in order to facilitate[10] the location of known molecular features in order to improve the reliability of location of the gibberellic acid part of this ester. In summary, this strategy was successful, but the disadvantages were the introduction of a relatively large number of extra atoms in the determination, and the occurrence of the strongly anisotropic thermal vibrations normal to the planes of the benzene rings.

(10) M. G. Rossmann and W. N. Lipscomb, *Tetrahedron*, **4**, 275 (1958).

Acknowledgment.—We wish to thank Professor E. J. Corey and Mr. S. Barcza for the preparation of this derivative, for helpful discussions, and for the measurement of the density of the crystal. We acknowledge use of the IBM 7090 computers at the Harvard and the MIT Computation Centers, and support of this research by the National Institutes of Health, the National Science Foundation (including a Fellowship to J. A. H.), and the Air Force Office of Scientific Research.

[CONTRIBUTION FROM THE CHANDLER LABORATORIES OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y., AND THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

Total Synthesis of Polycyclic Triterpenes: The Total Synthesis of (+)-α-Onocerin

BY GILBERT STORK, ALEX MEISELS, AND J. E. DAVIES[1]

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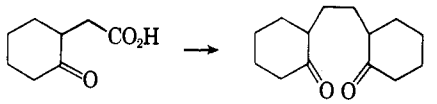
The total synthesis of the natural (+)-α-onocerin is described.

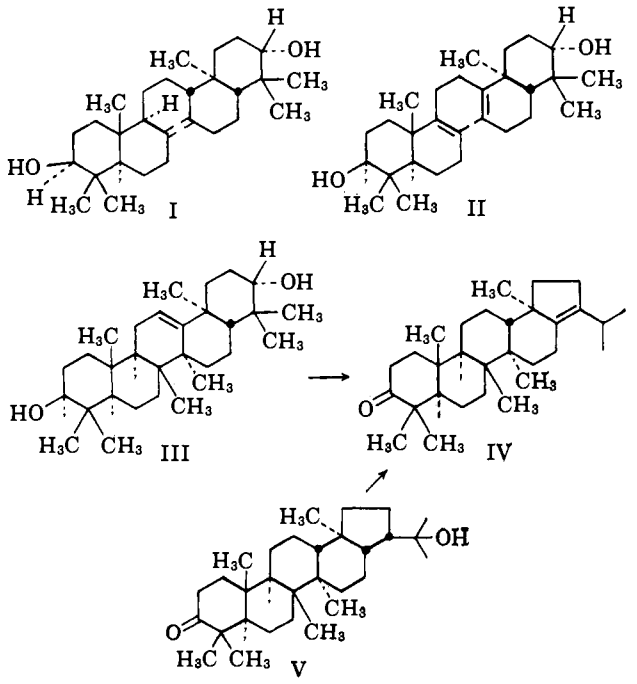
The elucidation of the structure of the triterpene α-onocerin (I) by Barton and Overton,[2] in 1955, was of considerable importance on two counts. First, this triterpene is an uncomplicated example of the squalene biogenetic hypothesis for the usual pentacyclic triterpenes and steroids, in which the assumed concerted cyclization is starting from both ends of the chain rather than proceeding unidirectionally.[3] Second, Barton and Overton[2] were able to cyclize α-onocerin, *via* the β-isomer II, to a pentacyclic triterpene system, γ-onocerin (III), which, although it has not been found in nature so far, is simply related to the natural pentacyclic triterpene hydroxyhopanone[4] (V). In fact, the dehydration product IV of hydroxyhopanone has been made from onocerin by partial synthesis by Schaffner, *et al.*[5] We now record the details of the total synthesis of natural α-onocerin. The starting point of the synthesis was the assumption that the Kolbe electrolytic coupling[6] of suitable γ-ketocarboxylic acids should be a simple solution to one of the problems of synthesizing this particular symmetrical molecule. Our initial experiments showed the feasibility of such a scheme: 2-oxocyclohexaneacetic acid, under the usual electrolytic coupling conditions, gave a very good yield of 1,2-di-(2-oxocyclohexyl)-ethane (VI). This result allowed the



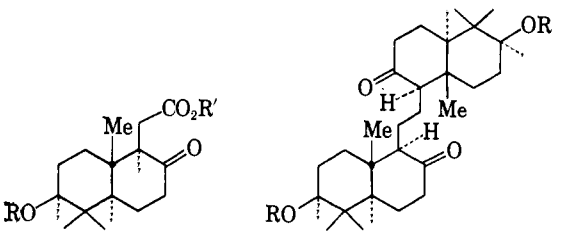
VI

dissection of the synthetic problem into three parts: (a) the construction of the proper ketoacid, *e.g.*, VII and its resolution; (b) the coupling of the substance to the symmetrical diketone VIII which should be identical with the known ozonolysis product from natural onocerin; (c) the transformation of the two carbonyl groups of the dione into the two exocyclic methylene groups of the final product.

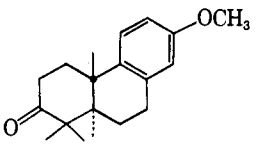
We will now turn our attention to the first goal, the construction of the (−)-hydroxyketoacid VII. The sequence of vicinal substituents present in VII ap-



I II III IV V



VII VIII



IX

(1) For a preliminary communication see *J. Am. Chem. Soc.*, **81**, 5516 (1959).

(2) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

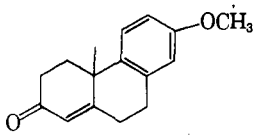
(3) *Cf.* G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(4) H. Fazakerley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1877 (1959).

(5) K. Schaffner, L. Cagliotti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **41**, 152 (1958).

(6) *Cf.* B. C. L. Weedon in "Advances in Organic Chemistry. Methods and Results," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1960, Chapter I. A related scheme has been used independently by E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 3925 (1957).

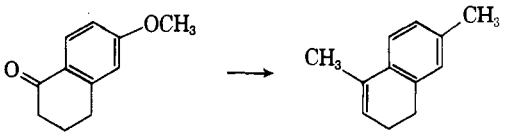
peared to us most easily constructed by the eventual transformation of an aromatic ring which would allow previous manipulation in the rest of the molecule. One candidate for such a precursor of VII is the tricyclic ketone IX. The choice of that particular substance was especially compelling because we had, several years previously, worked out a synthesis of its obvious precursor, the tricyclic enone X; and because we had shown in connection with the total synthesis of dehydroabietic acid[7] that substances of this type provide an easy entry to the 4,4-dialkyl-*trans*-decalin system



X

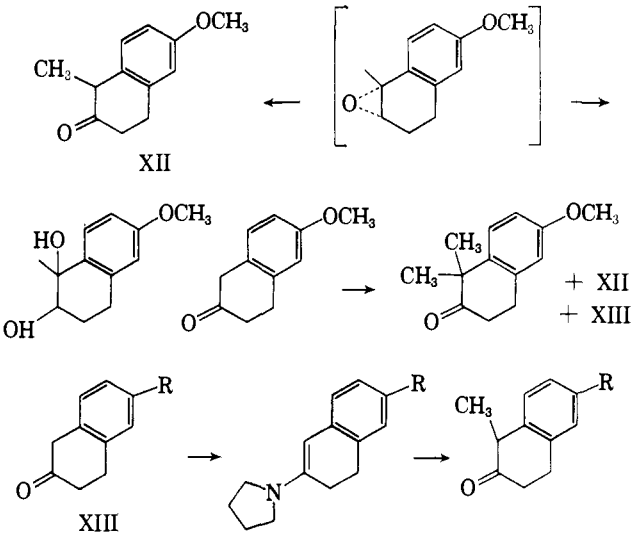
which is one of the features of the required ketoacid VII.

