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

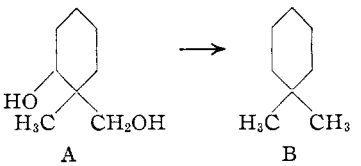
Terpenoids. XXXIV.[1] Iresin (Part 3).[2] Reactions of the Glycol System[3]

BY CARL DJERASSI, F. W. DONOVAN,[4a] S. BURSTEIN AND R. MAULI[4b]

RECEIVED NOVEMBER 30, 1957

The primary hydroxyl group of iresin readily forms a trityl ether (Ib) which upon oxidation of the secondary hydroxyl group and acid detritylation undergoes simultaneous retroaldol condensation with formation of the nor-ketone III and formaldehyde, thus affording definite proof for the presence and location of the primary hydroxyl group in iresin (Ia). Using isodihydroiresin trityl ether (Vb), various reactions *via* the corresponding ketone VI or mesylate Vc are described whereby it is possible to remove selectively first the secondary and then the primary hydroxyl groups. The reactions of several intermediate mesylates with sodium iodide in acetone solution are recorded and depending upon the structural features, no reaction, simple elimination or elimination with cyclopropane formation are observed.

We have presented evidence recently[2,5] that the sesquiterpene iresin[6] possesses structure Ia (or the alternative with the angular methyl group at C-5[7]) and that it constitutes the first sesquiterpene in which the presence of the bicyclofarnesol skeleton[8] typical of the higher (di- and tri-) terpenes has been demonstrated. In view of the importance of iresin in the biogenetic scheme of the terpenes, further work on this substance has been carried out in our laboratory and in particular there has been investigated the removal of one or both of the hydroxyl groups of iresin. Such transformation products might be useful for eventual correlations with other terpenes or terpene degradation products—commonly characterized by a non-oxygenated *gem*-dimethyl moiety—and it was necessary to examine possible routes to accomplish the type reaction A → B.



A B

Such a transformation is not only of intrinsic interest but also of potential importance in the triterpene series, where there are available various representatives possessing partial structure A and where removal of the oxygen functions would be of considerable utility in their structure elucidation.[9] Some of the more instructive and successful approaches concerned with this problem (A → B) form the subject matter of the present communication.

While complete oxidation of the hydroxyl groups of iresin leading either to a β-keto aldehyde or a β-keto acid would not be very desirable, because of the lability of these intermediates and the likelihood that removal of the oxygen functions would be accompanied by the loss of one carbon atom, partial oxidations might be more fruitful and the conversion of iresin to a hydroxy aldehyde already has been described.[2] Similar oxidation experiments in the isodihydroiresin series will be recorded in part 4 of this series where such products were found to be of importance for the determination of the absolute configuration by rotatory dispersion measurements.

An alternative approach involved selective manipulation of the two hydroxyl functions and as demonstrated below this was accomplished very readily by selective tritylation since only the primary hydroxyl group of iresin (Ia) was etherified with triphenyl methyl chloride. The resulting trityl ether Ib was oxidized with the chromium trioxide–pyridine complex[10] to afford the corresponding 3-keto trityl ether II. That the primary hydroxyl group was indeed etherified was proved by acid detritylation[11] which resulted in concomitant retroaldolization of the intermediate hydroxymethyl ketone[12] and formation of the nor-ketone III and formaldehyde. The isolation of formaldehyde represents unequivocal evidence for the presence of a hydroxymethyl function in iresin. Sodium borohydride treatment of the keto trityl ether II effected reduction of the carbonyl function as well as of the double bond[13] and acid detritylation of the crude product yielded dihydroiresin (IV).[6,14] Since the keto group of II is a reactive one, this sequence (II → IV) can be considered presumptive

(1) Paper XXXIII, C. Djerassi, M. Cais and L. A. Mitscher, THIS JOURNAL, **80**, 247 (1958).

(2) Part 2, C. Djerassi and W. Rittel, *ibid.*, **79**, 3528 (1957).

(3) Supported by grants from the National Cancer Institute (CY-2919) of the National Institutes of Health, U. S. Public Health Service, and from the Rockefeller Foundation.

