with a very powerful fresh cucumber-like odor (identical with that of the natural material), b.p. 94–95.5° (18 mm.), $n^{17}D$ 1.4699. In addition, unchanged acetal (1.0 g., 22%) was recovered.

The 2,4-dinitrophenylhydrazone was prepared from the acetal as well as from the aldehyde. In either case it crystallized from methanol as orange plates, m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{18}O_4N_4$: N, 17.61. Found: N, 17.80.

The 2,4-dinitrophenylhydrazone was also prepared from a sample of the natural aldehyde. It had m.p. 111–112° and was undepressed on admixture with the synthetic specimen.

The *p*-nitrophenylhydrazone crystallized from ligroin (b.p. 60–90°) as regular orange plates, m.p. 97.5–98.5°.

Anal. Calcd. for $C_{15}H_{19}O_2N_3$: N, 15.38. Found: N, 15.37.

The semicarbazone crystallized from aqueous methanol as sparkling plates, m.p. 156–157°. A sample prepared from the natural material had m.p. 157–158°, and no depression was observed on admixture.

The synthetic semicarbazone (0.5 g.), 2 *N* sulfuric acid (20 cc.) and petroleum ether were stirred and heated under reflux in a nitrogen atmosphere. After 3.5 hours, two clear layers were obtained. The aqueous layer was extracted with ether, the combined organic extracts were washed with water, dried and evaporated. Distillation of the residue furnished the pure aldehyde, b.p. 88° (10 mm.), $n^{21}D$ 1.4710.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.45.

The hydrolysis of the acetal could also be carried out by shaking an ethereal solution of the latter with saturated aqueous tartaric acid for 14 hours, but inferior yields of aldehyde were obtained by this method.

2,6-Nonadiyn-1-ol (VIII).—A solution of ethylmagnesium bromide in dry ether (80 cc.) was prepared from magnesium (1.95 g.) and ethyl bromide (12 g.) in the usual way. 1,5-Octadiyne (6.85 g.) in ether (30 cc.) was added during ten minutes, and the stirred solution was heated under reflux in a nitrogen atmosphere for 2.5 hours. Excess formaldehyde generated by the method of Gilman and Catlin,[20] was passed into the stirred Grignard reaction mixture by means of a slow current of nitrogen. The ether boiled gently, although no external heat was applied. The mixture was then heated under reflux for 30 minutes. It was poured into dilute sulfuric acid and ice, and the organic layer was washed with sodium bicarbonate solution and water. The dried extract was evaporated, and the residue was distilled through a Vigreux column. 2,6-Nonadiyn-1-ol (6.3 g., 72%) was obtained as a mobile liquid, b.p. 83–85° (0.3 mm.), $n^{24}D$ 1.4842.

Anal. Calcd. for $C_9H_{12}O$: C, 79.38; H, 8.89. Found: C, 79.01; H, 8.74.

2(*cis*),6(*cis*)-Nonadien-1-ol.—The diacetylenic alcohol (1.60 g.) in ethyl acetate (10 cc.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (0.2 g., 3% Pd) until two moles of gas (583 cc. at 21° (740 mm.)) had been absorbed. The residue, after removal of the catalyst and solvent, was distilled. 2(*cis*),6(*cis*)-Nonadien-1-ol (1.23 g., 75%) was obtained as a colorless liquid, b.p. 108–110° (24 mm.), $n^{23}D$ 1.4580.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.75; H, 11.85.

2(*trans*),6(*cis*)-Nonadienal (I) by Oxidation of 2(*cis*),6(*cis*)-Nonadien-1-ol.—The alcohol (0.5 g.) was oxidized with chromium trioxide in dilute sulfuric acid by the procedure described by Hunsdiecker[10] for the *trans,trans* isomer. The crude undistilled aldehyde was converted to the 2,4-dinitrophenylhydrazone (m.p. 112–113°) and semicarbazone (m.p. 155–156°) in the usual way; neither of these melting points was depressed on admixture with the corresponding derivatives prepared by the acetal route.

Infrared Absorption Spectra.—The infrared spectra were determined in chloroform solution with a Baird Infrared Recording Spectrophotometer, Model B.

Acknowledgments.—The author wishes to express his thanks to Dr. H. Schinz (Eidg. Technische Hochschule, Zürich) for the gift of samples of natural nonadienal and its derivatives, and to Dr. J. C. Lunt (Imperial College of Science, London) for carrying out the partial hydrogenation of tetrolaldehyde diethyl acetal.