The starting point for the synthesis of IX was taken as 6-methoxy-α-tetralone[8] which could be transformed readily by addition of methylmagnesium bromide or iodide into 3,4-dihydro-1-methyl-6-methoxynaphthalene (XI). The tertiary alcohol which might have



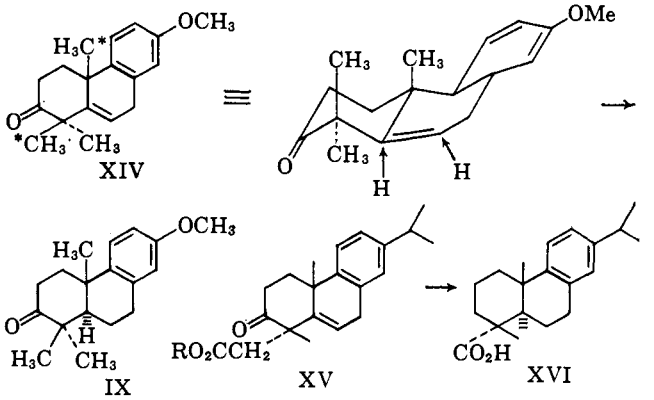
XI

been expected from the Grignard reaction was not isolated, undoubtedly because of its extremely easy dehydration owing to its tertiary and *p*-methoxybenzylic nature. Oxidation of the dihydronaphthalene was best effected with perphthalic acid in ether. The epoxide which might be anticipated as a product was not isolated because of its expected great lability. In fact, efforts to obtain it by direct chromatography of the ethereal oxidation mixture on alumina, after filtration of the precipitated phthalic acid, led only to the isolation of the crystalline 1,2-glycol from the opening of the epoxide. In practice, it was found that simple shaking of the ethereal oxidation mixture with hydrochloric acid sufficed to rearrange the presumed epoxide intermediate into the desired 6-methoxy-1-methyl-2-tetralone (XII). This particular sequence to the β-tetralone derivative XII was selected after it was found that the more direct route involving methylation of the well-known 6-methoxy-2-tetralone was complicated by the difficulty of preventing rapid formation of the 1,1-dimethyl derivative (together with recovered unalkylated ketone) even when only one equivalent of methyl iodide was employed. This difficulty with the monoalkylation of β-tetralone derivatives was eventually solved by our introduction of the enamine alkylation procedure[9] which allowed, for instance, the monomethylation of the related β-tetralone (XIII, R = isopropyl)[7] used in the total synthesis of dehydroabietic acid. Although this route could be used here,[10] we preferred the sequence from the readily available 6-methoxy-α-tetralone. Base-catalyzed condensation of the β-tetralone XII with methyl vinyl ketone in the presence of



XII XIII

aqueous methanolic potassium hydroxide gave the tricyclic ketone X, m.p. 108°,[11,12] which was to be the starting material for the synthesis of the hydroxydecaloneacetic acid VII. Dimethylation of the α,β-unsaturated ketone X with excess methyl iodide and potassium *t*-butoxide[13] led to the anticipated *gem*-dimethyl derivative XIV. Catalytic hydrogenation of the isolated double bond of XIV was then used to establish the necessary *trans*-decalin system: This stereochemical result was confidently anticipated since we had previously shown[7] that the hydrogenation of the tricyclic enone XV gave a homogeneous product which was ultimately transformed into dehydroabietic acid (XVI). As was then pointed out, this course of the hydrogenation results from the rigidity of the tricyclic ring system in which approach of the catalyst is hindered by the two starred methyl groups in XIV which are both axial. In fact, catalytic reduction over palladium proceeded readily to give a good yield of the ketone IX, m.p. 56–58°.



XIV XV XVI IX

We were now ready to transform the anisole ring of IX into the necessary ketoacid system of VII. Reduction of the tricyclic anisole derivative IX by the Birch procedure, using lithium in liquid ammonia and ethanol, followed by treatment with methanolic hydrochloric acid, converted it into the desired α,β-unsaturated ketone XVII (R = H). The stereochemistry assigned to the hydroxyl group of XVII is that expected from the lithium–ammonia–alcohol reduction of the

(7) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); **84**, 284 (1962).

(8) G. Stork, *ibid.*, **69**, 576 (1947).

(9) *Cf.* G. Stork, R. Terrell, and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

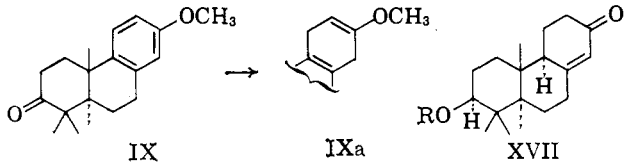
(10) The enamine procedure was in fact used in the synthesis of XII by R. B. Turner, E. G. Herzog, R. B. Morin, and A. Riebel, *Tetrahedron Letters*, No. **2**, 7 (1959). These authors also prepared the ketone XIV and a number of substances closely related to XVII in their very elegant syntheses of degradation products of cassaic acid.

(11) This was first prepared by this method by J. T. Rundquist (*cf.* Ph.D. Thesis, Harvard Univ., 1951).

(12) See also F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1248 (1958).

(13) *Cf.* R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *ibid.*, 1131 (1957).

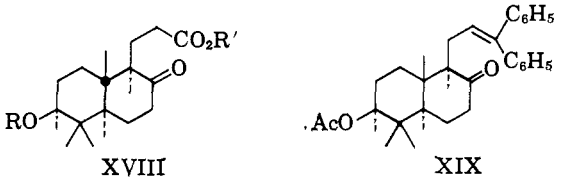
keto group, a process well known to lead to the more stable, equatorial alcohol[14]: in this case the 3β-epimer.



IX IXa XVII

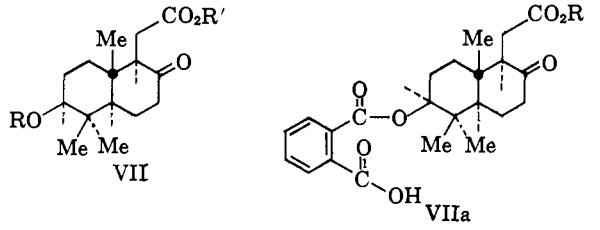
The crystalline hydroxyenone, m.p. 151–152°, thus obtained has an additional asymmetric center at C-9 to which the α-hydrogen configuration may be assigned since the enone is formed under conditions which would equilibrate that center to the more stable arrangement. This point is of practical importance since it is of course desirable that single substances rather than epimeric mixtures be involved in the synthetic sequence, but as will be apparent in the sequel the final stereochemical arrangement at C-9 will be established in the last step in the synthesis of onocerin.