(4) (a) Postdoctorate research fellow (1954–1955) on a Fulbright travel grant from the University of Sydney, Australia; (b) postdoctorate research fellow (1957–1958) from the University of Basel, Switzerland.

(5) C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herrán, THIS JOURNAL, **76**, 6410 (1954).

(6) C. Djerassi, P. Sengupta, J. Herrán and F. Walls, *ibid.*, **76**, 2966 (1954).

(7) Additional experiments bearing on the location of the angular methyl group and the absolute configuration of iresin will be reported in part 4 of this series.

(8) C. J. W. Brooks and K. H. Overton, *Proc. Chem. Soc.*, 322 (1957), have now shown that drimenol also belongs to this group. We are indebted to Dr. Overton for an advance copy of his manuscript.

(9) An example would be the conversion of hederagenin to 3-desoxyoleanolic acid which has so far not been accomplished (see Elsevier's "Encyclopedia of Organic Chemistry," Vol. 14-Supplement, p. 1010S, Amsterdam, 1952).

(10) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

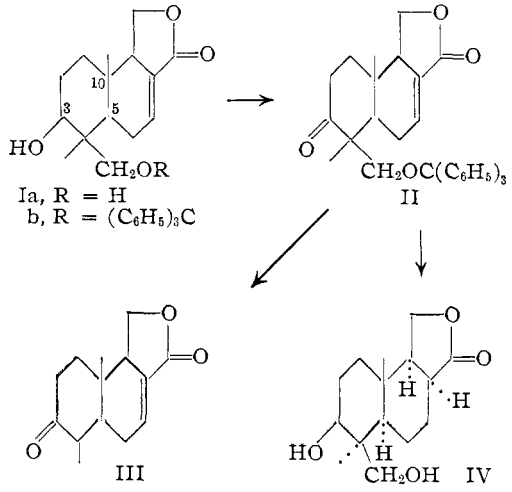
(11) As shown in the Experimental section, the conditions for effective detritylation of the keto trityl ether II were considerably more drastic than those needed for iresin trityl ether Ib. This may be due to protonation of the carbonyl group thus tending to offset the generation of another positively charged center in proximity to it.

(12) For a pertinent example see D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1953).

(13) See footnote 7 in ref. 2.

(14) The arguments for the *relative* configurations implied in stereoformulas IV and Va will be given in part 4 of this series. As has already been mentioned briefly (ref. 2, footnote 26), the all-*cis* relationship between the secondary hydroxyl group, the hydroxymethyl function and the 5–6 bond are implicit in the formation of the cyclic acetal described in ref. 2.

evidence[15] for the equatorial orientation of the hydroxyl group at C-3 of iresin.



All subsequent reactions were carried out with isodihydroiresin (Va)[14] which was converted into the trityl ether Vb in the manner described above for iresin (Ia). Chromium trioxide–pyridine oxidation yielded the corresponding keto trityl ether VI and treatment with ethane dithiol in the presence of boron trifluoride[16] resulted in mercaptal formation and accompanying detritylation.[17] The structure of this product VIIa, further characterized as the acetate VIIb, was proved by Raney nickel desulfurization to the alcohol VIIIa, oxidation to the aldehyde IXa and removal of the latter's carbonyl function *via* the mercaptal and desulfurization to yield the required lactone IXb in which both hydroxyl groups of iresin had been removed.

Two alternate routes to the key intermediate—3-desoxyisodihydroiresin (VIIIa)—were developed. The shortest one, though proceeding in poor yield, involved Wolff–Kishner reduction[18] of the keto trityl ether VI to 3-desoxyisodihydroiresin trityl ether (VIIIb) and detritylation of the latter. The other method, though longer, is of considerable mechanistic interest.

Isodihydroiresin trityl ether (Va) was transformed into the mesylate Vc or alternatively into the brosylate Vd or tosylate Ve and any one of these three esters underwent elimination with sodium iodide in acetone solution to furnish an unsaturated trityl ether, which also could be isolated by heating the tosylate Ve in collidine solution. *A priori*, two formulations appeared most reasonable depending upon whether elimination of the sulfonate ester Vc-Ve was XIa or was not Xa accompanied by ring contraction. The presence of the unrearranged octalin system X could be demonstrated in the following manner.