CAMBRIDGE 38, MASSACHUSETTS

(20) H. Gilman and W. E. Catlin, "Organic Syntheses," Coll. Vol. I John Wiley and Sons, Inc., New York, N. Y., 1941, p. 188.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XXX. The Isomeric Norechinocystenediones and Some Related Compounds[1a]

BY F. A. ALVES[1b] AND C. R. NOLLER

RECEIVED MARCH 25, 1952

The isomerization of the norechinocystenediones has been reinvestigated and additional examples of isomerization have been found. An explanation of the isomerizations is given.

When methyl echinocystate is oxidized with dichromic acid, a diketo methyl ester is formed which saponifies readily with loss of carbon dioxide. The product forms a dioxime and was called norechinocystenedione.[2,3] If echinocystic acid is oxidized in the same way as the methyl ester, carbon dioxide is lost directly, and a product isomeric with norechinocystenedione is obtained which was called isonorechinocystenedione.[3] This compound forms only a monoxime and is isomerized by alcoholic potassium hydroxide to norechinocystenedione. The absorption spectrum of the isonordione in ethyl ether failed to show the presence of a carbonyl group and, as a working hypothesis, it was suggested that the isonordine might be a cyclic hemiacetal of the monoenol form of a diketone.[2b] No evidence could be found for this structure, but during attempts to form a thioacetal by heating with butyl mercaptan in the presence of hydrogen chloride, a new isomeric diketone was obtained which is an α,β-unsaturated ketone.[4]

Since these results could not be explained readily, the work has been repeated and extended. Previous work has been confirmed except that all of our present preparations of the isonordione show simple

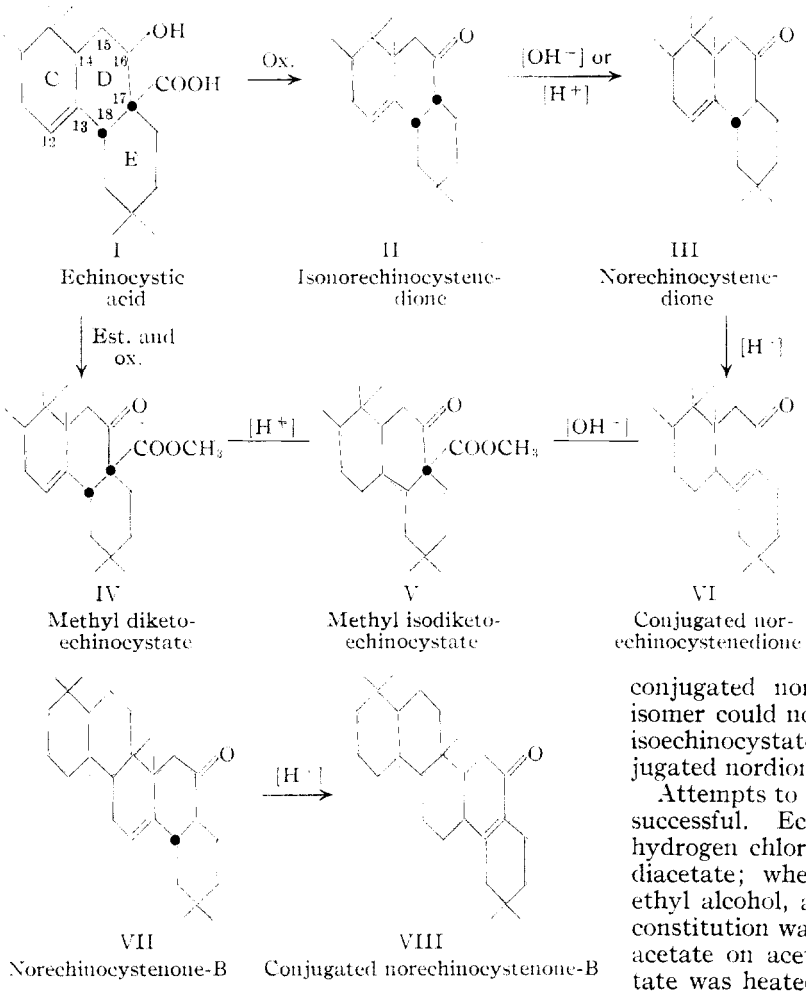
(1) (a) This paper is based on a portion of the Ph.D. dissertation of F. A. Alves, Instituto para a Alta Cultura Fellow; (b) Laboratorio Quimico, Universidade de Coimbra, Portugal.