Ozonolysis of the acetate of the hydroxyenone, followed by oxidative decomposition and esterification with diazomethane, formed the acetoxyketopropionic ester XVIII (R = Ac, R′ = CH_3), m.p. 84–86°, which is the homolog of the necessary ketoacid VII. Removal of the extra methylene group was achieved by the usual Barbier–Wieland degradation, suitably modified in certain respects to maintain the integrity of the various functional groups. The keto group of XVIII was protected as the ethylene ketal and the resulting substance was then transformed into the ketodiphenylethylene XIX, by reaction with phenylmagnesium bromide followed by heating with aqueous acetic acid and reacetylation with acetic anhydride in pyridine. The ketodiphenylethylene XIX, m.p. 128–130°, had λ_{max}^{EtOH} 249 and 255



XVIII XIX

mμ (log ε 4.33, 4.36) and the infrared absorption showed $\lambda_{max}^{CHCl_3}$ 1718 (acetate), 1712 (ketone), 1626 (ethylene), 1957, and 1494 cm.$^{-1}$ (phenyls). Oxidation of the diphenylethylene to the ketoacid could be done by ozonolysis but was best carried out, in excellent yield, by treating with ruthenium tetroxide and sodium periodate in aqueous acetone solution.[15] The resulting *dl*-acetoxyketoacid VII, R = Ac, R′ = H, m.p. 238–240°, was hydrolyzed with aqueous potassium hydroxide to *dl*-5,5-dimethyl-6-hydroxy-2-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneacetic acid (VII, R, R′ = H), m.p. 186–187°.[16]



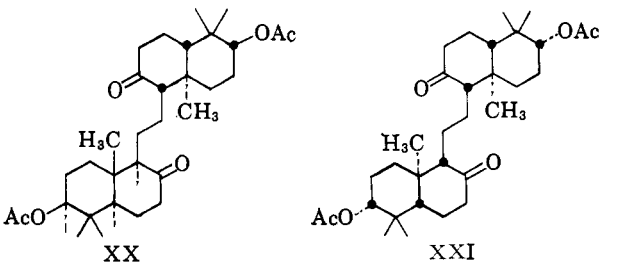
VII VIIa

The completion of the first part of the synthesis now required the resolution of our *dl*-acid. Transformation of *dl*-VII into the *dl*-half phthalate methyl ester VIIa (R = CH_3), m.p. 209–210°, by reaction with diazomethane and then with phthalic anhydride in pyridine was followed by treatment with strychnine. Concentration of the acetone solution of the salts led to the precipitation of the (+)-half phthalate strychnine salt, m.p. 225–227°, $[\alpha]^{24}D$ +5.1° in chloroform, from which the (+)-half phthalate, m.p. 185–187°, $[\alpha]^{24}D$ +23.5°, was regenerated on addition of aqueous hydrochloric acid and recrystallization from methylene chloride–benzene. Hydrolysis of the half phthalate with potassium hydroxide in aqueous methanol and removal of the phthalic acid gave the (+)-hydroxy acid (VII, R = R′ = H), m.p. 174–176°, $[\alpha]^{24}D$ +53.4° in chloroform.

The (−)-half phthalate was obtained by acidification of the acetone-soluble strychnine salt remaining after the precipitation of the (+)-enantiomer. Removal of some (+)-half phthalate by crystallization from methylene chloride–benzene then gave the pure (−)-half phthalate, m.p. 188–190°, $[\alpha]^{24}D$ −23.5°, which was hydrolyzed to the pure (−)-5,5-dimethyl-6-hydroxy-2-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneacetic acid (VII, R = R′ = H), m.p. 171–172°, $[\alpha]^{24}D$ −57.8° in chloroform.

At this stage the first goal, the synthesis of the (−)-hydroxyketoacid VII had been reached and we turned our attention to the second problem, the coupling of VII to the symmetrical dione VIII. We have mentioned at the beginning of this paper our successful coupling of the simple model 2-oxocyclohexaneacetic acid, and we now studied the coupling by Kolbe electrolysis of the *dl*-acetoxyketoacid VII (R = Ac, R′ = H), as well as the separate coupling of the (+)- and (−)-enantiomers of the hydroxyketoacid VII (R = R′ = H).

Electrolysis of the *dl*-acetoxyketoacid in a methanol solution containing a trace of sodium methoxide was carried out over platinum electrodes at 0.1 amp. and 50 v., at a temperature of 50°. Interruption of the electrolysis when the solution showed a definite alkaline reaction and work-up of the neutral product gave a crude crystalline mixture of diacetoxydione which was chromatographed on alumina. Elution with benzene gave in the initial fractions the *meso*-diacetoxydiketone XX which melted at 278–280° after recrystallization from methylene chloride–methanol–acetone. Later benzene fractions yielded the *dl*-isomer of XX (*cf.* VIII), m.p. 232–234° after crystallization from the same solvents. The two substances, which analysis showed to be isomeric, gave a strong depression on mixture melting point determination. The structures were assigned with confidence when it was shown by X-ray crystallographic examination[17] that the isomer of m.p. 278–280° had a center of symmetry while this was lacking in the isomer with m.p. 232–234°.



XX XXI

It is worth emphasizing at this point that the *meso*- and *dl*-isomers described above have essentially identical infrared absorption spectra in chloroform. Since

(14) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(15) *Cf.* R. Pappo and A. Becker, *Bull. Res. Council Israel*, **5A**, 300 (1956).

(16) Further syntheses of this important intermediate have been described recently; *cf.* (a) R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, **No. 1**, 34 (1961); (b) N. Danieli, Y. Mazur, and F. Sondheimer, *ibid.*, **No. 9**, 310 (1961).

(17) We thank Dr. G. M. J. Schmidt of the Weizmann Institute for carrying out this study.

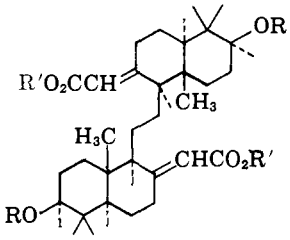
the two halves would necessarily have identical spectra if separated by solvent molecules (being related as *d*- and *l*-fragments), clear differences would result only if sufficient interaction between the connected halves markedly changed the energy of the infrared vibrations. It is not too surprising that this is not the case.

Electrolytic coupling was now performed with the optically active hydroxyketoacids in exactly the same manner as just described above. Starting with the (+)-hydroxyketoacid, the neutral product from the electrolysis, after acetylation with acetic anhydride–pyridine, chromatography on alumina, and crystallization from ether–hexane, gave in 40% yield the (+)-diacetoxydione XXI, m.p. 163–164°, $[\alpha]^{24}D$ +34.5° in chloroform; $\lambda_{max}^{CHCl_3}$ 1724 (acetate), 1706 cm.$^{-1}$ (ketone).

By the identical procedure, the (−)-hydroxyketoacid gave the (−)-diacetoxydione VIII, R = Ac, m.p. 165–166°, $[\alpha]^{24}D$ −33.9° in chloroform. In addition to the correct melting point, rotation, and analysis, the substance had an infrared spectrum which was identical with that of the (−)-diacetoxydione from the ozonolysis of natural α-onocerin diacetate. The mixture melting point of the two substances showed no depression.

With the successful completion of the synthesis of the (−)-diacetoxydione VIII we can now turn to the final stage in the synthesis of α-onocerin: the transformation of the two keto groups of VIII into two exocyclic methylenes.