The crystalline, unsaturated trityl ether Xa was detritylated with acid to the alcohol Xb, further characterized as the acetate Xc. If the elimination had been accompanied by rearrangement, the detritylated alcohol XIb would have been an allylic alcohol subject to oxidation with manganese dioxide.[19] In actual fact, the alcohol was resistant to such oxidation but was transformed readily into the corresponding aldehyde XIII by means of chromium trioxide in pyridine solution.[10] Since the aldehyde exhibited all of the spectral characteristics of an isolated aldehyde function, an allylic precursor XIb is eliminated. Furthermore, ozonolysis of the unsaturated alcohol acetate Xc did not yield a cyclopentanone derivative, as would have been expected of a rearranged allylic precursor XIc, but rather a dibasic acid which was analyzed as the oily dimethyl ester XII. Finally and most conclusively,[20] catalytic hydrogenation of the unsaturated alcohol Xb led to 3-desoxyisodihydroiresin (VIIIa), which proved to be identical with a specimen prepared by the above-described sequence from the keto trityl ether VI.

The structural factors influencing the course of mesylate elimination were studied in some detail. As indicated above, treatment of a 3-mesylate, such as isodihydroiresin trityl ether mesylate (Vc), with sodium iodide in acetone solution resulted in smooth elimination of the elements of methanesulfonic acid. On the other hand, VIIIc, the mesylate of the saturated primary alcohol VIIIa—a neopentyl alcohol—was recovered unchanged under those conditions (sealed tube at 100°) while decomposition was noted at higher temperatures (160°). With this information as a background, it was interesting to observe that reaction of isodihydroiresin dimesylate (Vf) with sodium iodide in acetone solution resulted in the loss of *both* mesyl functions and the formation of an unsaturated oxygen-free compound (aside from the lactone ring). Since the 3-mesyl function is known to eliminate under those conditions (*cf.* Vc → Xa), it appeared likely that the unsaturated primary mesylate Xd was an intermediate in the reaction of isodihydroiresin dimesylate (Vf) with sodium iodide. In point of fact, the same unsaturated lactone lacking additional oxygen atoms was isolated when the unsaturated primary mesylate Xd was subjected to these reaction conditions. While definite proof is lacking, it seems most likely that the unsaturated lactone is best represented as the unsaturated cyclopropane derivative XIV, accompanied probably by small amounts of rearrangement products since it was difficult to obtain a sharp melting specimen of either the unsaturated (XIV) or saturated (XV) cyclopropyl lactone. An excellent precedent for this type of reaction (Xd → XIV) is provided

(15) The basis for this conformational argument is summarized by D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