(2) W. R. White and C. R. Noller, THIS JOURNAL, **61**, 983 (1939).

(3) R. N. Jones, D. Todd and C. R. Noller, *ibid.*, **61**, 2421 (1939).

(4) J. F. Carson, D. B. Cosulich and C. R. Noller, *ibid.*, **66**, 1265 (1944).

carbonyl absorption with λ_{max} 287 mμ, log ϵ 2 in ether. The ultraviolet absorption of the monoxime is similar (λ_{max} 290 mμ, log ϵ 2 in alcohol) indicating that no important change in structure has taken place during oxime formation. Moreover the difference between the molecular rotation of methyl diketoechinocystate and its monoxime,[2] $\Delta[M]_D$ = −257, is nearly the same as that between isonorechinocystenedione and its monoxime,[2,4] $\Delta[M]_D$ = −267. The difference in molecular rotation between the conjugated nordione and its monoxime, $\Delta[M]_D$ = −295, is somewhat larger, probably because of the conjugation.



I Echinocystic acid

II Isonorechinocystenedione

III Norechinocystenedione

IV Methyl diketoechinocystate

V Methyl isodiketoechinocystate

VI Conjugated norechinocystenedione

VII Norechinocystenone-B

VIII Conjugated norechinocystenone-B

A more extensive study of the isomerization phenomena has been made, the results of which can be summarized briefly. (1) The nordione is an intermediate in the isomerization of isonordione to the conjugated nordione. Previous work indicated that refluxing the isonordione in alcoholic solution in the presence of hydrogen chloride for 16 hours gives the nordione, but that in the presence of butyl mercaptan the conjugated nordione is formed.[3] It now is found that refluxing the nordione an additional 16 hours with alcoholic hydrogen chloride alone also gives the conjugated nordione; that is, butyl mercaptan increases the rate of isomerization to the conjugated nordione but is not essential. The direct conversion of isonordione to conjugated nordione is brought about by refluxing 12 hours in hexane solution in the presence of benzoyl peroxide and hydrogen bromide. The conversion of isonordione to nordione and of nordione to conjugated nordione can be brought about also by refluxing benzene solutions containing iodine. Isonordione is converted to nordione by passing a solution in carbon tetrachloride through a column of activated alumina. Alumina which has been deactivated by previous passage of methyl alcohol does not cause isomerization. No isomerization of isonordione takes place when it is heated above the melting point, when a solution in ether is irradiated in a quartz cell with ultraviolet light (Labarc) for ten hours, or when it is allowed to stand for 24 hours at room temperature in an ether solution containing boron trifluoride.

The isomerization to conjugated nordione appears to be practically irreversible, since only the unchanged conjugated nordione can be recovered after refluxing it with alcoholic hydrogen chloride for 18 hours.

(2) The acid-catalyzed isomerization of two other derivatives of echinocystic acid was accomplished. Methyl diketoechinocystate, when refluxed with alcoholic hydrogen chloride, gives methyl diketoisoechinocystate, which shows only simple carbonyl absorption. Norechinocystenone-B[2,5] gives an isomer having an α,β-unsaturated carbonyl group, which will be called conjugated norechinocystenone-B. A conjugated isomer could not be obtained from methyl diketoisoechinocystate, but saponification gives the conjugated nordione.

Attempts to isomerize other derivatives were unsuccessful. Echinocystic acid, when heated with hydrogen chloride in acetic acid, gave the lactone diacetate; when heated with hydrogen chloride in ethyl alcohol, a high-melting product of unknown constitution was formed which gave the lactone diacetate on acetylation. When methyl echinocystate was heated with alcoholic hydrogen chloride, three products were formed, the high-melting compound obtained from echinocystic acid, a different high-melting compound, and methyl anhydroechinocystate.[6]

(3) As reported previously, bases, such as alcoholic potassium hydroxide or sodium acetate in acetic anhydride, convert isonordione to nordione.[2,4] The isomerization with alcoholic potassium hydroxide is more rapid than with alcoholic hydrogen chloride. When pure nordione was refluxed for two days with alcoholic potassium hydroxide, some isonordione could be isolated, but no trace of the conjugated nordione could be detected by scan-

(5) G. H. Harris and C. R. Noller, THIS JOURNAL, **66**, 1005 (1944).
(6) D. Frazier and C. R. Noller, *ibid.*, **66**, 1267 (1944).