The Wittig reaction was an obvious possibility but our efforts in that direction were unsuccessful and we turned to a different approach. Reaction of the (−)-diacetoxydione VIII with ethoxyacetylenemagnesium bromide in ether, followed by rearrangement of the crude carbinol with methanolic sulfuric acid,[18] gave the expected di-α,β-unsaturated ester XXII (R = Ac, R′ = Et), m.p. 154–155°, λ_{max}^{EtOH} 224 mμ (log ε 4.6); $\lambda_{max}^{CHCl_3}$ 1721 (acetate), 1706 (α,β-unsaturated ester), 1642 cm.$^{-1}$ (double bonds). Saponification with potassium hydroxide in aqueous methanol led to a

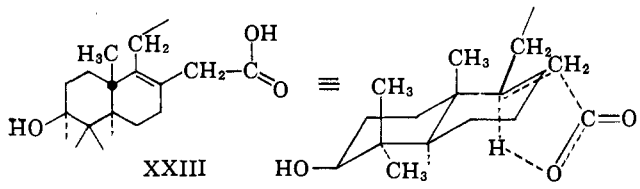


XXII

crude dihydroxydiacid which was now to be thermally decarboxylated to α-onocerin.

We will now comment upon the anticipated course of the decarboxylation reaction of the diacid XXII (R = R′ = H) to onocerin. The mechanism of this reaction requires the intermediacy of the β,γ-isomer of the unsaturated diacid and, of the two possible β,γ-positions for the double bond, we know that in this system (*cf.* α-onocerin → β-onocerin transformation[2] under the influence of mild treatment with formic acid) the preferred position should be that shown in the partial structure XXIIIa. In other words, the asymmetric center at C-9 has now been destroyed and while the C-9 stereochemistry of the various synthetic intermediates is that of natural α-onocerin, it is in the decarboxylation of the β,γ-unsaturated acid system of XXIII that the stereochemistry at C-9 is ultimately established. We anticipated the stereospecific introduction of the carboxyl proton at C-9 in the axial position because this allows maintaining continuous overlap of the developing sp_3-orbital on C-9 with the p-orbitals of the incipient methylene group in the decarboxylation reaction. The decarboxylated product should therefore have the requisite α-hydrogen at C-9 as in α-onocerin (I) itself. The clean formation of only one isomer identical with α-onocerin in this reaction showed the validity of these mechanistic considerations: Decarboxylation of the dihydroxydiacid by refluxing in quinoline containing copper chromite[19] gave α-onocerin, isolated as its diacetate after treatment with acetic anhydride–pyridine. The (+)-onocerin diacetate thus obtained melted at 220–221° and had $[\alpha]^{24}D$ +29.8° in chloroform. It was shown to be identical in all respects with an authentic specimen of diacetate of (+)-α-onocerin (I) by comparison of the infrared spectra and rotations, and the melting point of a mixture of the synthetic and natural materials was undepressed.

The total synthesis of (+)-α-onocerin is thus completed, and since α-onocerin had already been converted into the hydroxyhopanone series (*cf.* VI), this synthesis also constituted the first total synthesis of a naturally occurring pentacyclic triterpene system.



XXIII XXIIIa

Experimental

1-Methyl-6-methoxy-3,4-dihydronaphthalene (XI).[20]—To a solution of methylmagnesium iodide prepared from 580 g. of methyl iodide and 80 g. of magnesium in 3 l. of dry ether was added dropwise with stirring a solution of 510 g. of 6-methoxy-α-tetralone in 2 l. of dry benzene. Gentle heating was supplied to maintain the solution at the refluxing temperature during the addition, and after a further 2 hr. of refluxing the solution was cooled to 0° and decomposed with saturated ammonium chloride solution. The organic layer was separated and combined with the ether extract of the aqueous solution. Evaporation of the solvent after washing with cold 5% sodium bicarbonate solution and drying with magnesium sulfate left a residue which was distilled *in vacuo* under nitrogen to give 401 g. of XI, b.p. 93–94° (1 mm.), reported[12] b.p. 149–150° (17 mm.). The substance is very sensitive to light and to traces of acid. It should be used immediately for the next step.

1-Methyl-6-methoxy-3,4-dihydro-2(1H)-naphthalenone (XII).[11]—A solution of 400 g. of the above dihydronaphthalene XI in 1 l. of anhydrous ether was added with stirring to 6 l. of an ether solution of monoperphthalic acid (0.07 g. per ml.) while the temperature was kept at −5 to 0°. The reaction mixture was then kept in a refrigerator overnight and finally at room temperature for 10 hr. The precipitated phthalic acid was filtered off and the ether solution was shaken with 1.5 l. of 10% hydrochloric acid. The pink ether layer was then allowed to stand at room temperature overnight. The ether solution was then again shaken with 1.5 l. of 10% hydrochloric acid, allowed to stand for 2 hr., and finally it was once more washed with 1 l. of 10% hydrochloric acid, then water, and 5% sodium bicarbonate solution. Removal of solvent after drying over magnesium sulfate gave a residue which was distilled under nitrogen to give 241 g. of the ketone XII as a yellowish oil, b.p. 100–110° (0.2 mm.), reported[12]: b.p. 120–128° (0.05 mm.).

4,4a,9,10-Tetrahydro-7-methoxy-4a-methyl-2(3H)-phenanthrone (X).[11,21]—To a solution of 58 g. of potassium hydroxide in 1 l. of methanol and 100 ml. of water kept under nitrogen at 0° was added with stirring a solution of 143 g. of the tetralone XII. The mixture was cooled to −20° in an ice–salt bath and 61 ml. of freshly distilled methyl vinyl ketone was slowly added to the solution. At the completion of the addition the cooling bath was removed and stirring was continued overnight. The mixture was then refluxed for 4 hr., cooled, poured onto ice, neutralized

(18) *Cf.* J. F. Arens, in "Advances in Organic Chemistry. Methods and Results," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 159.

(19) *Cf.* M. L. Sherrill and E. S. Mellack, *J. Am. Chem. Soc.*, **59**, 2134 (1937).

(20) *Cf.* E. M. Chamberlin, Ph.D. Thesis, Harvard Univ., 1946.

(21) Improvements in the original method of preparation (*cf.* II) were made by Dr. N. K. Sareen.

with hydrochloric acid, and extracted with ether. Removal of the ether after washing with water and drying over magnesium sulfate left an oil which was dissolved in a small amount of ethanol. The mixture was placed in a refrigerator and deposited 85.8 g. of yellowish crystals of X, m.p. 107–109°. A further 16.3 g., m.p. 102–106°, was obtained on cooling the mother liquors. Recrystallization from ligroin (charcoal) gave white needles, m.p. 108.3–108.5°, reported[12] m.p. 106–108°.

The 2,4-dinitrophenylhydrazone crystallized in red needles from ethyl acetate–ethanol and had m.p. 174–174.5°.

Anal. Calcd. for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25. Found: C, 62.66; H, 5.20.

3,4,4a,9-Tetrahydro-7-methoxy-1,1,4a-trimethyl-2(1H)-phenanthrone (XIV).—To a solution of 24.2 g. of the above ketone in 600 ml. of anhydrous *t*-butyl alcohol containing 67.3 g. of potassium *t*-butoxide was added 180 g. of methyl iodide, dropwise and with stirring, during 20 min. After standing overnight at room temperature the mixture was poured into 4 l. of water. The solution was neutralized with dilute hydrochloric acid and was extracted with ether. The ether extracts were washed with water, dilute sodium hydroxide, and again with water. Drying over sodium sulfate and removal of the solvents left 27 g. of a dark oil which was chromatographed over *ca.* 1 kg. of acid-washed alumina, eluting with hexane–benzene mixtures (from 4:1 to 3:7) or with benzene alone. The crude dimethylated ketone thus obtained was recrystallized from hexane to give 12 g. of crystalline XIV, m.p. 80–81°. A second crop weighing 3.9 g. was obtained, m.p. 76–79°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.97; H, 8.20. Found: C, 79.83; H, 8.36.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate and had m.p. 195–195.5°.