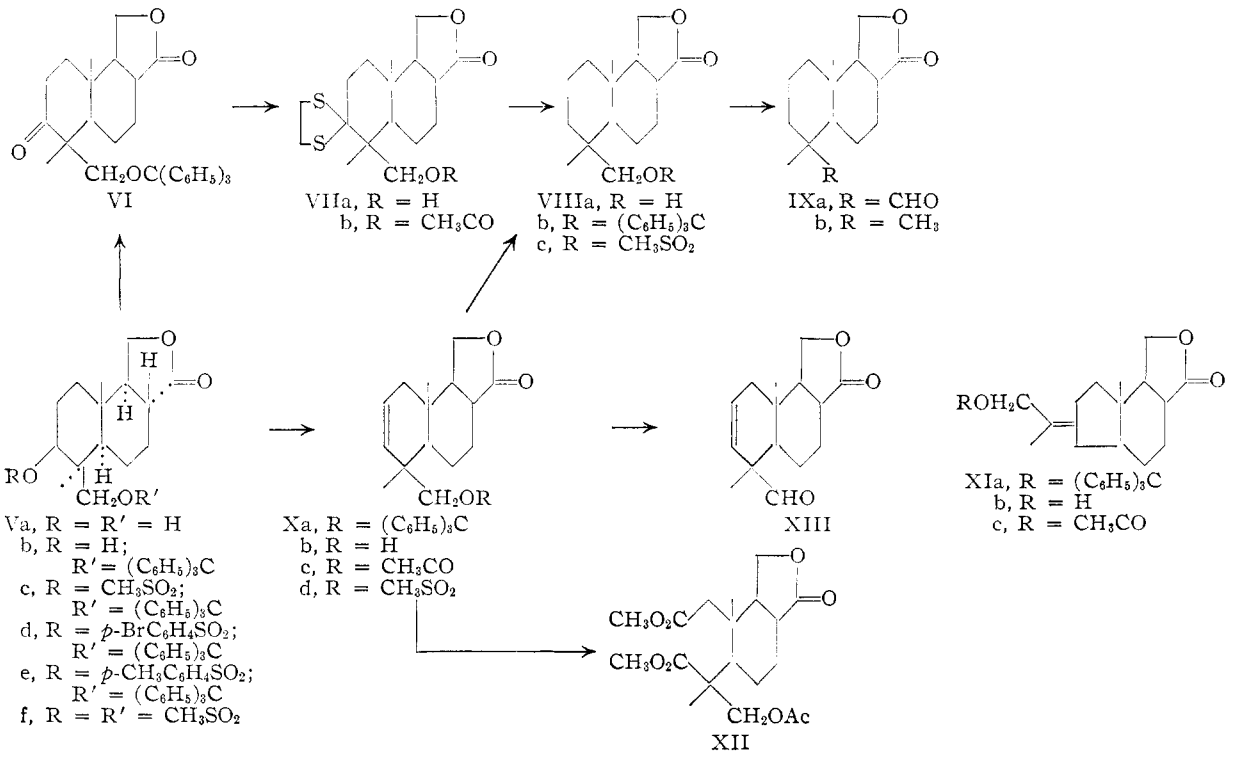
(16) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

(17) In this connection, it is pertinent to mention that the acid detritylation of the keto trityl ether VI required as drastic conditions as the corresponding iresin derivative II and that detritylation could not be accomplished with hydrogen and palladium (*cf.* L. Zerova and D. M. Theodoropoulos, *ibid.*, **78**, 1359 (1956)) or with Raney nickels catalyst. On the other hand, isodihydroiresin trityl ether (Vb) was converted readily into isodihydroiresin (Va) by heating under reflux with Raney nickel in ethanol.

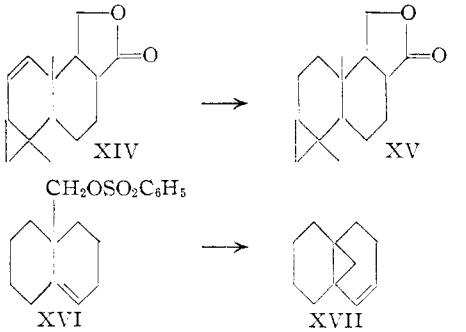
(18) The trityl group withstands Wolff–Kishner reduction conditions as shown recently in a similar case in the triterpene series: A. Sandoval, A. Manjarrez, P. R. Leeming, G. H. Thomas and C. Djerassi, *ibid.*, **79**, 4468 (1957).

(19) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(20) At the time this reduction was first carried out, an authentic specimen of 3-desoxyisodihydroiresin (VIIIa) was not yet available and consequently the alternative structure proof outlined above had to be carried out.



by the reported[21] solvolysis of $\Delta^{1(9)}$-10-hydroxymethyloctalin tosylate (XVI) to the unsaturated cyclopropane XVII whose structure was established rigorously. The tosylate XVI contains the same type of homo-allylic neopentyl sulfonate ester as the iresin derivative Xd.



The presently recorded reactions of iresin and isodihydroiresin trityl ethers (Ib, Vb)—aside from accomplishing the initial aim of removing the hydroxyl functions of iresin—illustrate profitable routes for the selective manipulation of hydroxyl groups in a system such as A and should be of general applicability, especially among triterpenes.

