra: ultraviolet (95% alcohol), λ_{max} 250 mμ (ε 11,200) and 285 mμ (ε 3,040); infrared (CCl_4), C=O 5.81(s) μ, 5.96(s) μ, C=C 6.28(m) μ.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.66; H, 7.73.

Oxidation of 200 mg. of *trans*-3,4,4a,9,10,10a-hexahydro-4a-methyl-2-(1H)phenanthrone (XI) formed 98 mg. of acidic material and 90 mg. of neutral products. Alumina chromatography of the latter gave 31 mg. of starting ketone from the 20:1 petroleum ether–ether eluates and 25 mg. of *trans*-1,3,4,4a,10,10a-hexahydro-4a-methyl-2,9-phenanthrenedione, m.p. 117–124°, from the ether eluates. Four recrystallizations from petroleum ether gave colorless needles, m.p. 125–126°; spectra: ultraviolet (95% alcohol), λ_{max} 250 mμ (ε 11,500) and 290 mμ (ε 1,850); infrared (CCl_4), C=O 5.81(s) μ, 5.93(s) μ, C=C 6.26μ.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.04. Found: C, 78.83; H, 6.98.

Oxidation of 140 mg. of *cis*-3,4,4a,9,10,10a-hexahydro-4a-methyl-2-(1H)phenanthrone (XII) gave 65 mg. of acidic products and 40 mg. of neutral material. Alumina chromatography of the latter yielded 15 mg. of starting ketone from the 99:1 petroleum ether–ether eluates and 22 mg. of *cis*-1,3,4,4a,10,10a-hexahydro-4a-methyl-2,9-phenanthrenedione, m.p. 107–108°, from the ether eluates. Three recrystallizations from methanol–water gave colorless needles, m.p. 110–111°; spectra: ultraviolet (95% alcohol), λ_{max} 250 mμ (ε 13,800) and 288 mμ (ε 2,640); infrared (CCl_4), C=O 5.81(s) μ, 5.93(s) μ, C=C 6.26 μ.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.04. Found: C, 78.66; H, 7.46.

6α-Acetoxydesoxypodocarponitrile Enantiomer (XX).—A mixture of 200 mg. of the diketone XVI, 82 mg. of anhydrous sodium acetate and 5 ml. of acetic anhydride was refluxed for 1 hr. The solvent was evaporated under vacuum, the resulting residue dissolved in chloroform and water, the organic layer separated and the aqueous phase further extracted with chloroform. The combined organic extracts were washed with 10% sodium bicarbonate solution, dried over magnesium sulfate and concentrated in vacuum. The crude enolacetate XVIII weighed 216 mg.; spectra: ultraviolet (95% alcohol), λ_{max} 257 mμ (ε 9,400); infrared (CCl_4), C≡N 4.49(w) μ, C=O 5.65(s) μ, 5.99(s) μ, C=C 6.14(w) μ, 6.25(m) μ.

A mixture of 214 mg. of the enolacetate (XVIII), 75 mg. of 5% palladium-on-carbon, 0.1 ml. of concentrated sulfuric acid and 15 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake ceased spontaneously after an absorption of approximately two molar equivalents. After filtration of the catalyst, the solution was washed with 10% sodium bicarbonate solution, dried over magnesium sulfate and evaporated. Chromatography of the resulting residue on alumina yielded 11 mg. of presumably desoxypodocarponitrile enantiomer (XXIV), m.p. 70–80°, infrared spectrum (CCl_4), C≡N 4.50(w) μ, from the petroleum ether eluates; 91 mg. of XX, m.p. 116–117°, from 20:1 petroleum ether–ether eluates; and 18 mg. of presumably 7-ketodesoxypodocarponitrile, m.p. 213–214°, infrared spectrum ($CHCl_3$), C≡N 4.48(w) μ, C=O 5.98(s) μ and C=C 6.26(m) μ, from 4:1 petroleum ether–ether elution.

Three recrystallizations of acetate XX in aqueous methanol yielded colorless needles, m.p. 118–118.5°, $[\alpha]D$ −15.5° (EtOH); infrared spectrum (CCl_4), C≡N 4.50(w) μ, C=O 5.77(s) μ.

Anal. Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80. Found: C, 76.93; H, 7.96.

