gave the pure dichloride, b.p. 58–60° (5.7 mm.), $n^{20}D$ 1.5090–1.5094. Its infrared spectrum showed no carbonyl and identified it with the dichloride obtained on chlorinolysis of the 2,4-dinitrobenzenesulfenyl chloride adduct.

The molar refraction and dipole moment of the dichloride were measured on the product from this run since it is the purest sample obtained; MR_D: calcd., 39.9; found, 39.7.

(b) *anti*-7-Chloro-*exo*-norbornyl Acetate.—The residue from the distillation of the dichloride was distilled through the 6″ Widmer to give 20.5 g. of distillate, $n^{20}D$ 1.5051–1.4868. These cuts were systematically refractionated in the manner described previously. 3.3 g. of practically pure chloroacetate, b.p. 40.3° (0.2 mm.), $n^{20}D$ 1.4842, was obtained. The infrared spectrum of this cut showed it to be identical with the chloroester previously obtained.

Addition of 2,4-Dinitrobenzenesulfenyl Chloride to Norbornene in Acetic Acid.—To a stirred solution of norbornene (20 g., 0.213 mole) in 50 ml. of glacial acetic acid was added, dropwise, a solution of 2,4-dinitrobenzenesulfenyl chloride (45.0 g., 0.192 mole) in 600 ml. of acetic acid. The addition was made during 4 hours, to keep the temperature low (26°). A yellow precipitate was filtered off and washed with hot carbon tetrachloride to give 3.2 g. (5.0%) of product of m.p. 164–166°, mixed m.p. with known *endo*-2-chloro-*exo*-norbornyl 2,4-dinitrophenyl sulfide, 164.5–167°.

The filtrate was stirred into 2 l. of water; the oily mass which separated was extracted repeatedly with about 2 l. of benzene. The benzene extract, after washing with water, sodium carbonate solution, and again with water, was concentrated to 300 ml. The remainder of the benzene was allowed to evaporate. The orange oil which was obtained in that way failed to crystallize on long standing. When recrystallization from hot ethanol was attempted, it was found that an oil separated as the solution cooled, and then a solid appeared after long standing. The entire mass was then extracted repeatedly with ethanol by boiling, cooling, decanting the clear solution, and allowing crystallization to proceed. This lengthy process gave 35.3 g. of product in four crops with long, indefinite melting ranges, *ca.* 80–140°. The oil was discarded.

A portion of the yellow solid was crystallized repeatedly from hot carbon tetrachloride to give, in minute quantity, a solid with constant m.p. of 191.5–192.5°. The amount of this product was too small to warrant further work.

Another portion of the yellow solid was chromatographed on an 18 × 1000 mm. column of alumina. Benzene elution, followed by evaporation of solvent, gave, from 1.0 g. of starting mixture, 0.9 g. of a mixture with the m.p. 115–130°. Purification by the flotation and recrystallization method previously described gave nortricyclyl 2,4-dinitrophenyl sulfide, m.p. 142–144°, mixed m.p. with an authentic specimen, 142.5–143.5°, and a small amount of the high melting (185–190° after three recrystallizations) compound. Analysis of the crude first fraction from another chromatogram showed 0.91% chlorine, indicating that the nortricyclyl compound is the main constituent of the yellow solid. The last fraction from the chromatography was an oil; it contained no chlorine at all, as evidenced by a negative Beilstein test, and is therefore probably an unsaturated sulfide.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXV.[1] The Structure of the Cactus Triterpene Dumortierigenin[2,3]

BY CARL DJERASSI, C. H. ROBINSON[4] AND D. B. THOMAS[5]

RECEIVED MAY 2, 1956

Degradative evidence coupled by a direct conversion to erythrodiol has led to the structure elucidation of dumortierigenin, a hexacyclic triterpene isolated from the Mexican cactus *Lemaireocereus dumortieri*. Dumortierigenin is the 28 → 15-lactone of 15β,22α-dihydroxyoleanolic acid and attention is called to the pronounced shielding effect of the lactone ring upon the 12–13 double bond.

The preliminary characterization of dumortierigenin, a triterpenoid lactone isolated from the Mexican cactus *Lemaireocereus dumortieri*, has already been reported in an earlier paper.[6] No definite decision could be made at that time[6] between the empirical formulas $C_{30}H_{46}O_4$ and $C_{30}H_{48}O_4$, but it will now be shown that the former is correct. The four oxygen atoms were demonstrated to be present as a five-membered lactone ring and as two secondary hydroxyl groups. Evidence was also adduced that both alcoholic functions are equatorially oriented and attached to six-membered rings and that one of them is almost certainly present as the conventional 3β-hydroxyl group. The relative accessibility of this cactus[6] has permitted the isolation of adequate amounts of this triterpene and the present communication is concerned with its structure elucidation.

The probable presence of a double bond in dumortierigenin was indicated[6] by the high terminal ultraviolet absorption[7] and by a weak coloration with tetranitromethane observed with certain dumortierigenin derivatives (though not with the parent lactone). The absence of any perceptible reaction[6] with perbenzoic acid did not shed any further light on this point since triterpenes of the α-amyrin series react only very slowly under those conditions.[8] Direct proof for the presence of the typical 12–13 double bond was provided by the course of the chromium trioxide oxidation of dumortierigenin diacetate which led to an α,β-unsaturated ketone. It should be noted that the ultraviolet absorption maximum (241 mμ) occurred at a lower wave length than is usually observed (*ca.* 250 mμ) for 11-keto-Δ^{12}-triterpenes[9] and this suggested the influence of some additional structural feature upon this chromophore.[10] Dumortierigenin diacetate did not react with selenium dioxide in glacial acetic solution under conditions

(1) Paper XXIV, C. Djerassi, J. A. Henry, A. J. Lemin, T. Rios and G. H. Thomas, THIS JOURNAL, **78**, 3783 (1956).

(2) We are indebted to the National Science Foundation for financial support.

(3) Presented at the Symposium on Recent American Terpene Research at the Dallas A.C.S. Meeting, April 11, 1956.

(4) Postdoctorate research fellow, 1954–1955.

(5) Postdoctorate research fellow, 1955–1956.

(6) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, THIS JOURNAL, **76**, 2969 (1954).