Experimental[22]

Iresin Trityl Ether (Ib).—A solution of 600 mg. of iresin (Ia) and 630 mg. of triphenylmethyl chloride in 12 cc. of pyridine was heated on the steam-bath for 2 hr. and then left at room temperature overnight. After pouring into 500 cc. of ice-water, the gummy material, which separated, was removed by extraction with chloroform and the extract was washed with water and dried over sodium sulfate. Evaporation of the chloroform left 1.06 g. of solid, m.p. 245–250°, which after successive recrystallizations from benzene–hexane and acetone–hexane led to an analytical sample with m.p. 258–260°, $[\alpha]_D$ −22°.

Anal. Calcd. for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 80.74; H, 7.13.

The trityl ether (175 mg.) was cleaved by letting it stand overnight at room temperature in 2 cc. of glacial acetic acid containing a few drops of 1% sulfuric acid. Removal of the acetic acid *in vacuo*, dilution with water and extraction with ether gave triphenylcarbinol, while iresin (35 mg.) was extracted subsequently with chloroform. No attempt was made to determine the optimum conditions in this ether cleavage.

3-Dehydroiresin Trityl Ether (II).—A solution of 500 mg. of iresin trityl ether (Ib) in 5 cc. of pyridine was added gradually with stirring to an ice-cold mixture of 315 mg. of chromium trioxide in 5 cc. of pyridine. After 10 hr. at room temperature, 10 cc. of methanol was added and following an additional 3 hr., most of the methanol and pyridine were removed under reduced pressure. The dark residue was extracted several times with boiling acetone, the solvent was distilled and the solid was recrystallized from chloroform–ether and from acetone–ether; yield 345 mg., m.p. 295–298°, $[\alpha]_D$ +53°, $\lambda_{max}^{CHCl_3}$ 5.65 and 5.80 μ.

Anal. Calcd. for $C_{34}H_{34}O_4$: C, 80.60; H, 6.76. Found: C, 80.92; H, 7.01.

Acid Cleavage of 3-Dehydroiresin Trityl Ether (II) and Isolation of Formaldehyde.—Treatment of the keto trityl ether II with acetic acid–1% sulfuric acid or with 1:1 dioxane–ethanol containing 5% sulfuric acid at room temperature led to recovered starting material. The following more drastic procedure was required for cleavage of the trityl ether II.

A mixture of 500 mg. of the keto trityl ether II, 150 cc. of dioxane and 50 cc. of 10% sulfuric acid was heated under reflux for 24 hr. and a total of 80 cc. was then distilled into 50 cc. of an aqueous solution of dimedone (containing 200 mg. of reagent). After standing overnight in the refrigerator and concentrating the volume to *ca.* 50 cc., colorless needles of the formaldehyde–dimedone derivative separated; yield 53 mg., m.p. 190–192°, undepressed upon ad-

(21) J. W. Rowe, A. Melera, D. Arigoni, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **40**, 1 (1957).

(22) Melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for the infrared spectral determinations obtained with a Baird double-beam spectrophotometer and to Geller Laboratories (Hackensack, N. J.) and Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses. Unless noted otherwise, rotations were measured in chloroform solution in 1-dm. tubes.

mixture with an authentic specimen. A blank run under exactly the same conditions but omitting the trityl ether II gave no formaldehyde.

The aqueous dioxane solution was concentrated to 20 cc., diluted with water and extracted with chloroform. The resulting gum (455 mg.) was allowed to stand overnight with 10 g. of potassium hydroxide in 60 cc. of water and 140 cc. of methanol,[23] acidified and extracted with chloroform. Chromatography of the resulting gum on alumina yielded triphenylcarbinol first while subsequent elution with benzene furnished the nor-ketone III, which was recrystallized from chloroform–ether; yield 73 mg., m.p. 138–144°, undepressed upon admixture with a specimen prepared by an alternate method.[2] Identity was confirmed further by comparison of the infrared spectra.