TABLE I: MOLECULAR ROTATION DIFFERENCES FOR $\Delta^{12,13}$ AND $\Delta^{13,18}$ TRITERPENES[a,b]

$\Delta^{12,13}$ Compounds	Mol. wt.	$[\alpha]_D$	$[M]_D$	$\Delta^{13,18}$ Compounds	$[\alpha]_D$	$[M]_D$	Diff.
β-Amyrene-II[c]	411	+96	+395	β-Amyrene-III[c] (lupenene-II[d])	−33	−136	−531
β-Amyrin[e]	427	88	376	δ-Amyrenol (lupenol-II)[d]	−51	−218	−594
β-Amyrin acetate[e]	469	81	380	δ-Amyrenol acetate[d]	−34	−159	−539
β-Amyrin benzoate[f]	531	100	531	δ-Amyrenol benzoate[d]	−8	−42	−573
β-Amyrone[g]	425	106	451	δ-Amyrenone (lupenone-II)[d]	−12	−51	−502
Deoxoglycyrrhetinic acid methyl ester[h]	469	108	507	$\Delta^{13,18}$-2-Hydroxyoleanen-30-oic acid[i]	+7	+33	−474
Deoxoglycyrrhetinic acid acetate methyl ester[h]	511	120	613	$\Delta^{13,18}$-2-Acetoxyoleanen-30-oic acid[i]	+6	+31	−582
$\Delta^{12,13}$-2,24-Diacetoxyoleanene[j]	527	80	422	$\Delta^{13,18}$-2,24-Diacetoxyoleanene[k]	−29	−153	−575
$\Delta^{12,13}$-2,24-Dihydroxyoleanene[j]	443	95	421	$\Delta^{13,18}$-2,24-Dihydroxyoleanene[k]	−41	−182	−603
Erythrodiol[l]	443	75	332	2,28-Dihydroxyolean-13(18)-ene[m]	−45	−199	−531
Erythrodiol diacetate[l]	527	59	311	2,28-Diacetoxyolean-13(18)-ene[m]	−54	−285	−596
Hederagenin diacetate methyl ester[n]	571	75	428	*epi*-Hederagenin diacetate methyl ester[o]	−27	−154	−582
Homooleanenedione[p]	453	91	412	δ-Homooleanenedione[p]	+23	+104	−308
Oleanolic acid acetate methyl ester[q]	511	67	342	$\Delta^{13,18}$-2-Acetoxyoleanen-28-oic acid methyl ester[i]	−68	−347	−689
Oleanonic acid methyl ester[q]	467	88	411	Methyl δ-oleanonate[p]	−45	−210	−621
Soyasapogenol-B[j]	459	90	413	$\Delta^{13,18}$-2,24,x-Trihydroxyoleanene[k]	−52	−239	−652
Soyasapogenol-B triacetate[j]	585	78	456	$\Delta^{13,18}$-2,24,x-Triacetoxyoleanene[k]	−24	−140	−596
$\Delta^{12,13}$-2-Acetoxy-19-ketooleanen-28-oic acid methyl ester[r]	525	110	578	$\Delta^{13,18}$-2-Acetoxy-19-ketooleanen-28-oic acid methyl ester[r]	−203	−1066	−1644
$\Delta^{12,13}$-2,19-Diketooleanen-28-oic acid methyl ester[r]	481	141	678	$\Delta^{13,18}$-2,19-Diketooleanen-28-oic acid methyl ester[r]	−189	−909	−1587