(7) T. G. Halsall, *Chemistry & Industry*, 867 (1951).

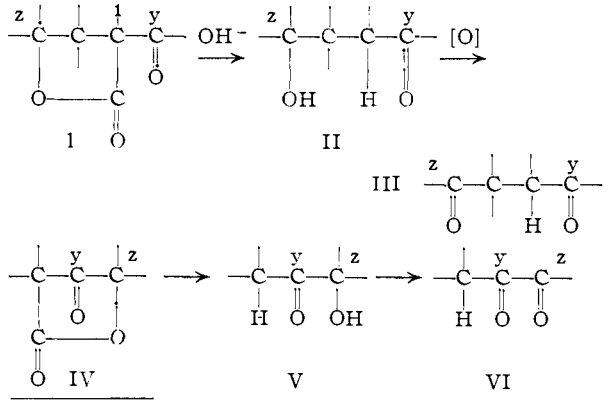
(8) *Cf.* L. Ruzicka, H. Silbermann and M. Furter, *Helv. Chim. Acta*, **15**, 482 (1932).

(9) For leading references see C. R. Noller, THIS JOURNAL, **66**, 1269 (1944).

(10) 11-Keto-A1-barrigenyl pentaacetate (A. R. H. Cole, D. T. Downing, J. C. Watkins and D. E. White, *Chemistry & Industry*, 254 (1955)) exhibits a maximum at 245 mμ.

where all known triterpenes of the β-amyrin series are converted to $\Delta^{11,13(18)}$-dienes.[11] Since α-amyrins are recovered essentially unchanged,[12] the presently observed resistance of dumortierigenin toward both selenium dioxide and perbenzoic acid suggested an α-amyrin skeleton. Treatment of dumortierigenin diacetate with N-bromosuccinimide gave ambiguous results, but as has been pointed out recently[1] this reagent cannot be used as a safe means of differentiation between α- and β-amyrins. As will become apparent from the sequel, even the reactivity of the 12–13 double bond toward selenium dioxide and perbenzoic acid can be affected radically by certain substituents in ring D.

In the initial investigation[6] on dumortierigenin, it was shown that selective manipulation of the two hydroxyl groups was possible and it was decided, therefore, to approach the structural problem by stepwise removal of these substituents. Partial saponification of dumortierigenin diacetate gave a 3-monoacetate and this could be oxidized to 3-monoacetoxy-y-keto-dumortierigenin.[13] The key to the subsequent structure elucidation was provided by the course of the alkaline saponification of the 3-monoacetoxy-y-ketone which was accompanied by concomitant decarboxylation and led to a nor-y-keto-3,z-diol (II or V). It is clear, therefore, that the potential carboxyl function of the lactone ring must be situated β to the y-keto group as expressed in partial structures I and IV. Furthermore, the newly formed z-hydroxyl substituent must be axially oriented in order to be involved in lactone formation and should not be responsive to mild acetylation conditions (axial secondary or tertiary alcohol) sufficient to convert the 3β-alcohol to its acetate. This proved to be the case and the resulting nor-3β-acetoxy-y-keto-z-alcohol (II or V) could be oxidized with chromium trioxide to a nor-3-acetoxy-y,z-dione. The above sequence requires that the z-hydroxyl group, which represents the termination point of the five-membered lactone ring, be secondary (and axially oriented) and leaves only two partial structures, III or VI, for consideration for the nor-3-acetoxy-y,z-dione. The two possibilities could be differentiated readily since VI now contains an α-diketone moiety while III does not. As demonstrated in the Experimental portion, the nor-diketone was not an α-diketone, thus requiring partial structure I for dumortierigenin from which it follows that the carbon atoms bearing the y and z substituents must be located in two different rings. It is also pertinent to the subsequent discussion to point out that neither I, II or III contained an α,β-unsaturated carbonyl system.



With this information at hand and assuming a normal triterpene skeleton, it is possible to reduce the permissibile structural expressions for dumortierigenin to three[14] by eliminating all alternatives which cannot accommodate partial structures I, II and III. Carbon atoms 23 or 24 (*cf.* VII) cannot be involved in the lactone ring because there is not available an adjacent methylene group as a potential site for the y-keto substituent of I. Position 25 is excluded because this would require partial structure VII for 3-acetoxy-y-ketodumortierigenin[13] (I) and base treatment would have involved decarboxylation with dehydration to yield an α,β-unsaturated ketone VIII which was not the case. Furthermore, dumortierigenin-dione would then be a 1,3-diketone subject to β-diketone cleavage, while in actual fact the diketone grouping proved to be stable to boiling alkali. Similarly, an α,β-unsaturated ketone X would have been formed if the lactone ring had originated at C-27, in which case the keto-acetate would have been represented by IX. Positions 29 and 30 can be eliminated irrespective of whether dumortierigenin belonged to the α- or β-amyrin series. The first alternative could only involve structure XI which would ultimately furnish an α-diketone VI while a β-amyrin skeleton would require structure XII which upon base treatment would lead to an α,β-unsaturated ketone XIII.

The above analysis leaves only three possibilities[14]—XIV, XV and XVI—which should be amenable to experimental verification. *A priori*, structure XVI appeared to be the most likely one on biogenetic grounds since cactus triterpenes are known which carry hydroxyl groups at C-16 (cochalic acid)[15] or C-21 (machaeric acid (XXVIII)),[16] while XIV seemed to be the least probable since no naturally occurring triterpene has as yet been encountered which is oxygenated at C-7 and/or C-26.

All subsequent work was concentrated on removing the y and z oxygen functions (*cf.* I), since on the basis of structures XV or XVI this would lead to the known uvaol or erythrodiol (XXVIa) (depending upon the presence of an α- or β-amyrin skeleton in dumortierigenin) while the obtention of an unknown diol would point toward XIV or some abnormal triterpene ring system. In order to simplify the subsequent discussion, the correct structures (XIX) for dumortierigenin and its transformation products will be employed and alterna-

(11) L. Ruzicka, G. Müller and H. Schellenberg, *Helv. Chim. Acta*, **22**, 767 (1939); see also D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).