Sodium Borohydride Reduction of 3-Dehydroiresin Trityl Ether (II).—The keto trityl ether II (105 mg.) dissolved in 20 cc. of 1:1 ethanol–dioxane was treated with a solution of 100 mg. of sodium borohydride in 20 cc. of 1:1 ethanol–dioxane. After 6 hr. at room temperature, 10 cc. of 25% sulfuric acid was added and the solution was heated under gentle reflux for 14 hr. Concentration *in vacuo*, dilution with water, extraction with chloroform, washing, drying and evaporating yielded an oil which was chromatographed on neutral alumina. The benzene eluates containing triphenylcarbinol were discarded, while from the chloroform eluates there was obtained 31 mg. of colorless crystals, m.p. 138–140°. Further recrystallization from methanol–ether raised the m.p. to 145–146°, undepressed when mixed with an authentic specimen[6] of dihydroiresin (IV).

Isodihydroiresin Trityl Ether (Vb).—A mixture of 1.0 g. of isodihydroiresin (Va),[6] 1.34 g. of triphenylmethyl bromide and 20 cc. of pyridine was heated on the steam-bath for 6 hr. and then left at room temperature overnight. After pouring into ice-water, extracting with chloroform, evaporating the solvent and recrystallizing from chloroform–hexane, there was isolated (in ten different experiments) 73–88% of the trityl ether, m.p. 276–281°. The melting point varied greatly depending upon the rate of heating, and an analytical sample, recrystallized from ethyl acetate and from methanol, exhibited m.p. 275–278°, $[\alpha]_D$ −60°.

Anal. Calcd. for $C_{34}H_{38}O_4$: C, 79.97; H, 7.50. Found: C, 80.17; H, 7.78.

When 200 mg. of the trityl ether was heated under reflux in ethanol solution with 5 g. of Raney nickel, there was isolated by direct crystallization of the crude reaction product 82 mg. of isodihydroiresin (Va), m.p. 204–207°, not depressed when mixed with an authentic sample.[6]

Alternatively, hydrogen chloride gas was passed for 6 hr. through a chloroform solution of the trityl ether whereupon 24% of isodihydroiresin was encountered in addition to appreciable amounts of recovered trityl ether.

3-Dehydroisodihydroiresin Trityl Ether (VI).—The chromium trioxide–pyridine oxidation of the trityl ether Vb was conducted exactly as described above for iresin trityl ether (Ib) and proceeded in 75–83% yield, m.p. 284–289°. The analytical specimen was obtained by successive recrystallization from chloroform–hexane, ethyl acetate and acetone–hexane, whereupon it exhibited m.p. 288–290°, $[\alpha]_D$ +7°, $\lambda_{max}^{CHCl_3}$ 5.62 and 5.84 μ.

Anal. Calcd. for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 80.20; H, 7.44.

3-Dehydroisodihydroiresin Cycloethylene Mercaptal (VIIa).—A mixture of 500 mg. of the keto trityl ether VI, 15 cc. of ethane dithiol and 12 cc. of freshly distilled boron trifluoride etherate was allowed to stand at 20° for 20 min. and then poured into ice-water. The product was extracted with ether, washed well with water and then evaporated to dryness, using a high vacuum pump at the end. Solution in acetone, precipitation by addition of hexane, and filtration furnished 320 mg. of mercaptal, m.p. 179–185°, while the analytical sample, obtained from the same solvent pair, exhibited m.p. 185–186.5°, $[\alpha]_D$ +10°, $\lambda_{max}^{CHCl_3}$ 2.95 and 5.61 μ.

Anal. Calcd. for $C_{17}H_{26}O_3S_2$: C, 59.63; H, 7.65; S, 18.73. Found: C, 59.70; H, 7.64; S, 18.75.

(23) The alkali treatment was incorporated in order to complete the retroaldolization of any remaining hydroxymethyl ketone. Distillation of the acidified reaction mixture into dimedone solution did not yield any formaldehyde derivative, thus indicating that this step was superfluous.

The acetate VIIb was prepared by acetylation of VIIa with acetic anhydride–pyridine for 1 hr. on the steam-bath and recrystallization from acetone–hexane; m.p. 176–177°, $[\alpha]_D$ +24°; $\lambda_{max}^{CHCl_3}$ 5.60, 5.72 and 8.03 μ.