Desoxypodocarponitrile Enantiomer (XXIV).—The acetate XX (91 mg.) was heated for five minutes at 350° in a nitrogen atmosphere. The resulting gum was dissolved in chloroform, the solution washed with 10% sodium bicarbonate solution, dried over magnesium sulfate and evaporated. The residue was chromatographed on alumina and eluted with petroleum ether, yielding 48 mg. of XXII as colorless gum, $[\alpha]D$ +86.5° (EtOH); spectra: ultraviolet (95% alcohol), λ_{max} 224 mμ (ε 16,600) and 263 mμ (ε 8,800); infrared (CCl_4), C≡N 4.51(w) μ, C=C 6.03(m) μ.

A mixture of 46 mg. of the styrene XXII, 25 mg. of 5% palladium-on-carbon and 15 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure. Hydrogenation was complete after one mole uptake in 3 hr. time. The residue obtained after filtration of the catalyst and evaporation of the solvent was chromatographed on alumina. Elution with petroleum ether and subsequent crystallization from aqueous methanol gave 19 mg. of the nitrile XXIV, m.p. 71–83°. Two recrystallizations from methanol–water and sublimation produced a solid, m.p. 87–88°, $[\alpha]^{27}D$ −85° (EtOH), infrared spectrum (KBr), C≡N 4.51(w) μ.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 85.30; H, 8.53.

Desoxypodocarponitrile (XXV).—A mixture of 300 mg. of desoxypodocarpic acid (II, Y = OH) and 5 ml. of thionyl chloride was refluxed for 1 hr. After previous trials had shown the thus-formed acid chloride to be inert to aqueous ammonia, the residue, obtained by evaporation of the excess thionyl chloride in vacuum, was dissolved in 10 ml. of tetrahydrofuran and added to a suspension of sodamide (from 1 g. of sodium metal) in *ca.* 75 ml. of liquid ammonia. The mixture was allowed to stand until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid, the organic layer separated and the aqueous phase extracted with chloroform. Drying over magnesium sulfate and evaporation of the combined chloroform extracts yielded a crude product which on crystallization from methanol–water gave 76 mg. of amide (II, Y = NH_2), m.p. 160–171°. Evaporation of the filtrate, chromatography on alumina, elution with petroleum ether and crystallization in aqueous methanol led to 20 mg. of desoxypodocarponitrile (XXV), m.p. 82–86°. After two recrystallizations from aqueous methanol and subsequent sublimation, the material melted at 87–89°, $[\alpha]^{27}D$ +90°; infrared spectrum (KBr), C≡N 4.51(w) μ, identical in all respects to that of XXIV.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 84.99; H, 8.59.

Further elution with methanol gave 35 mg. of desoxypodocarpamide (II, Y = NH_2), m.p. 190–193°. Three recrystallizations from methanol–water gave fluffy needles, m.p. 191–195°, $[\alpha]D$ +157°; infrared spectrum (CCl_4), NH 2.85(m) μ, 2.93(w) μ, 3.09(w) μ, 3.18(m) μ, 3.28(w) μ, C=O 5.97(s) μ.

Anal. Calcd. for $C_{17}H_{25}ON$: C, 79.33; H, 9.01. Found: C, 79.35; H, 9.21.

A mixture of 75 mg. of amide (II, Y = NH_2), 1 ml. of thionyl chloride and 4 ml. of benzene was refluxed for 6 hr. The residue obtained after evaporation of the solvent was dissolved in chloroform, the latter washed with 10% sodium bicarbonate solution, dried over magnesium sulfate and evaporated in vacuum. Alumina chromatography, elution

with petroleum ether and subsequent crystallization from methanol–water gave 41 mg. of desoxypodocarponitrile (XXV), m.p. 83–87°, identical in all respects with the nitrile obtained directly by the sodamide treatment of the acid chloride (mixed m.p. 83–87°).

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Partial Degradation and Reconstitution of Podocarpic Acid. A Novel Method of Hydrolysis of Highly Sterically Hindered Esters[1]

BY ERNEST WENKERT AND B. G. JACKSON

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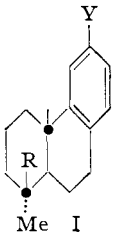
The degradation of podocarpic acid to its desoxy derivative and the latter's conversion to the resin acid is portrayed. Lithium–liquid ammonia treatment of highly sterically hindered methyl esters has been shown to yield preponderantly acids. The utility of this method for easy hydrolysis of hindered esters as well as for diagnosis of the steric disposition of ester functions on rigid ring systems is described.