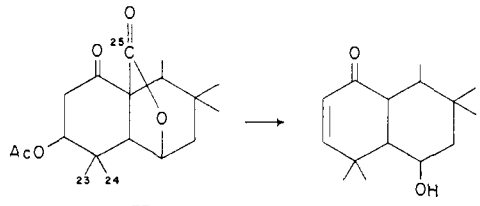
(12) *Cf.* J. D. Easton, W. Manson and F. S. Spring, *ibid.*, 943 (1953).

(13) Referred to in the original paper (ref. 6) as x-acetoxy-y-keto-dumortierigenin.

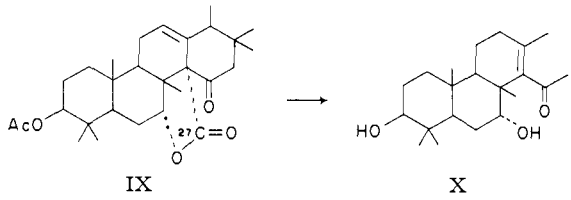
(14) The question of an α- or β-amyrin system being left open for the time being.

(15) C. Djerassi, G. H. Thomas and H. Monsimer, THIS JOURNAL, **77**, 3579 (1955).

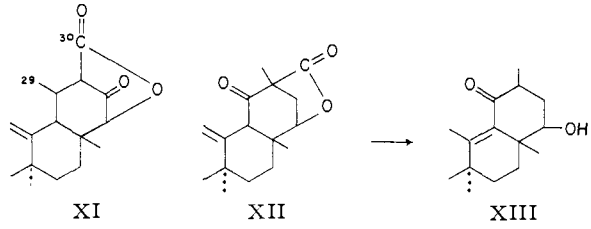
(16) C. Djerassi and A. E. Lippman, *ibid.*, **77**, 1825 (1955).



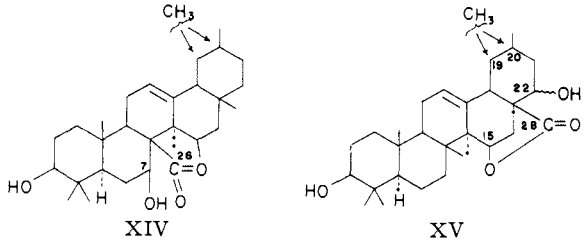
VII VIII



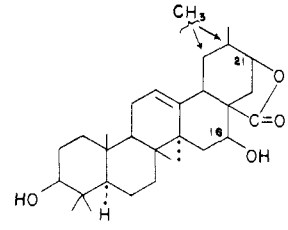
IX X



XI XII XIII



XIV XV



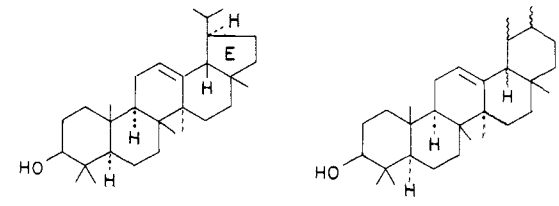
XVI

tives will be considered only at those stages where they enter upon the logical development of the constitution of this triterpene.

As pointed out earlier, the circumstantial evidence favored membership in the comparatively rare α-amyrin group of triterpenes and if structures XV or XVI (methyl group at C-19) were the correct ones, this would mean that dumortierigenin would be the first ring E oxygenated representative of this class. At this stage of our investigation, there appeared the first of a series of papers by Spring and collaborators,[17] in which it was suggested that α-amyrin should be represented by XVII, ring E being five-membered, rather than by the previously accepted[18] formulation XVIII.

(17) J. M. Beaton, F. S. Spring, R. Stevenson and W. S. Strachan, *J. Chem. Soc.*, 2610 (1955).

(18) *Cf.* O. Jeger in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VII, Springer, Vienna, 1950, pp. 47–60. For further references see A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **39**, 441 (1956).



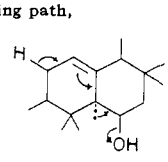
XVII XVIII

Infrared examination of ring E ketones of the α-amyrin series (hitherto unknown) would offer a simple means of settling the question of the size of ring E and appropriate derivatives of dumortierigenin were consequently prepared. The decarboxylation product (now known to be XXa) of 3-acetoxy-y-keto-dumortierigenin (I, now known to be XIXd) was the first such test case, since on the basis of an α-amyrin skeleton involving XV (methyl group at C-19) the y-keto group should be at C-22. The resulting carbonyl group was clearly part of a six-membered ring ($\lambda_{max}^{CHCl_3}$ 5.87 μ), but this could also have referred to C-16 if structure XVI were the correct one. Therefore, the triketone XXIb was synthesized since in that case, irrespective of the correctness of formulations XV or XVI, one of the carbonyl groups would have to be located in ring E. Infrared examination again demonstrated that no cyclopentanone was present, whereupon it was concluded that dumortierigenin was either a member of the β-amyrin group or that structure XVII for α-amyrin[17] could be excluded definitely. Since a rigorous decision could only be reached by direct correlation with a triterpene of known constitution, this was eventually accomplished by the following sequence of reactions.

The second hydroxyl group (now known to be at C-22, *cf.* XIXa) of dumortierigenin was removed by oxidation of dumortierigenin 3-monoacetate (XIXc) to the corresponding 3-acetoxy-ketone XIXd, transformation to the cycloethylene mercaptal XIXf by the perchloric acid method[19] and desulfurization to (22)-desoxydumortierigenin 3-acetate (XIXg). Reduction with lithium aluminum hydride led to Δ^{12}-oleanene-3β,15β,28-triol (XXIIa) which was converted directly to the 3,28-diacetate, the 15β-hydroxyl group being unaffected by the acetylation conditions since it is even more hindered than a steroidal 11β-hydroxy substituent. Since all attempts to dehydrate the diacetate XXIIb to the olefin XXVa were abortive,[20] it was oxidized to the corresponding 3,28-diacetoxy-15-ketone XXIIIb. However, even the

(19) D. L. Klass, M. Fieser and L. F. Fieser, THIS JOURNAL, **77**, 3829 (1955).