[a] The names of the compounds listed are approximately those used in the cited literature. The $\Delta^{13,18}$ compounds now frequently are called δ compounds but the nomenclature of the triterpenes has not become stabilized as yet. [b] All rotations are of chloroform solutions; all figures are rounded to the nearest whole number. [c] G. S. Davy, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 458 (1951). [d] T. R. Ames, T. G. Halsall and E. R. H. Jones, *ibid.*, 450 (1951). [e] N. H. Cohen, *Rec. trav. chim.*, **28**, 393 (1909). [f] A. Zinke, A. Friedrich and A. Rollet, *Monatsh.*, **41**, 253 (1920). [g] L. Ruzicka and W. Wirz, *Helv. Chim. Acta*, **24**, 248 (1941). [h] L. Ruzicka, H. Leuenberger and H. Schellenberg, *ibid.*, **20**, 1271 (1937). [i] O. Jeger, J. Norymberski and L. Ruzicka, *ibid.*, **27**, 1532 (1944). [j] A. Meyer, O. Jeger and L. Ruzicka, *ibid.*, **33**, 672 (1950). [k] *Ibid.*, **33**, 687 (1950). [l] J. Zimmermann, *Rec. trav. chim.*, **51**, 1200 (1932). [m] D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951). [n] A. Winterstein and G. Stein, *Z. physiol. Chem.*, **211**, 5 (1932). [o] Z. Kitasato, *Acta Phytochim.*, **8**, 220 (1935). [p] G. S. Davy, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 2696 (1951). [q] Ref. *o*, p. 219. [r] L. Ruzicka, A. Grob, R. Egli, and O. Jeger, *Helv. Chim. Acta*, **26**, 1218 (1943).

ning all fractions for absorption in the ultraviolet.

Most of these results can be explained by the following series of reactions in which only the C, D and E rings of echinocystic acid are indicated. Thus the conversion of the isonordione, II, to the nordione, III, is the result of the inversion of the C-17 carbon atom as first postulated by Bilham and Kon.[7] Alkali does not convert the γ,δ-unsaturated nordione, III, to the conjugated nordione, VI, presumably because no mechanism is available for the transformation, but prolonged treatment with acid causes migration of the double bond to conjugation with the carbonyl group. In methyl diketoechinocystate (IV) the presence of the carbomethoxy group at C-17 prevents inversion at C-17 or migration beyond the β,γ-position. Saponification of of the β,γ-unsaturated β′-keto ester, V, with loss of carbon dioxide permits migration of the double bond to conjugation with the carbonyl group. The conversion of norechinocystenone-B(VII) to conjugated norechinocystenone-B(VIII) may be assumed to be analogous to the conversion of the nordione to the conjugated nordione, since the molecular rotation differences of +543 and +586° for each pair are similar.

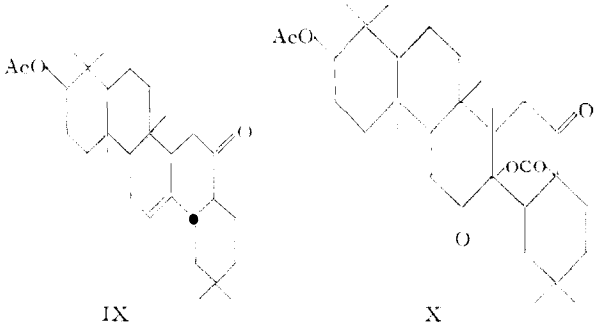
The assumption that the conversion of methyl diketoechinocystate to methyl diketoisoechinocystate is due to the migration of the double bond is in agreement with the decrease in molecular rotation of 748°. An examination of the literature shows that a marked decrease in rotation occurs when a double bond migrates from the 12,13- to the 13,18-position. The examples located are summarized in Table I.

One objection to the above interpretation of the isomerization of the diones is that the difference in molecular rotation between the isonordione and the nordione of −758° is identical within experimental error with that between the isomeric diketo methyl esters. Normally one would assume that the same structural changes must have taken place in both isomerizations. The behavior of the several nordiones to alkali, however, is against the assumption that the change from the isonordione to the nordione is due to the migration of a double bond, and the similarity in molecular rotation differences must be fortuitous.

An attempt was made to obtain another series of

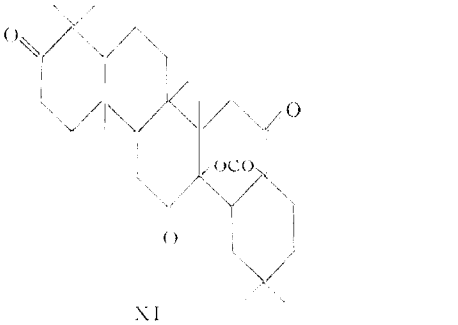
(7) P. Bilham and G. A. R. Kon, *J. Chem. Soc.*, 1469 (1940).

isomers in analogy to the group isonorechinocystenedione, norechinocystenedione and conjugated norechinocystenedione. Since the known 2-acetylnorechinocystenol-16-one (IX) has a high negative rotation, it is assumed to be an analog of norechinocystenedione. It was thought that it should be possible to obtain a compound analogous to the isonordione by carrying out the oxidation of 2-acetylechinocystic acid by the same procedure used to obtain the isonordione from echinocystic acid. Analysis of the only product isolated, however, indicates that it is the acetyl diketo lactone of echinocystic acid (X).