Anal. Calcd. for $C_{24}H_{26}O_5N_4$: C, 63.97; H, 5.82. Found: C, 64.18; H, 5.64.

3,4,4a,9,10a-Hexahydro-7-methoxy-1,1,4a-trimethyl-2(1H)-phenanthrone (IX).—A solution of 20 g. of the above ketone XIV in 250 ml. of acetic acid was hydrogenated in the presence of 2 g. of 10% palladium-on-charcoal in a Parr shaker under an initial pressure of 50 p.s.i. of hydrogen. The hydrogenation was quite slow and was sometimes completed only after 2–3 days. Removal of catalyst and solvent left an oil which was purified by chromatography on 800 g. of acid-washed alumina. Elution starting with 3:1 hexane–benzene and ending with 9:1 benzene–ether and crystallization from hexane gave 16.5 g. of colorless prisms of IX, m.p. 56–58°. A second crop, m.p. 52–55°, weighing 1.2 g. was obtained.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.38; H, 8.88. Found: C, 79.57; H, 8.89.

1,2,3,4,4a,5,8,9,10,10a-Decahydro-7-methoxy-1,1,4a-trimethyl-2-phenanthrol (IXa).—To a mixture of 15 g. of the above ketone IX, 750 ml. of anhydrous ether, and 2.5 l. of anhydrous liquid ammonia was added 40 g. of lithium in small pieces. The mixture was stirred for half an hour and 400 ml. of absolute ethanol was added slowly to the stirred mixture. Stirring was continued until disappearance of the blue color; after the mixture had stood overnight at room temperature to allow the ammonia to evaporate, water was added and the reduced product was extracted with ether. The extracts were washed with water until neutral, and, after drying over sodium sulfate, the ether was removed leaving an oily residue which crystallized from a mixture of ether and pentane on standing overnight in the refrigerator, giving 7.2 g. of the solid enol ether IXa, m.p. 131–133°, which was pure enough for the hydrolysis described below. The substance could be recrystallized from hexane–ether to give the pure enol ether, m.p. 138–139°. The same substance has been described by Turner, *et al.*,[10] who prepared it by a slightly different route and reported its m.p. at 139–139.5°.

4,4a,4b,5,6,7,8,8a,9,10-Decahydro-7-hydroxy-4b,8,8-trimethyl-2(3H)-phenanthrone (XVII).—The enol ether (5 g., m.p. 131–133°) obtained from the Birch reduction above was hydrolyzed by heating on the steam bath for 1.5 min. in a mixture of 450 ml. of methanol, 250 ml. of water, and 150 ml. of concentrated hydrochloric acid. The mixture was poured into cold water and extracted with ether. Washing with 5% potassium carbonate solution then with water, drying over magnesium sulfate, and removal of the solvent gave an oil which was crystallized from ether–pentane to give 3.7 g. of XVII (R = H), m.p. 151–152°. The infrared spectrum showed the expected α,β-unsaturated ketone and hydroxyl absorption bands.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.60; H, 9.91.

The acetate XVII (R = Ac) was prepared by treating a solution of 16 g. of the unsaturated ketoalcohol in 200 ml. of pyridine with 200 ml. of acetic anhydride and keeping at room temperature overnight. The mixture was poured into 4 l. of water and extracted with ether. The extracts were washed with dilute hydrochloric acid, with dilute aqueous potassium carbonate, and finally with water. Drying (magnesium sulfate) and removal of the ether left 19 g. of crude solid which was recrystallized from pentane to give 15.3 g. of the acetate, m.p. 117–118.5°. An additional 1.1 g., m.p. 114–115.5°, was obtained from the mother liquors.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.79; H, 9.35.

Acetate of 1,2,3,4,4a,5,6,7,8,8a-Decahydro-6-hydroxy-2-oxo-5,5,8a-trimethyl-1-naphthalenepropionic Acid (XVIII, R = Ac, R′ = H).—A solution of 500 mg. of the above unsaturated ketoacetate XVII (R = Ac) in 20 ml. of ethyl acetate was cooled to −70° in Dry Ice–acetone, and ozone was passed through the solution until the color turned blue-violet, and then for an additional 5 min.[22] The solvent was then removed at 20° under vacuum. A solution of 5 ml. of acetic acid and 0.5 ml. of 30% hydrogen peroxide was added to the residue and the mixture was kept at room temperature overnight. The acetic acid was then removed under vacuum below 40°, dilute potassium bicarbonate was added, and the mixture was extracted with ether to remove nonacidic material. Acidification with dilute hydrochloric acid and ether extraction, followed by washing with saturated sodium chloride solution and drying over magnesium sulfate, gave the acid as an oil which was crystallized from ether–hexane. Further acid was obtained from the neutral material removed above, by treatment with 200 mg. of periodic acid in 5 ml. of acetic acid overnight at room temperature, followed by work-up as above. The total yield of acid, m.p. 161–165°, was 320 mg. Recrystallization from ether–hexane gave the pure substance, m.p. 170–171°.

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 66.64; H, 8.70. Found: C, 66.55; H, 9.09.

The methyl ester XVIII (R = Ac, R′ = CH_3) was prepared with ethereal diazomethane. Recrystallization from hexane gave the pure substance, m.p. 84–86°.

Anal. Calcd. for $C_{19}H_{30}O_6$: C, 67.43; H, 8.94. Found: C, 67.36; H, 8.88.

Ethylene Ketal of XVIII (R = Ac, R′ = CH_3).—A mixture of benzene (5 l.), ethylene glycol (120 ml.), acetoxyketoacid methyl ester XVIII (9.9 g., m.p. 84–86°), and *p*-toluenesulfonic acid monohydrate (15 g. added at the beginning and 15 g. after 6 hr.) was boiled for 2 days, while 3.5 l. of distillate was removed through a helix-packed column equipped with a total condensation partial take-off still head.[23] The cooled solution was treated with sodium hydroxide (60 g.) in methanol (400 ml.), extracted with ether, and washed with water. The neutral extract was worked up in the usual way and yielded a yellow glassy product (10.3 g.) which could not be obtained in crystalline form; infrared absorption in $CHCl_3$: 1724 and 1712 cm.$^{-1}$ for ester carbonyls, 1160 and 1070 cm.$^{-1}$ for ketal.