(20) The conditions tried were of the type which worked successfully with 11β-hydroxy steroids, but in this instance only dark, oily products were formed. With phosphorus oxychloride in pyridine, rearrangement, possibly by the following path,



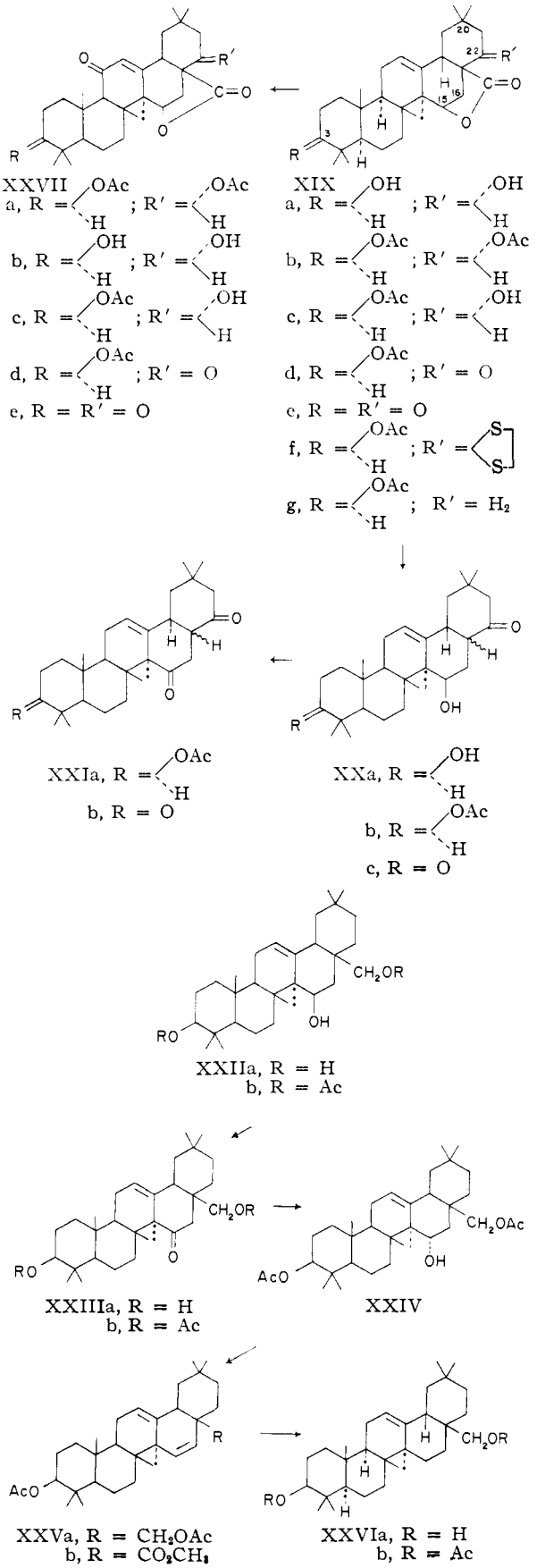
occurred since the resulting oil now exhibited strong ultraviolet absorption in the 260–270 mμ region. A similar observation also has been made with Δ^7-9α-methyl-11β-hydroxy steroids (ref. 23).

most drastic Wolff–Kishner reduction conditions,[21] which served satisfactorily in the reduction of a strongly hindered 6-ketone of the sumaresinolic acid series,[22] failed completely in this instance. The 15-ketone thus is sterically the most hindered carbonyl group in the triterpene series; it contains the same environment as the recently synthesized Δ^7-9α-methyl-11-oxygenated steroids[23] and a close similarity in chemical behavior can be noted.

Since 15α-hydroxyl groups in the triterpene series[24] can be dehydrated without rearrangement, the diacetoxy-15-ketone XXIIIb was reduced with lithium in liquid ammonia[25] to afford, after reacetylation, Δ^{12}-oleanene-3β,15α,28-diacetate (XXIV). Dehydration with phosphorus oxychloride now proceeded smoothly and the resulting olefin XXVa was hydrogenated to erythrodiol diacetate XXVIb, which was identified by direct comparison with an authetic sample.[26]

The direct correlation of dumortierigenin with erythrodiol (XXVI) proves that this cactus triterpene belongs to the β-amyrin series (in spite of the fact that the chemical non-reactivity of its double bond resembles that of α-amyrins) and while it does not rigorously differentiate between structures XV and XVI (methyl group at C-20), the reactivity of several intermediates requires structure XV (methyl group at C-20) = XIXa for dumortierigenin. The degree of hindrance of the keto group (in XXIII) is only compatible with its location at C-15, since by the alternative formulation (XVI, methyl at C-20), this keto group would be at C-21 and such carbonyl functions are known[16] to behave normally. This also applies to the resistance of the C-15 alcohols (XXII or XXIV) toward acetylation under conditions where C-21 alcohols are esterified readily.[16] Furthermore, the lack of reactivity of the 12–13 double bond in dumortierigenin, approaching that of α-amyrins, can only be explained by a shielding effect of the lactone ring and this is probably also responsible for the hypsochromic shift in the ultraviolet absorption maximum[9] of the derived 11-ketones (XXVII).

The alternative dumortierigenin expression XVI (methyl at C-20) would require that the last intermediate in the transformation to erythrodiol (XXVI) possesses structure XXIXb rather than the assigned Δ^{15}-formulation (XXVa). In view of the fact that the corresponding methyl ester XXIXa had recently been prepared[16] from machaeric acid (XXVIII), it proved a simple matter to synthesize $\Delta^{12,21}$-oleadiene-3β,28-diol diacetate



(21) D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(22) C. Djerassi, G. H. Thomas and O. Jeger, *Helv. Chim. Acta*, **38**, 1304 (1955).

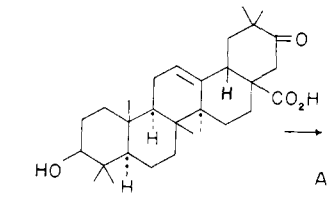
(23) Private communication from Prof. E. R. H. Jones (Oxford University). See E. R. H. Jones, G. D. Meakins and J. S. Stephenson, Abstract No. 283, Congress Handbook, XIVth International Congress of Pure and Applied Chemistry, Zurich, 1955.

(24) Such a step was employed in the recent partial synthesis of taraxerol from β-amyrin (J. M. Beaton, F. S. Spring, R. Stevenson and J. L. Stewart, *J. Chem. Soc.*, 2131 (1955).