IX

X



XI

From the oxidation of relatively large quantities of echinocystic acid, a second neutral product has been obtained which appears to be the triketo lactone, XI.

Experimental[8]

Oxidation of Echinocystic Acid.—Oxidation of 25 g. of echinocystic acid by the procedure previously reported[2] gave 13 g. of pure isonorechinocystenedione. Dilution of the acid mother liquors gave a precipitate from which 4.5 g. of a neutral fraction and 1.5 g. of an acidic fraction were obtained. Crystallization of the neutral fraction once from methyl alcohol and five times from ethyl alcohol gave a compound melting at 289–293°. Solutions show an absorption maximum at 285 mμ, log ε 2.05; $[\alpha]^{22}D$ −89°. Analysis indicates that the compound is a triketo lactone, probably the lactone of 2,12,16-triketo-13-hydroxyoleananoic acid[9] (XI).

Anal. Calcd. for $C_{30}H_{42}O_5$: C, 74.65; H, 8.77. Found: C, 74.49; H, 8.86.

Methyl Diketoisoechinocystate (V).—A slow stream of dry hydrogen chloride was passed into a refluxing solution of 2 g. of methyl diketoechinocystate in 100 cc. of absolute alcohol for 22 hours. Dilution with water gave a precipitate which was dissolved in 75 cc. of carbon tetrachloride and passed through a column of 50 g. of alumina (activity I[10]). Twenty-three fractions were obtained by elution in 100-cc. portions with 500 cc. of carbon tetrachloride, 500 cc. of carbon tetrachloride–ether (3:1 by vol.), 500 cc. of carbon tetrachloride–ether (1:1), 500 cc. of ether and 300 cc. of methyl alcohol. Fractions 6 and 7 gave unchanged ester, fractions 8–10 gave the conjugated nordione formed by hydrolysis and isomerization, and fractions 13–23 gave the isomeric ester. Crystallization of the last fractions from methyl alcohol gave a product melting at 203.5–204°, which depressed the melting point of methyl diketoechinocystate; λ_{max} 292 mμ; log ε 2.14; $[\alpha]^{22}D$ −153°.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 77.13; H, 9.61. Found: C, 76.89; H, 9.27.

Reaction with hydroxylamine and crystallization from aqueous methyl alcohol gave a product that melted with decomposition at 252–259°; $[\alpha]^{27}D$ −183°. The nitrogen analysis agreed with that expected for the dioxime of the hydroxamic acid.

Anal. Calcd. for dioxime, $C_{31}H_{48}O_4N_2$: N, 5.46. Calcd. for a dioxime hydroxamic acid, $C_{30}H_{47}O_4N_3$: N, 8.18. Found: N, 8.18.

Saponification of the iso ester with alcoholic potassium hydroxide gave conjugated norechinocystenedione. The iso ester was recovered unchanged after refluxing for 20 hours with alcoholic hydrogen chloride.

Norechinocystenone-B (VII) and Conjugated Norechinocystenone-B (VIII).—From the Clemmensen reduction of methyl diketoechinocystate followed by saponification,[2] only one ketone could be isolated, in contrast to the results of Bilham and Kon.[7] The purified product melted at 227–232°, approximately as reported previously[2] and higher than the 218° reported by Bilham and Kon.[7] $[\alpha]^{20}D$ was −107° in dioxane and −119° in chloroform compared with $[\alpha]D$ −147° in chloroform reported by Bilham and Kon.[7] The compound showed simple carbonyl absorption, λ_{max} 292 mμ, log ε 1.98.

Refluxing this ketone with alcoholic hydrogen chloride for 20 hours gave a product which melted after three crystallizations at 233–237°; $[\alpha]^{26}D$ +25°. The absorption spectrum, λ_{max} 252, 312 mμ, log ε 3.97, 1.88, shows that the double bond is conjugated with the carbonyl group, and it was called conjugated norechinocystenone-B (VIII).

Anal. Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.30. Found: C, 84.82; H, 11.43.