Reaction of Ketal of XVIII (R = Ac, R′ = CH_3) with Phenylmagnesium Bromide.—The crude ethylene ketal above (10.3 g.) was dissolved in ether (450 ml.) and added with stirring at 0° during 1 hr. to a solution of phenylmagnesium bromide, prepared from magnesium (13.5 g.) and bromobenzene (70 ml.) in ether (400 ml.). The mixture was stirred at room temperature overnight, and then the carbinol was liberated under stirring by dropwise addition of saturated ammonium chloride solution (87 ml.). The ether layer was decanted and the precipitated salts were washed with ether by decantation. The combined extracts were steam distilled and the remaining solid in water (100 ml.) was treated with ethanol (200 ml.) and sodium hydroxide (10% in 100 ml. of water). The mixture was heated under reflux for 2 hr. to saponify any unreacted ester. The alcohol was removed by distillation and the organic material extracted into ether, and washed with water. Concentration of the neutral ether extracts gave the crude diphenylcarbinol as an amorphous residue (9.86 g.). When a part of it (650 mg.) was chromatographed on alumina (acid-washed, 20 g.), ether eluted a crystalline substance (250 mg., m.p. 108–110°), which after two crystallizations from acetone–hexane melted at 122–123°. Further recrystallization did not change the m.p. of the compound, but according to its infrared spectrum (band at 1712 cm.$^{-1}$ for ketone carbonyl) the ketal group was partly hydrolyzed.

Diphenylethyleneacetoxyketone XIX.—The above crude carbinol (9.2 g.) was dissolved in glacial acetic acid (750 ml.) and water (150 ml.) and the solution was refluxed for 6 hr. All the solvent was removed by distillation and the residue was treated with acetic anhydride (80 ml.) and pyridine (80 ml.) at room temperature overnight. Water was added, the mixture was extracted with ether and the ether was washed with 2 *N* sulfuric acid and then with 2 *N* sodium carbonate. The neutral residue (9.1 g.) was dissolved in benzene and filtered through alumina (100 g.). The first 750 ml. of benzene eluted 8.6 g. of crystalline material, which after recrystallization from ether–pentane gave 5.25 g. of acetoxyketone XIX, m.p. 124–126°. For analysis a

(22) *Cf.* R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

(23) *Cf.* H. Hirschmann and J. W. Corcoran, *ibid.*, **78**, 2325 (1956).

sample was recrystallized twice from ether–pentane and dried for 14 hr. at 0.07 mm. (60°), m.p. 128–130°; infrared absorption in $CHCl_3$: 1718 cm.$^{-1}$ for ester carbonyl, 1712 cm.$^{-1}$ for ketone carbonyl, 1626 cm.$^{-1}$ for ethylene, 1597 and 1494 cm.$^{-1}$ for phenyl; ultraviolet absorption: λ_{max}^{EtOH} 249, 255 mμ; log ε 4.33, 4.36.

Anal. Calcd. for $C_{30}H_{36}O_3$: C, 81.04; H, 8.16. Found: C, 81.28; H, 8.14.

Acetoxyketoacid VII, R = Ac, R′ = H. (a) By Ozonization of XIX.—The acetoxyketone XIX (100 mg.) was dissolved in ethyl acetate (20 ml.) and ozone was passed through the solution at 0° for 1 hr. until a sample (after being boiled with water for 15 min. and extracted with ether) did not show any increase in its benzophenone content (measured with the help of its carbonyl band at 1658 cm.$^{-1}$ in the infrared). Acetic acid (5 ml.) and hydrogen peroxide (30%, 0.5 ml.) were added and the solution was left at room temperature overnight. The reaction mixture was taken up in ether and the acidic components were extracted with 2 *N* sodium carbonate solution. The ether solution yielded the neutral fraction (60 mg.), whereas acidification of the sodium carbonate extract with sulfuric acid and extraction with ether gave the crude crystalline acetoxyketoacid VII, R = Ac, R′ = H (43 mg.). Crystallization from acetone–benzene yielded 38 mg. of colorless rhombs, m.p. 234–236°.

(b) By Oxidation with Ruthenium Tetroxide and Sodium Periodate.—The acetoxyketone XIX (2.22 g.) dissolved in acetone (100 ml.) was treated at room temperature under stirring with a yellow solution of freshly prepared ruthenium tetroxide (500 mg.) and sodium periodate (2 g.) in water (40 ml.).[16] When black ruthenium dioxide precipitated, another portion of sodium periodate (3 g.) was added to dissolve the precipitate. This was repeated twice during the following 10 hr. Then propyl alcohol (15 ml.) was added, the black precipitate was filtered off and washed thoroughly with acetone. The solvent was stripped off *in vacuo;* the residue was taken up in ethyl acetate and was extracted with a 2 *N* sodium carbonate solution. Distillation of the ethyl acetate yielded an oily residue (628 mg.) of neutral products, whereas acidification of the sodium carbonate extracts and extraction with ethyl acetate gave the crude crystalline acetoxyketoacid VII, R = Ac, R′ = H (1.45 g.), which after recrystallization from acetone–benzene formed colorless rhombs, m.p. 234–236°. For analysis a sample was recrystallized twice from acetone–benzene, and dried for 14 hr. at 0.08 mm. (60°); m.p. 238–240°.

Anal. Calcd. for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.50; H, 8.19.

The methyl ester VII, R = Ac, R′ = CH_3, was prepared by treating a solution of the acid VII, R = Ac, R′ = H, in methanol and ether with ethereal diazomethane at 5° overnight. Recrystallization from pentane yielded white needles, m.p. 132–134°. A sample for analysis was dried for 14 hr. at 0.07 mm. (60°).

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.61; H, 8.78.

Diacetoxydione XX (*dl-* **and** *meso*-**Forms**).—A solution of the *dl*-acetoxyketoacid ((±)VII, R = Ac, R′ = H, 100 mg.) in methanol (2.5 ml.), containing 0.05% sodium methoxide was electrolyzed (current 0.1 amp., voltage 50 v.) in a 5-ml. electrolysis cell containing two smooth 5.5 × 5.5 mm. platinum electrodes at a distance of 2 mm., to which was fitted a reflux condenser and which was placed in a water bath at 50°. After 21 min. the solution showed an alkaline reaction and the current was cut off. The methanol was distilled off *in vacuo;* the residue was taken up in a mixture of methylene chloride–ether and washed with 5% sodium carbonate solution. The crystalline product (83 mg.) was chromatographed on alumina (15 g.). Benzene eluted first 31 mg. of crystals A, which after recrystallization from methylene chloride–methanol and acetone yielded 18 mg., m.p. 278–280°. Later benzene fractions yielded 21 mg. of crystals B, which after recrystallization from the same solvents gave 13 mg. of m.p. 232–234°. Samples A and B were dried for analysis for 14 hr. at 0.08 mm. (60°). Their infrared absorption spectra were identical, but on admixture the m.p. showed a depression to 224–227°.

Anal. Calcd. for $C_{32}H_{50}O_6$: C, 72.41; H, 9.50. Found for A: C, 72.21; H, 9.30. Found for B: C, 72.31; H, 9.42.

It follows from the crystallographic constants of A, that the molecule has a center of symmetry.[17] Therefore, A can be identified as the *meso*-form of the diacetoxydione XX; B has no center of symmetry and must be the racemic form.

***dl*-Hydroxyketoacid VII, R = R′ = H.**—The *dl*-acetoxyketoacid VII, R = Ac, R′ = H (1.077 g.), in methanol (200 ml.) was fluxed for 2 hr. with potassium hydroxide (20 g.), previously dissolved in water (10 ml.). Water was then added, the methanol was stripped off, and the remaining solution was acidified with sulfuric acid and extracted with ether. The residue obtained by the usual work-up of the dried extracts was purified by crystallization from acetone–hexane to give 963 mg. of the *dl*-hydroxyketoacid VII, R = R′ = H. For analysis a sample was recrystallized twice from acetone–hexane and dried for 4 hr. at 0.08 mm. (60°), m.p. 186–187°.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.09; H, 8.97.