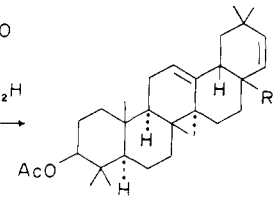
(25) Using the conditions which served satisfactorily in the reduction of 11-keto steroids to 11α-alcohols (F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953)).

(26) C. Djerassi, R. N. McDonald and A. J. Lemin, *ibid.*, **75**, 5940 (1953).

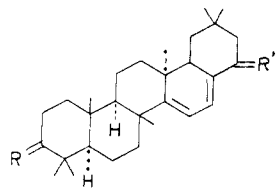
(XXIXb) by lithium aluminum hydride reduction, by acetylation and, as was to be expected, this olefin (XXIXb) was quite different from the one (XXVa) derived from dumortierigenin. The latter olefin XXVa could, however, be synthesized from the known[27] methyl-Δ^{15}-dehydro-oleanolate acetate (XXVb) by lithium aluminum hydride reduction and acetylation, thus proving structure XIXa for dumortierigenin.[28]

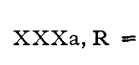
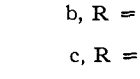


XXVIII



XXIXa, R = CO_2CH_3
b, R = CH_2OAc



XXXa, R =  ; R′ = O
b, R = R′ = O
c, R = R′ = 

Dumortierigenin is the first cactus triterpene for which oxygenation at both positions 15 and 22 has been demonstrated. The presence of a 22β-hydroxyl group has recently been established in three triterpenes[29] but C-15 hydroxylation has not yet been proved rigorously in any other member of this class of natural products.[30]

At an early stage of our investigation, there was examined the dehydration of the 28-nor-22-ketones XXb and XXc with the aim of eventual correlation with certain decarboxylation products of echinocystic acid.[31] The acid-catalyzed dehydration did not proceed by the expected path but rather involved a rearrangement, which can now be rationalized readily in the light of the established structure XX for the 28-nor-22-ketones of the dumortierigenin series. Both the 3-acetate XXb and the 3-ketone XXc upon treatment with hydrochloric and acetic acids yielded unsaturated ketones characterized by a strong ultraviolet absorption maximum at 325 mμ, which is only compatible with a linearly conjugated dienone, the diene chromophore of which is homoannular.[32] This assumption could be supported by lithium aluminum hydride reduction to a non-crystalline product (XXXc) which did not contain a ketone group and which exhibited an ultraviolet absorption maximum at 275 mμ, typical of homoannular dienes. These results are mechanistically (protonation of double bond and methyl migration *via* C-13 carbonium ion) and spectroscopically consistent with structures XXXa and XXXb for the unsaturated dienones and XXXc for the lithium aluminum hydride reduction product.

(27) D. Frazier and C. R. Noller, THIS JOURNAL, **66**, 1267 (1944).

(28) The equatorial (α) orientation is assigned to the 22-hydroxyl group on the basis (ref. 6) of the ease of acetylation, saponification (of the acetate) and reformation of dumortierigenin (XIXa) in the sodium borohydride reduction of the 3,22-dione XIXe.

(29) D. H. R. Barton and P. de Maho, *J. Chem. Soc.*, 887, 900 (1954); D. H. R. Barton, P. de Mayo, E. W. Warnhoff, O. Jeger and G. W. Perold, *ibid.*, 3689 (1954).

(30) Soyasapogenol A (A. Meyer, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 672 (1950)) and A_1-barrigenol (ref. 10) probably contain hydroxyl groups in that position.

(31) F. A. Alves and C. R. Noller, THIS JOURNAL, **74**, 4043 (1952), and earlier papers.

(32) For typical examples see T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 468 (1953).

Experimental[33]

Δ^{12}-28-Nor-oleanene-3β,15β-diol-22-one (XXa).—A solution of 200 mg. of the 3β-acetoxy-22-ketone XIXd[6,34] in 3 cc. of dioxane was refluxed for 1 hour with 3 cc. of methanolic potassium hydroxide. The crude, neutral product (170 mg.) isolated by ether extraction, was chromatographed on alumina.[35] Elution with 4:1 benzene–ether afforded 95 mg. of solid which on crystallization from methanol–chloroform had m.p. 227–237°. The analytical sample crystallized as needles, m.p. 233–238°, $\lambda_{max}^{CHCl_3}$ 5.87 μ.[36]

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.74; H, 10.60.

In a second experiment starting with 400 mg. of keto acetate XIXd, the total crude material was acetylated and then chromatographed to yield, after crystallization from methanol–chloroform, 120 mg. of the 3-mono-acetate XXb as platelets, m.p. 231–237°, $[\alpha]_D$ +10°; $\lambda_{max}^{CHCl_3}$ 5.81, 5.89 and type A band[37] at 8.0 μ.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.69; H, 10.12.

The 3-acetoxy-22-ketone XIXd was recovered unchanged (mixture melting point and infrared comparison) after refluxing for 3 hours with 4:1 acetic acid–hydrochloric acid (see below for reaction of XXb and XXc with this reagent).

Δ^{12}-28-Nor-oleanen-3β-ol-15,22-dione Acetate (XXIa).—The above 28-nor-3-acetoxy-15-hydroxy-22-ketone XXb (175 mg.) was oxidized in 20 cc. of acetone with the chromium trioxide sulfuric acid reagent[34,38] and the product was crystallized three times from chloroform–methanol to give 55 mg. of needles, m.p. 275–280°, $[\alpha]_D$ −2°.

Anal. Calcd. for $C_{31}H_{46}O_4$: C, 77.13; H, 9.61. Found: C, 77.33; H, 10.05.

Small samples of this substance were refluxed with 5% methanolic potassium hydroxide or with methanolic hydrochloric acid but in neither case did the total reaction product exhibit high selective ultraviolet absorption in the region 220–360 mμ.

Δ^{12}-28-Nor-oleanene-3,15,22-trione (XXIb). (a) From the 3-Monoacetoxy-22-ketone XIXd.—The keto acetate (200 mg.) was treated with methanolic potassium hydroxide and dioxane as described above and the crude, neutral product was directly oxidized (12 hours, 23°) with 80 mg. of chromium trioxide in 5 cc. of acetic acid. Careful chromatography on alumina and crystallization of the benzene eluates from methanol afforded the triketone XXIb as needles (80

(33) All melting points were obtained on the Kofler block. Unless noted otherwise, rotations were measured in chloroform solution. We are indebted to Mrs. Dolores Phillips for the infrared spectra and to Geller Laboratories (Hackensack, N. J.) and Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses.