Action of Hydrogen Chloride on Echinocystic Acid.—When 11 g. of echinocystic acid in 200 cc. of glacial acetic acid and 75 cc. of concentrated hydrochloric acid was heated at 65° for eight hours, and the reaction mixture diluted with water, a product was obtained which melted after crystallization from methyl alcohol at 285–286°; $[\alpha]^{18}D$ −32°. It gave no color with tetranitromethane and analysis indicated that it is the diacetylechinocystic acid lactone.

Anal. Calcd. for $C_{34}H_{52}O_6$: C, 73.33; H, 9.42. Found: C, 73.14; H, 9.19.

Dry hydrogen chloride was passed into a refluxing solution of 1.5 g. of echinocystic acid in 150 cc. of absolute alcohol for 24 hours. Dilution with water gave 1.37 g. of solid, which was dissolved in a large volume of ether and extracted with 5% aqueous sodium hydroxide. Only about 0.03 g. of the solid was acidic. The neutral fraction was crystallized from methyl alcohol to give a product melting with decomposition at 361–366°. This compound gives no color with tetranitromethane, is free of halogen, and shows no selective absorption in the ultraviolet. It is soluble readily only in pyridine; $[\alpha]^{24}D$ −13° in pyridine. The analysis corresponds to a compound formed by loss of one molecule of water from two molecules of echinocystic acid.

Anal. Calcd. for echinocystic acid, $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Calcd. for $C_{60}H_{94}O_7$: C, 77.70; H, 10.21. Found: C, 77.85; H, 10.26.

When this compound is heated with acetic anhydride in pyridine, the diacetyl lactone of echinocystic acid is formed, identical with that obtained by the action of hydrochloric acid and acetic acid on echinocystic acid.

Action of Hydrogen Chloride on Methyl Echinocystate and Methyl Diacetylechinocystate.—Dry hydrogen chloride was passed into a refluxing solution of 2 g. of methyl echinocystate in 125 cc. of absolute ethyl alcohol for 24 hours. Dilution with water, filtering and drying gave a product that was extracted with 1 l. of ether. The ether-insoluble

(8) Melting points are corrected, absorption spectra are for solutions in absolute ethyl alcohol, and optical rotations are for solutions in dioxane unless otherwise noted. All analyses by Microchemical Specialties, Berkeley 3, Calif.

(9) For nomenclature see footnote to page 261 of the article by D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, for 1951.

(10) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

portion weighed 0.17 g. and melted after one crystallization from methyl alcohol at 360–372°.

The ether solution was extracted with aqueous sodium hydroxide, which removed a small amount of acidic material that was not investigated. Evaporation of the ether gave 1.74 g. of a neutral fraction which was crystallized from methyl alcohol to give 0.56 g., m.p. 362–372°, identical with the ether-insoluble fraction. Concentration of the mother liquor gave 0.9 g. of crystals melting at 170–340°. After extraction with hot carbon tetrachloride, about one-fifth was insoluble and melted after crystallization from methyl alcohol at 354–364°. Acetylation gave a product, m.p. 280–282°, that did not depress the melting point of diacetylechinocystic acid lactone. Hence the original fraction is identical with the high-melting product formed by the action of alcoholic hydrogen chloride on echinocystic acid.

The four-fifths soluble in carbon tetrachloride, after several crystallizations from methyl alcohol and from acetone, melted at 191–193°. It gave a yellow color with tetranitromethane and was transparent in the ultraviolet. The melting point was not depressed when the compound was mixed with either methyl echinocystate or with methyl anhydroechinocystate, nor did mixing of the last two compounds result in a lowering of their melting points. However, when the fraction was acetylated it depressed the melting point of methyl diacetylechinocystate but not that of methyl acetylanhydroechinocystate. Moreover, hydrogenation of the acetate gave a product, m.p. 213–215°, that did not depress the melting point of methyl acetyloleanolate. Hence the chief action of the alcoholic hydrogen chloride on methyl echinocystate was to dehydrate it to methyl anhydroechinocystate.

The initial ether-insoluble fraction, m.p. 360–372°, is different from the carbon tetrachloride-insoluble fraction, m.p. 354–364°, since acetylation gives a product, m.p. 308–310°, that lowers the melting point of diacetylechinocystic acid lactone. No satisfactory formulas could be deduced from the analyses of either the original compound or its acetate.

Treatment of methyl diacetylechinocystate with alcoholic hydrogen chloride gave methyl anhydroechinocystate and the material, m.p. 350–360°, which on acetylation gave diacetylechinocystic acid lactone. None of the second high melting product was obtained.