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.34. Found: C, 58.97; H, 7.27.

Δ^2-Anhydroisodihydroiresin Trityl Ether (Xa). (a) **From Isodihydroiresin 3-Mesylate Trityl Ether (Vc).**—Isodihydroiresin trityl ether (Vb) (1.1 g.) dissolved in 5 cc. of pyridine was added to 0.24 g. of methanesulfonyl chloride and left at room temperature overnight. Dilution with ice-water, extraction with chloroform, thorough washing and evaporation gave 1.3 g. of the mesylate trityl ether Vc as a colorless foam, which resisted crystallization even after chromatography.

A 1.0-g. sample of the mesylate and 3.6 g. of sodium iodide in 60 cc. of acetone was kept in a sealed tube at 100°[24] for 40 hr. The crystals of sodium methanesulfonate which separated on cooling were collected and the filtrate was concentrated until sodium iodide crystallized out. The solution was diluted with much chloroform and washed thoroughly with sodium thiosulfate solution and water, dried and evaporated. Crystallization of the residue from aqueous acetone or chloroform–hexane gave a variable yield (120–450 mg.) of olefin, m.p. 268–274°. The analytical sample of Xa exhibited m.p. 273–276°, $[\alpha]_D$ −78°.

Anal. Calcd. for $C_{34}H_{36}O_3$: C, 82.89; H, 7.37. Found: C, 82.44; H, 7.61.

(b) **From Isodihydroiresin 3-Brosylate Trityl Ether (Vd).**—Isodihydroiresin trityl ether (Vb) (1.0 g.) and *p*-bromobenzenesulfonyl chloride (0.76 g.) in 10 cc. of pyridine were left at room temperature for 3 days and then worked up in the usual manner. Crystallization from acetone or from benzene–hexane gave 0.6 g. of brosylate Vd, m.p. 161–163° dec., $[\alpha]_D$ −20°.

Anal. Calcd. for $C_{40}H_{41}BrO_6S$: C, 65.83; H, 5.60; Br, 10.96. Found: C, 66.27; H, 5.54; Br, 10.95.

When 370 mg. of the brosylate Vd was heated with 750 mg. of sodium iodide in the manner described under (a) for the mesylate, there was isolated 158 mg. (64%) of the unsaturated trityl ether Xa.

(c) **From Isodihydroiresin 3-Tosylate Trityl Ether (Ve).**—The tosylate (1.22 g., m.p. 180–181°) was obtained when 1.0 g. of isodihydroiresin trityl ether and 0.41 g. of *p*-toluenesulfonyl chloride in 10 cc. of pyridine were kept at room temperature for 2 days. The material appears to exist in two polymorphic forms and recrystallization from benzene–petroleum ether gave crystals with m.p. 172–175°, $[\alpha]_D$ −13°.

Anal. Calcd. for $C_{41}H_{44}O_6S$: C, 74.07; H, 6.67; S, 4.81. Found: C, 73.98; H, 6.96; S, 4.61.

A solution of 650 mg. of the tosylate trityl ether Ve in 10 cc. of collidine[25] was heated at 120° for 5 hr., whereupon 580 mg. of unchanged tosylate was recovered. When this material was heated under reflux with collidine[25] for 3 hr., a very dark reaction mixture was obtained from which 64% of colorless, unsaturated trityl ether Xa could be isolated after chloroform extraction and repeated washing with dilute hydrochloric acid and bicarbonate solution followed by crystallization from chloroform–hexane.