(34) The partial saponification of dumortierigenin diacetate (XIXb) could be carried out on a larger scale than reported previously (ref. 6) without any difficulty. From 6.6 g. of diacetate XIXb, there was obtained 0.7 g. of recovered diacetate, 3.1 g. of the desired 3-monoacetate XIXc and 2.3 g. of dumortierigenin (XIXa). The oxidation of 2 g. of the 3-monoacetate XIXc was performed in 150 cc. of acetone using 1.06 cc. of chromium trioxide solution (2.667 g. of chromium trioxide in 7.7 cc. of water and 2.3 cc. of concd. sulfuric acid) for 30 minutes at 5–10°. The crude product (1.93 g.) was chromatographed to yield 1.1 g. of suitable 22-ketone XIXd (m.p. 324–328° *after* drying by azeotropic distillation with benzene).

(35) All alumina used in this work was Alcoa alumina which had been standing for one day covered with ethyl acetate, filtered, washed with petroleum ether and reactivated by heating for 48 hours at 110°.

(36) We are indebted to Dr. R. Norman Jones (National Research Council, Ottawa) for this determination carried out with a Perkin-Elmer double beam spectrophotometer.

(37) *Cf.* R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951).

(38) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

mg.), m.p. 240–245°, $[\alpha]_D$ +11°, $\lambda_{max}^{CHCl_3}$ 5.87 μ,[36] λ_{max}^{EtOH} 290 mμ, ε 120, no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.40; H, 9.65. Found: C, 79.24; H, 9.61.

(b) **From Dumortierigenin Dione (XIXe).**—A solution of 300 mg. of the dione XIXe[6] was refluxed for 1 hour with 3 cc. each of dioxane and of 10% methanolic potassium hydroxide and the crude, neutral material (XXc) was oxidized directly with chromium trioxide–sulfuric acid[38] in acetone. After chromatographing in the usual manner, there was obtained 200 mg. of the triketone XXIb, m.p. 240–245°, which proved to be identical in all respects with a specimen prepared according to (a). No high, selective ultraviolet absorption was produced when the triketone was refluxed for 1 hour with 5% methanolic potassium hydroxide solution.

Δ^{12}-28-Nor-oleanen-15β-ol-3,22-dione (XXc).—In another experiment, the crude decarboxylation product from the alkaline treatment of dumortierigenin dione was chromatographed and it was possible to isolate two isomers, probably differing only in the configuration at C-17. Isomer A crystallized from chloroform–methanol as platelets, m.p. 232–238°, $[\alpha]_D$ +25°.

Anal. Calcd. for $C_{29}H_{44}O_3$: C, 79.04; H, 10.07. Found: C, 79.00; H, 10.06.

Isomer B was eluted after isomer A and crystallized as needles from methanol, m.p. 226–231°, $[\alpha]_D$ +31°. The infrared spectra were quite similar but a mixture of the two isomers melted at *ca.* 200–210°. Chromium trioxide oxidation furnished the triketone XXIb described above.

Anal. Calcd. for $C_{29}H_{44}O_3$: C, 79.04; H, 10.07. Found: C, 79.43; H, 10.29.

11-Ketodumortierigenin Diacetate (XXVIIa).—To a refluxing solution of 150 mg. of dumortierigenin diacetate (XIXb)[6] in 10 cc. of acetic acid was added over a period of 1 hour 75 mg. of chromium trioxide in 5 cc. of acetic acid and heating was continued for 1 hour. The product, isolated in the usual manner, was crystallized twice from methanol–chloroform to yield 45 mg. of colorless needles, m.p. 345° dec., $[\alpha]_D$ ± 0°, λ_{max}^{EtOH} 241 mμ, ε 12,000; $\lambda_{max}^{CHCl_3}$ 5.60, 5.80, 5.99, 6.10 μ and type B band[37] at 8.1 μ.

A 1.2-g. sample of the above diacetate in 600 cc. of methanol was refluxed for 40 minutes with 2.75 g. of potassium carbonate in 110 cc. of 1:1 water–dioxane and the crude product was chromatographed on alumina. Elution with 1:3 benzene–ether gave 600 mg. of the **3-mono-acetate XXVIIc**, m.p. above 345°, $[\alpha]_D$ −24°.

Anal. Calcd. for $C_{32}H_{46}O_6$: C, 72.97; H, 8.80. Found: C, 72.34; H, 8.47.

Elution with 9:1 chloroform–methanol yielded **11-ketodumortierigenin (XXVIIb)**, which crystallized from methanol–chloroform as prisms, m.p. 334–338°, $[\alpha]_D$ −22°, $\lambda_{max}^{CHCl_3}$ 5.65 and 6.0 μ.

Anal. Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 73.98; H, 9.19.

Oxidation of 11-ketodumortierigenin in acetone solution with chromium trioxide–sulfuric acid[38] followed by crystallization from chloroform–methanol furnished the **3,11,22-triketone XXVIIe**, m.p. 315–320°, $[\alpha]_D$ −10°; $\lambda_{max}^{CHCl_3}$ 5.62, 5.90 and 6.01 μ.

Anal. Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.33.

Similar oxidation of 290 mg. of the 3-mono-acetate XXVIIc produced 200 mg. of needles (from methanol) of the **3-acetoxy-11,22-dione XXVIId**, m.p. 321–327°, $[\alpha]_D$ −27°; $\lambda_{max}^{CHCl_3}$ 5.60, 5.80–5.85 (broad) and 6.00 μ.

Anal. Calcd. for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.59; H, 8.68.