Oxidation of 2-Acetylechinocystic Acid.—Oxidation of 2-acetylechinocystic acid under the same conditions used to prepare isonorechinocystenedione gave a product which, after several crystallizations from methyl alcohol, melted at 290–295° in an evacuated capillary tube; $[\alpha]^{24}D$ −90°; λ_{max} 300 mμ, log ε 1.98. The analysis indicates that the product is not the expected 2-acetylnorechinocystenone but is the acetyl diketo lactone of echinocystic acid (X).

Anal. Calcd. for $C_{32}H_{46}O_6$: C, 72.96; H, 8.80. Found: C, 72.53; H, 8.87.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Carcinolytic Compounds. III. 9-(1′-Glycityl)-isoalloxazines

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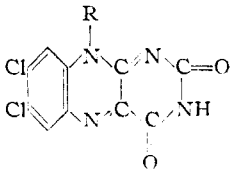
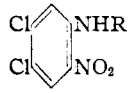
Four riboflavin analogs, 6,7-dichloro-9-(1′-D-mannityl)-isoalloxazine, 6,7-dichloro-9-(1′-D-arabityl)-isoalloxazine, 6,7-dichloro-9-(1′-D-xylityl)-isoalloxazine and 9-(1′-D-sorbityl)-isoalloxazine have been prepared and have been found to be ineffective in enhancing the rate of regression of established lymphosarcoma implants in mice. 6,7-Dichloro-9-(1′-D-ribityl)-isoalloxazine seemed to show slight activity. The rate of condensation of glycamines with 1,2-dinitro-4,5-dichlorobenzene to produce substituted nitroanilines has been shown to be markedly dependent upon the configuration of the glycamines.

Subsequent to the discovery of the activity of 6,7-dichloro-9-(1′-D-sorbityl)-isoalloxazine (I)[1] in enhancing regression of lymphosarcoma implants in mice, four additional dichloroglycitylisoalloxazines and one isoalloxazine containing no chlorine have been prepared.



I, R = D-sorbityl
II, R = D-mannityl
III, R = D-arabityl
IV, R = D-xylityl
V, R = D-ribityl

The dichloroisoalloxazines, 6,7-dichloro-9-(1′-D-mannityl)-isoalloxazine (II), 6,7-dichloro-9-(1′-D-arabityl)-isoalloxazine (III) and 6,7-dichloro-9-1′-D-xylityl)-isoalloxazine (IV), were synthesized by the general procedure described previously.[1] D-Mannamine, D-arabinamine[2] and D-xylamine,[2] were prepared by hydrogenation of the corresponding sugars in liquid ammonia over a nickel catalyst. These glycamines were allowed to react with 1,2-dinitro-4,5-dichlorobenzene in aqueous alcohol to produce 2-nitro-4,5-dichloro-N-(1′-D-mannityl)-aniline (VI), 2-nitro-4,5-dichloro-N-(1′-D-arabityl)-aniline (VII)[2] and 2-nitro-4,5-dichloro-N-(1′-D-xylityl)-aniline (VIII).[2]



VI, R = D-mannityl
VII, R = D-arabityl
VIII, R = D-xylityl

A striking difference was observed in the rate of reaction of D-mannamine with 1,2-dinitro-4,5-dichlorobenzene as compared with the rate at which D-arabinamine and D-xylamine reacted. The latter two gave good yields of the substituted anilines (VII and VIII) in one hour at 90°; under the same conditions with D-mannamine, no reaction was detectable, and after 18 hours at 90° only the dinitrodichlorobenzene was isolated. At 140° for four hours, a reaction occurred and the mannitylnitroaniline (VI) was produced. This rate of reaction of D-mannamine with 1,2-dinitro-4,5-dichlorobenzene is similar to the slow rate at which D-ribamine[2,3] also reacts. The glycamines D-glucamine, L-arabinamine and D-galactamine reacted with 1,2-dinitro-4,5-dichlorobenzene in one minute at 80° to yield the substituted nitroanilines.[1]

(1) F. W. Holly, E. W. Peel, R. Mozingo and K. Folkers, THIS JOURNAL, **72**, 5416 (1950).

(2) F. W. Holly, E. W. Peel, J. J. Cahill and K. Folkers, *ibid.*, **73**, 332 (1951).

(3) R. Kuhn, F. Weygand and E. F. Möller, *Ber.*, **76B**, 1044 (1943).