***dl*-Methyl Ester–Hydrogen Phthalate VIIa, R = CH_3.**—The *dl*-hydroxyketomethyl ester VII, R = H, R′ = CH_3, was prepared by treating a solution of the acid VII, R = R′ = H (894 mg.), in methanol and ether with ethereal diazomethane at 5° overnight. It crystallized from acetone–hexane to give 867 mg. of the crystalline *dl*-hydroxyketoester which was dissolved in pyridine (15 ml.) and treated overnight at room temperature with phthalic anhydride (1400 mg.). The pyridine was distilled off *in vacuo*, the residue was taken up in chloroform, and the solution was shaken with 10% sulfuric acid and then with sodium carbonate solution. The latter was then acidified and extracted with ethyl acetate, the extract was dried, and the solvent was evaporated to yield 1235 mg. of a mixture of the *dl*-hydrogen phthalate and phthalic acid. Treatment of this residue with chloroform permitted separation from the insoluble phthalic acid, whereas recrystallization of the soluble product from methylene chloride–benzene yielded 950 mg. of the *dl*-hydrogen phthalate VIIa, R = CH_3, m.p. 209–210°. For analysis a sample was recrystallized from methylene chloride–benzene, and dried for 14 hr. at 0.07 mm. (60°); m.p. 209–210°.

Anal. Calcd. for $C_{24}H_{36}O_7$: C, 66.96; H, 7.02. Found: C, 66.80; H, 7.15.

Strychnine Salts of the (+)- and the (−)-Hydrogen Phthalates (+)VIIa and (−)VIIa.—Strychnine (719 mg.) dissolved in methylene chloride (5 ml.) was added to a solution of the *dl*-hydrogen phthalate VIIa, R = CH_3 (927 mg.), in methylene chloride (5 ml.). The solvent was then distilled off and replaced gradually by acetone. The solution was concentrated to 8 ml. and left overnight for crystallization. The pure strychnine salt of the (+)-hydrogen phthalate, (+)-VIIa, R = CH_3 (761 mg.), separated as white clusters, m.p. 225–226°. For analysis a sample was recrystallized from methylene chloride–acetone and dried for 14 hr. at 0.06 mm. (60°); m.p. 225–227°, $[\alpha]^{24}D$ +5.1° (*c* 1.06 in $CHCl_3$).

Anal. Calcd. for $C_{45}H_{52}O_5N_2$: C, 70.66; H, 6.85. Found: C, 70.21; H, 6.91.

The acetone-soluble strychnine salt of the (−)-hydrogen phthalate (−)-VIIa, R = CH_3 (810 mg.), $[\alpha]^{24}D$ of the crude salt −22.1° (*c* 1.44 in $CHCl_3$), could not be purified by recrystallization.

(+)-Hydrogen Phthalate (+) VIIa, R = CH_3.—For regeneration of the (+)-hydrogen phthalate, 745 mg. of the acetone-insoluble strychnine salt was dissolved in ethyl acetate (300 ml.) and washed with 10% hydrochloric acid (four portions of 50 ml. each). The solution was dried and the residue (414 mg.) was recrystallized from methylene chloride–benzene to give 400 mg. of the (+)-hydrogen phthalate (+)-VIIa, R = CH_3. For analysis a sample was recrystallized from methylene chloride–benzene, and dried for 14 hr. at 0.05 mm. (60°), m.p. 185–187°, $[\alpha]^{24}D$ + 23.5° (*c* 0.98 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.05. Found: C, 66.99; H, 7.01.

(+)-Hydroxyketoacid (+)-VII, R = R′ = H.—The (+)-hydrogen phthalate (+)-VIIa, R = CH_3 (384 mg.), in methanol (50 ml.) was refluxed for 2 hr. with potassium hydroxide (5 g.), previously dissolved in water (3 ml.). Water was then added, the methanol was stripped off *in vacuo*, and the remaining solution was acidified with sulfuric acid and extracted with ethyl acetate. Evaporation of the ethyl acetate yielded a crystalline residue (361 mg.) consisting of a mixture of phthalic acid and the (+)-hydroxyketoacid. Two recrystallizations from acetone–chloroform separated most of the phthalic acid. The dried mother liquors were recrystallized twice from acetone-benzene and gave the pure (+)-hydroxyketoacid VII, R = R′ = H (120 mg.), as colorless crystals, m.p. 174–175°. For analysis a sample was recrystallized from acetone–benzene and dried for 14 hr. at 0.07 mm. (60°); m.p. 174–176°, $[\alpha]^{24}D$ +59.4° (*c* 1.13 in $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.05; H, 8.95.

(+)-Diacetoxydione XXI from the (+)-Acid VII, R = R′ = H.—A solution of the (+)-acid VII, R = R′ = H (50 mg.), in methanol (2.5 ml.), containing 0.05% sodium methoxide, was electrolyzed (current 0.1 amp., voltage 80 v.) in a 5-ml. electrolysis cell containing two smooth 5.5 × 5.5 mm. platinum electrodes at a distance of 2 mm., to which was fitted a reflux condenser and which was placed in a water bath at 50°. After 6 min. the solution showed an alkaline reaction and the current was cut off. The methanol was distilled off *in vacuo* and the residue was taken up in a mixture of methylene chloride–ether and washed with 5% sodium carbonate solution. The residue (45 mg.) after evaporation of the solvent was dissolved in pyridine (0.5 ml.) and acetic anhydride (0.5 ml.) and kept at room temperature overnight.

Water was added, the solution was extracted with ether, and the extract was washed with 2 *N* sulfuric acid and 2 *N* sodium carbonate. The product was chromatographed on alumina (1.5 g.). The major portion crystallized from ether–hexane (20 mg.) to give the (+)-diacetoxydione XXI, m.p. 162–163°; infrared absorption in $CHCl_3$: 1724 cm.$^{-1}$ for ester carbonyl, 1706 cm.$^{-1}$ for ketone carbonyl. For analysis a sample was recrystallized from ether–hexane and dried for 14 hr. at 0.06 mm. (60°), m.p. 163–164°, $[\alpha]^{24}D$ +34.5° (*c* 1.01 in $CHCl_3$).

Anal. Calcd. for $C_{32}H_{50}O_6$: C, 72.41; H, 9.50. Found: C, 72.25; H, 9.45.

(−)-Hydrogen Phthalate (−)-VIIa, R = CH_3.—The crude acetone-soluble strychnine salt (788 mg.) was dissolved in ethyl acetate (300 ml.) and, in order to regenerate the (−)-hydrogen phthalate, was washed with 10% hydrochloric acid (four portions of 50 ml. each). The crude product (377 mg.), $[\alpha]^{24}D$ −14.5° (*c* 1.08 in $CHCl_3$), contained besides the (−)-hydrogen phthalate some of the (+)-hydrogen phthalate. Recrystallization from methylene chloride–benzene separated the (+)-form as the racemate (120 mg.), m.p. 209–210°, and the mother liquors, when recrystallized from acetone–hexane yielded the pure (−)-hydrogen phthalate as needles (210 mg.), m.p. 187–189°. A sample was recrystallized for analysis twice from acetone–hexane, and dried for 14 hr. at 0.08 mm. (60°); m.p. 188–190°, $[\alpha]^{24}D$ −23.5° (*c* 1.10 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.89; H, 6.93.