As part of a chemical investigation in the diterpene field it became of interest to remove the phenolic hydroxyl group of podocarpic acid (Ia) as well as to convert the resulting desoxy compound back to the natural product.



I

a, R = CO_2H, Y = OH
b, R = CO_2Me, Y = OH
c, R = CO_2H, Y = H
d, R = CO_2Me, Y = H
e, R = CH_2OH, Y = H
f, R = CO_2Me, Y = Ac
g, R = CO_2Me, Y = OAc
h, R = CO_2Me, Y = $OPO(OEt)_2$
i, R = $CONH_2$, Y = H

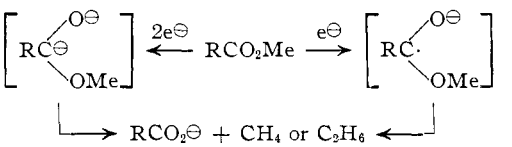
On exposure of methyl podocarpate (Ib) to a Kenner desoxygenation,[2] *i.e.*, phosphorylation followed by reduction with lithium in liquid ammonia, desoxypodocarpic acid (Ic), its methyl ester (Id) or desoxypodocarpinol (Ie) were formed. Methyl desoxypodocarpate (Id), prepared in this manner or obtained by diazomethane treatment of desoxypodocarpic acid (Ic), could be acetylated with acetyl chloride and aluminum chloride in carbon disulfide solution yielding a ketoester If. Emmons oxidation[3] of the latter led to methyl podocarpate acetate (Ig), identical in all respects with the product obtained from a reaction between methyl podocarpate (Ib) and acetic anhydride. Treatment of the acetate with aqueous sodium hydroxide gave a quantitative yield of methyl podocarpate (Ib).

One of the less readily explicable results of the above reaction cycle was associated with the metal reduction of methyl podocarpate phosphate (Ih). When the reaction was quenched rapidly by early addition of ammonium chloride, the major product was the expected desoxy ester Id, accompanied by small amounts of its acid Ic and alcohol Ie. However, a procedure of adding ethanol to the reaction mixture upon the complete dissolution of the lithium in the medium followed by slow evaporation of the ammonia led preponderantly to the acid Ic and some alcohol Ie.

The formation of desoxypodocarpinol (Ie) was not at all astonishing, since esters are well known to be susceptible to reduction under the above reaction conditions, but the production of desoxypodocarpic acid required explanation. Two ready interpretations, based on the possibility of water, undoubtedly present in the liquid ammonia, having been the important reagent, readily could be dismissed. Base-catalyzed hydrolysis of the methyl ester was inconceivable due to the known stability of the axial carbomethoxy group to even more stringent hydrolytic conditions,[4] and Cannizzaro disproportionation of an intermediate aldehyde was highly improbable because of the production of grossly unequal amounts of acid and alcohol and because of the non-isolation of aldehyde in rapidly quenched reactions.

The possibility existed that the strongly nucleophilic amide ion, a product of the phosphate reduction,[2] could have hydrolyzed the ester by a displacement on the methoxy carbon atom in analogy with hydrolyses of other sterically hindered esters, albeit under more energetic conditions.[5] However this suggestion was abandoned when it was shown that methyl desoxypodocarpate (Id) yielded only starting material and 15% amide Ii on exposure to lithium amide in liquid ammonia. Finally, any possible participation of the phosphate group in acid production was dismissed on discovery that lithium–liquid ammonia reduction of methyl podocarpate (Ib) led mainly to podocarpic acid (Ia).

This novel hydrolysis of a methyl ester thus appeared to be a reductive process of the following *formal* representation



Its successful competition with normal ester reduction must be due to the great resistance of the

(1) This work was presented in part to the Symposium of the Chemical Society on "Recent Advances in the Chemistry of Terpenoid Compounds," Glasgow, Scotland, July 11–12, 1957, and in part to the 16th International Congress of Pure and Applied Chemistry, Paris, France, July 18–25, 1957.

(2) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(3) W. B. Emmonds and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955).

(4) W. P. Campbell and D. Todd, *ibid.*, **64**, 928 (1942).

(5) *Cf.* H. L. Goering, T. Rubin and M. S. Newman, *ibid.*, **76**, 787 (1954).