22-Desoxydumortierigenin Acetate (XIXg).—The 3-acetoxy-22-ketone XIXd[6,34] (250 mg.) was dissolved in 4 cc. of ethanedithiol and 4 cc. of benzene, one drop of 70% perchloric acid was added with shaking and the solution was left at room temperature for 5 minutes. Approximately one-half of the solvent was removed by heating on the steam-bath under reduced pressure and after standing for a further 15 minutes the reaction mixture was diluted with ether and washed with alkali. Removal of the ether afforded the solid **mercaptal XIXf** which crystallized from methanol–chloroform as blades, m.p. 333–336°, $[\alpha]_D$ ±0°; $\lambda_{max}^{CHCl_3}$ 5.65, 5.80 and 8.0 μ. The yield is approximately 70% but is reduced considerably if the scale of operation is increased. Consequently, several runs of this size were combined and processed together in order to secure adequate quantities of the mercaptal.

Anal. Calcd. for $C_{34}H_{50}O_4S_2$: C, 69.59; H, 8.58; S, 10.92. Found: C, 69.74; H, 8.57; S, 10.60.

The desulfurization was accomplished by refluxing 1.5 g. of the mercaptal XIXf in 1 l. of ethanol with *ca.* 10 g. of W-2 Raney nickel catalyst for 18 hours, filtering hot and extracting the catalyst three times with 200-cc. portions of boiling ethanol. The residue, obtained on evaporation of the ethanol filtrate and washings, was recrystallized from chloroform–methanol; yield 1.0 g., m.p. 332–336° (after azeotropic distillation with benzene). The analytical sample of **22-desoxydumortierigenin acetate (XIXg)** exhibited m.p. 336–339°, $[\alpha]_D$ −21°, $\lambda_{max}^{CHCl_3}$ 5.67 and 5.80 μ.

Anal. Calcd. for $C_{32}H_{48}O_4$: C, 77.37; H, 9.74. Found. C, 76.83; H, 9.94.

Δ^{12}-Oleanene-3β,15β,28-triol 3,28-Diacetate (XXIIb).—A solution of 1.0 g. of 22-desoxydumortierigenin acetate (XIXg) in 90 cc. of dry tetrahydrofuran was left at room temperature for 19 hours with a large excess of lithium aluminum hydride. Unreacted reagent was destroyed by cautious addition of ethyl acetate, a large quantity of ether was added and then a saturated aqueous solution of sodium sulfate was added dropwise until the inorganic salts just coagulated. The ethereal layer was decanted and the residue was extracted several times with ether. The combined extracts were washed with water, dried and evaporated to dryness yielding 0.9 g. of the triol XXIIa as a colorless froth. This material was acetylated directly with pyridine-acetic anhydride at room temperature overnight and purified by chromatography on alumina. Elution with benzene and recrystallization from chloroform–methanol afforded 0.46 g. of the triol diacetate XXIIb as needles, m.p. 251–255°, $[\alpha]_D$ +53°.

Anal. Calcd. for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.14; H, 10.12.

Dehydration with thionyl chloride in pyridine (18 hours at 0°) or with mesyl chloride at room temperature led only to oils without selective ultraviolet absorption. Treatment with phosphorus oxychloride in pyridine solution at room temperature furnished an oil with a broad ultraviolet absorption maximum at 260–270 mμ, ε 7000 which probably represented a rearrangement product.[20]

Δ^{12}-Oleanene-3β,28-diol-15-one Diacetate (XXIIIb).—The above triol diacetate was oxidized in the standard manner in acetone solution with chromium trioxide-sulfuric acid[38] and the product was recrystallized from methanol–chloroform; yield 85%, m.p. 229–232, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{34}H_{52}O_5$: C, 75.51; H, 9.69. Found: C, 75.61; H, 9.91.

The diacetoxy ketone was recovered unchanged in quantitative yield when it was treated with ethanedithiol in the presence of perchloric acid as described above for XIXf.

Saponification was accomplished by refluxing for 30 minutes with 5% methanolic potassium hydroxide (containing some dioxane) and recrystallization from chloroform–methanol led to needles of **Δ^{12}-oleanene-3β,28-diol-15-one (XXIIIa)**, m.p. 246–250°, $[\alpha]_D$ +31°, $\lambda_{max}^{CHCl_3}$ 5.88 μ.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 79.12; H, 10.77.

Modified Wolff–Kishner reduction[21] for five days followed by reacetylation and chromatography gave as the only recognizable product about 20% of unreacted keto-acetate XXIIIb.

Δ^{12}-Oleanene-3β,15α,28-triol 3,28-Diacetate (XXIV).—The 15-ketone diacetate XXIIIb (280 mg.) in 30 cc. of ether was added to 170 cc. of liquid ammonia containing 6 cc. of methanol at the reflux temperature of ammonia. The stirred solution was treated with 500 mg. of lithium in small pieces over a period of 15 minutes and as soon as the blue color had disappeared, 8 g. of ammonium chloride was added and, after evaporation of the ammonia, ether and water. The ether-soluble material (270 mg.) was acetylated with acetic anhydride and pyridine at 0° for 4 hours and the product was chromatographed on 15 g. of alumina. Elution with 1:1 benzene–ether furnished 170 mg. of the desired triol diacetate XXIV which was recrystallized for analysis from chloroform–methanol; m.p. 260–265°, $[\alpha]_D$ +57°.

Anal. Calcd. for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03; acetyl, 15.90. Found: C, 75.24; H, 10.05; acetyl, 14.52.

$\Delta^{12,15}$-Oleadiene-3β,28-diol Diacetate (XXVa).—The above triol diacetate XXIV (100 mg.) was treated with 5 cc. of pyridine and 0.5 cc. of phosphorus oxychloride at reflux temperature for 2 hours. After pouring into ice the product was extracted with ether and the ethereal solution was washed with dilute hydrochloric acid and water. Removal of solvent gave a residue which was chromatographed on 5 g. of alumina. The desired diacetate XXVa (65 mg.) was eluted with benzene and crystallized from chloroform–methanol to give colorless rods, m.p. 210–212°, $[\alpha]_D$ +53°.

Anal. Calcd. for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.56; H, 9.88.

The same product (mixture melting point and infrared comparison) was obtained when methyl Δ^{15}-dehydrooleanolate acetate (XXVb)[27] was reduced with lithium aluminum hydride and acetylated as described below for XXIXb.