(−)-Hydroxyketoacid (−)-VII, R = R′ = H.—A solution of the (−)-hydrogen phthalate (200 mg.) in methanol (50 ml.) was refluxed for 2 hr. with a solution of potassium hydroxide (5 g.), in water (3 ml.). Water was then added, the methanol was stripped off *in vacuo*, and the remaining solution was acidified with sulfuric acid and extracted with ethyl acetate. The crystalline crude product (190 mg.) containing both phthalic acid and the (−)-hydroxyketoacid VII, R = R′ = H, was crystallized from acetone–chloroform to separate off the phthalic acid, m.p. 201–202°. Crystallization of the residue from the mother liquors from acetone–benzene yielded the pure (−)-hydroxyketoacid (51 mg.)., m.p. 171–172°. For analysis a sample was dried for 14 hr. at 0.06 mm. (60°); $[\alpha]^{24}D$ −57.8° (*c* 1.11 in $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.22; H, 9.15.

(−)-Diacetoxydione VIII from the Acid (−)-VII, R = R′ = H.—A solution of the (−)-acid (−)-VII, R = R′ = H (37 mg.), in methanol (2.5 ml.) containing 0.05% sodium methoxide, was electrolyzed like the (+)-acid VII, R = R′ = H. The methanol was distilled off *in vacuo* and the residue was taken up in a mixture of methylene chloride–ether and washed with 5% sodium carbonate solution. The residue (33 mg.) after evaporation of the solvent was treated with pyridine (0.5 ml.) and acetic anhydride (0.5 ml.) at room temperature overnight. The reaction mixture was worked up as usual. The crude product was chromatographed on alumina (1.0 g.), and the major fractions were crystallized from ether–hexane to give the pure (−)-diacetoxydiketone VIII, R = Ac (11 mg.)., m.p. 165–166°, $[\alpha]^{24}D$ −33.9° (*c* 1.10 in $CHCl_3$), identical in all respects (infrared absorption spectrum, mixture melting point) with the diacetoxydiketone obtained by degradation from natural α-onocerin diacetate. A sample was dried for analysis for 14 hr. at 0.06 mm. (60°).

Anal. Calcd. for $C_{32}H_{50}O_8$: C, 72.41; H, 9.50. Found: C, 72.31; H, 9.48.

Diacetoxy-di-α,β-unsaturated Diester XXII, R = Ac, R′ = Et.—A solution of ethyl bromide (freshly distilled, 290 mg.) in absolute ether (5 ml.) was added under stirring to magnesium (58 mg.) in ether (3 ml.) and the stirring was continued until all the magnesium had disappeared. A solution of ethoxyacetylene (200 mg., prepared according to *Org. Syntheses*, **34**, 46 (1954)) in ether (5 ml.) was now added, and the reaction mixture was boiled for 2.5 hr., during which a brown oil separated. A solution of the (−)-diacetoxydiketone XXII (100 mg.) in ether (10 ml.) was added dropwise, and the mixture was boiled for 2 hr. and stirred overnight until the brown precipitate had disappeared completely. The mixture was then cooled to 0°, poured into 20 ml. of an ice-cooled saturated solution of ammonium chloride, and extracted with ether. The crude product (110 mg.) showed in the infrared absorption bands at 2283 cm.$^{-1}$ for an acetylene bond and at 1724 cm.$^{-1}$ for the acetate functions. It was dissolved in methanol (30 ml.), treated with 10% sulfuric acid (3 ml.), and the mixture was then shaken for 2 hr. to effect rearrangement. Water (50 ml.) was then added, the mixture was extracted with ether, and the ether was washed with sodium bicarbonate solution. The product (110 mg.) was chromatographed on alumina (3 g.) and the benzene fractions (41 mg.) crystallized from methanol to yield the pure di-α,β-unsaturated ester XXII, R = Ac, R′ = Et (35 mg.), m.p. 154–155°. For analysis a sample was dried for 14 hr. at 0.07 mm. (60°); infrared absorption in $CHCl_3$: 1721 cm.$^{-1}$ for acetate carbonyls, 1706 cm.$^{-1}$ for α,β-unsaturated ester carbonyls, and 1642 cm.$^{-1}$ for ethylene bonds; ultraviolet absorption: λ_{max}^{EtOH} 224 mμ, log ε 4.60.

Anal. Calcd. for $C_{40}H_{62}O_8$: C, 71.61; H, 9.32. Found: C, 71.85; H, 9.23.

α-Onocerin Diacetate.—To a solution of the di-α,β-unsaturated ester XXII (25 mg.) in methanol (2 ml.) was added 8 ml. of a 10% solution of potassium hydroxide in 75% aqueous methanol and the mixture was refluxed for 2 hr. Water was added, the mixture was extracted with ether, and the aqueous solution was acidified with dilute sulfuric acid and extracted again with methylene chloride. The crude diacid (22 mg.), obtained from the methylene chloride extract, was dissolved in quinoline (2 ml., freshly distilled), copper–chromite catalyst (20 mg.) was added, and the mixture was refluxed for 1 hr. Ether was then added, and the ether solution was washed with dilute sulfuric acid and then with 10% sodium hydroxide. The residue (20 mg.) was dissolved in pyridine (0.5 ml.) and acetic anhydride (0.5 ml.) and left at room temperature overnight. Ice-water was added, the solution was extracted with ether, and the ether extract was washed with dilute sulfuric acid and then with 10% sodium carbonate. The residue (20 mg.) was chromatographed on alumina (1 g.). The main crystalline fraction (15 mg.) was sublimed under high vacuum (0.08 mm.) for analysis. The sample (12 mg.), m.p. 220–221°, $[\alpha]^{24}D$ + 29.8° (*c* 0.69 in $CHCl_3$), was identical in all respects (infrared absorption spectra, mixture melting point) with an authentic specimen of natural α-onocerin diacetate.[2]

Anal. Calcd. for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.70; H, 10.39.

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[CONTRIBUTION FROM THE MEDICAL RESEARCH LABORATORIES, CHAS. PFIZER & CO., INC., GROTON, CONN.]

Chemistry of Indolmycin[1]

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Indolmycin, an antibiotic elaborated by *Streptomyces albus*, was shown to be 2-methylamino-5-α-(β-indolyl)-ethyl-2-oxazolin-4-one (**1**). Its stereochemistry was deduced from acid hydrolysis products, some of which resulted from 1–2 migration of the indolyl moiety. The epimeric isoindolmycin (**12**) did not rearrange in this manner. Indolmycin was reconstituted from the α-hydroxy acid **2**, which in turn was prepared in its racemic form by stereospecific synthesis from indole and ethyl 2,3-epoxybutyrate.

The fermentation broth of *Streptomyces albus* strain BA-3972, isolated from an African soil, exhibits antimicrobial activity against strains of staphylococci resistant to commercially available antibiotics.[2] Rao first isolated and characterized the major active component which had been designated PA-155A.[3] Subsequently we have referred to this compound as indolmycin. This paper describes studies concerned with the structure elucidation as well as the synthesis of this antibiotic.

(1) Preliminary communication, M. Schach von Wittenau and H. Els, *J. Am. Chem. Soc.*, **83**, 4678 (1961).

(2) W. S. Marsh, A. L. Garretson, and E. M. Wesel, *Antibiot. Chemotherapy*, **10**, 316 (1960).

(3) K. V. Rao, *ibid.*, **10**, 312 (1960).