Hydrogenation of $\Delta^{12,15}$-Oleadiene-3β,28-diol Diacetate to Erythrodiol Diacetate (XXVIb).—The hydrogenation of 43 mg. of the diene diacetate XXVa was carried out for 20 hours at room temperature and atmospheric pressure in 20 cc. of acetic acid in the presence of 180 mg. of platinum oxide catalyst. Removal of catalyst and solvent followed by recrystallization from chloroform–methanol gave 28 mg. of erythrodiol diacetate, m.p. 182–185°, $[\alpha]_D$ +62°, which was shown to be identical with an authentic specimen[2] by mixture melting point determination and comparison of the infrared spectra.

$\Delta^{12,21}$-Oleadiene-3β,28-diol Diacetate (XXIXb).—Methyl Δ^{21}-dehydrooleanolate acetate (XXIXa)[16] (220 mg.) was treated with excess lithium aluminum hydride in ether for 6 hours. After addition of ethyl acetate and dilute hydrochloric acid, ether extraction produced a gum which was acetylated with acetic anhydride and pyridine overnight at room temperature. Chromatography on 10 g. of alumina, elution with benzene and recrystallization from methanol and from dilute ethanol led to 110 mg. of colorless plates, m.p. 182–185°, $[\alpha]_D$ +38°.

Anal. Calcd. for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.37; H, 10.02.

Dehydration of Δ^{12}-28-Nor-oleanene-3β,15β-diol-22-one 3-Monoacetate (XXb) and Δ^{12}-28-Nor-oleanene-3,22-dione-15β-ol (XXc).—A 250-mg. sample of the crude 28-nor 3-monoacetate XXb in 10 cc. of a 4:1 mixture of glacial acetic acid and concd. hydrochloric acid was heated under reflux for 4 hours and the product was chromatographed on alumina. Elution with benzene–ether (4:1) furnished 110 mg. of solid (XXXa) which crystallized from methanol–chloroform as colorless needles, m.p. 240–245°, $[\alpha]_D$ −63°, λ_{max}^{EtOH} 326 mμ, ϵ 10,500; $\lambda_{max}^{CHCl_3}$ 5.80, 6.08 and 6.38 μ (double bond band nearly as intense as 5.8 acetate band).

Anal. Calcd. for $C_{31}H_{46}O_3$: C, 79.78; H, 9.94. Found: C, 79.77; H, 10.03.

Similar dehydration of the crude 28-nor-3,22-dione XXc proceeded in 65% yield to afford the diene-dione XXXb, m.p. 192–196° (from ethanol), $[\alpha]_D$ −47°, λ_{max}^{EtOH} 325 mμ, ϵ 12,500; $\lambda_{max}^{CHCl_3}$ 5.85, 6.08 and 6.35 μ.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 82,41; H, 10.02. Found: C, 82.71; H, 10.14.

Lithium aluminum hydride reduction (ether solution, 20°, 14 hours) of either XXXa or XXXb led to an oil which could not be crystallized even after chromatography and acetylation. The total product exhibited no carbonyl absorption in the infrared but showed λ_{max}^{EtOH} 275 mμ, ϵ 7,500, indicating that it possessed structure XXXc.

Reaction of Dumortierigenin Diacetate with N-Bromosuccinimide.—The diacetate XIXb was treated with N-bromosuccinimide using the conditions employed in the queretaroic acid series[1] or in the presence of calcium carbonate,[39] but in each case there was obtained a mixture which could not be separated completely. The predominant products appeared to be a bromo-triene[1] (m.p. 264–269°, λ_{max}^{EtOH} 317 mμ, ϵ *ca.* 10,000) and a ($\Delta^{9(11),12}$?)-diene (m.p. 224–234°, broad ultraviolet maximum at 285–290 mμ).

(39) G. G. Allan and F. S. Spring, *J. Chem. Soc.*, 2125 (1955).

DETROIT, MICHIGAN

COMMUNICATIONS TO THE EDITOR

THE SYNTHESIS OF CERTAIN DEGRADATION PRODUCTS OF THE ANTIBIOTIC 1703-18B. THE SYNTHESIS OF *neo*-INOSAMINE-2

Sir:

The isolation and characterization of a new inosamine, *neo*-inosamine-2 (V),[1] was reported recently from these Laboratories by Patrick and his coworkers.[3] This inosamine was obtained by hydrolysis of a new antibiotic (designated in these Laboratories as 1703-18B) with concentrated hydrochloric acid. We now wish to report the synthesis of this degradation product.

Catalytic oxidation[4] of *neo*-inositol (I)[5] gave an inosose, which was isolated as its phenylhydrazone derivative (47% yield), m.p. 201–204° (dec.).[6] (*Anal.* Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.68; H, 6.21; N, 10.53).

Treatment of the phenylhydrazone derivative with benzaldehyde in the presence of benzoic acid[7] gave the inosose (69% yield), m.p. 218–220° (dec.). (*Anal.* Calcd. for $C_6H_{10}O_6$: C, 40.45; H, 5.66. Found: C, 40.49; H, 5.42). Hydrogenation of the inosose in the presence of platinum furnished an inositol (88% yield), m.p. 314° when dropped on a preheated block. (*Anal.* Calcd. for $C_6H_{12}O_6$: C, 40.00; H, 6.71. Found: C, 40.05; H, 6.91). This material and its hexaacetate, m.p. 252–253°, (*Anal.* Calcd. for $C_{18}H_{24}O_{12}$: C, 50.00; H, 5.60. Found: C, 50.28; H, 5.83) were identical with authentic samples of *neo*-inositol (I)[5] and its hexaacetate.

Reduction of the inosose with sodium amalgam followed by acetylation gave in 40% yield *myo*-

(1) The system of nomenclature proposed by Fletcher and his associates[2] is used in this paper.

(2) H. G. Fletcher, Jr., L. Anderson and H. A. Lardy, *J. Org. Chem.*, **16**, 1238 (1951).

(3) J. B. Patrick, R. P. Williams, C. W. Waller and B. L. Hutchings, THIS JOURNAL, **78**, 3652 (1956).

(4) For previous examples of the utilization of this technique in the inositol field see (a) K. Heyns and H. Paulsen, *Ber.*, **86**, 833 (1953); (b) **89**, 1152 (1956).

(5) S. J. Angyal and N. K. Matheson, THIS JOURNAL, **77**, 4343 (1955).

(6) All melting points were determined on the Kofler hot stage and are corrected.

(7) T. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).