Δ^2-Anhydroisodihydroiresin (Xb).—The detritylation of the unsaturated trityl ether Xa was very erratic and gave widely divergent yields of unsaturated alcohol. In the best experiment, 1.5 g. of the olefin trityl ether Xa was heated for 7 hr. on the steam-bath with 100 cc. of dioxane and 20 cc. of 10% sulfuric acid and then concentrated to a small volume. Dilution with water, extraction with chloroform and chromatography on 35 g. of acid-washed alumina afforded 760 mg. of triphenylcarbinol (m.p. 162°) in the benzene eluates, while chloroform removed 680 mg. of crystals. Recrystallization of the latter from chloroform–hexane provided the analytical sample of the unsaturated alcohol Xb, m.p. 115–116°, $[\alpha]_D$ −53°. Ultraviolet measurement carried out at the University of Manchester on a Unicam SP 500 spectrophotometer through the courtesy of Prof. E. R. H. Jones confirmed the presence of a disubstituted

(24) When the reaction was carried out at the reflux temperature of acetone, the mesylate was recovered unchanged.

(25) Coal tar collidine obtained from Schweizerische Teerindustrie, A.G., Pratteln, Switzerland.

olefin: 200 mμ (ε 3360), 205 mμ (ε 1730), 210 mμ (ε 1070), 215 mμ (ε 1060), 220 mμ (ε 876), 226 mμ (ε 655).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.41; H, 8.86.

The alcohol Xb (100 mg.) was recovered unchanged when it was shaken for 17 hr. with 1.0 g. of manganese dioxide in 100 cc. of chloroform. Oxidation could, however, be effected smoothly by mixing 80 mg. of alcohol Xa and 110 mg. of chromium trioxide in 9 cc. of pyridine at 0° and leaving at room temperature for 40 min. Methanol was added, the mixture was filtered after 30 min., and the solid was washed with pyridine. The filtrate and washings were evaporated to dryness *in vacuo* and the residue was extracted with boiling ethyl acetate. Evaporation of this extract left 76 mg. of colorless crystals, m.p. 167–171°, raised to m.p. 179–180° after recrystallization from chloroform–ether. The non-conjugated nature of the aldehyde XIII was demonstrated by the absence of high, selective ultraviolet absorption and by the infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.63 and 5.80 μ). Furthermore, the *yellow* 2,4-dinitrophenylhydrazone (m.p. 235–242°), though crystallizing poorly and hence not being analyzed, exhibited a maximum (chloroform solution) at 356 mμ, typical[26] of saturated aldehydes.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.23.

Acetylation of the alcohol Xb with acetic anhydride–pyridine at room temperature overnight and recrystallization from acetone–hexane afforded the **acetate Xc**, m.p. 171–173°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.18; H, 8.28.

Ozone was passed through a solution of 255 mg. of the acetate Xc in ethyl acetate solution at −70° until a permanent blue color developed. After heating with water for 1 hr. and leaving at room temperature overnight, the product was extracted with ethyl acetate, washed with bicarbonate solution, water, dried and evaporated. The resulting neutral gum (175 mg.)—presumably the dialdehyde—was heated on the steam-bath for 3 hr. with 10 cc. of glacial acetic acid and 1 cc. of 30% hydrogen peroxide. The oxidation product was extracted with chloroform, washed with sodium bicarbonate and the latter acidified and again extracted with chloroform, leaving 64 mg. of acidic material. This was methylated with diazomethane and since the resulting methyl ester could not be crystallized, even after chromatography, it was distilled twice at a bath temperature of 160° and 0.005 mm. The analytical and infrared spectral data ($\lambda_{max}^{CHCl_3}$ 5.63, 5.80 and 8.15 μ) are in concordance with structure XII.

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 59.36; H, 7.34; OCH_3, 16.16. Found: C, 60.07; H, 7.24; OCH_3, 15.81.

3-Desoxyisodihydroiresin (VIIIa). (a). By Hydrogenation of Xb.—A solution of 600 mg. of the unsaturated alcohol Xb in 100 cc. of ethyl acetate was shaken overnight with 10% palladized charcoal catalyst in an atmosphere of hydrogen at room temperature and atmospheric pressure. The catalyst was filtered, the filtrate was evaporated to dryness and recrystallized from acetone–hexane to yield 465 mg. of colorless crystals, m.p. 105–110°, raised to m.p. 110–111°, $[\alpha]_D$ +10°, upon repeated recrystallization from the same solvent pair.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.63.

(b) By Desulfurization of VIIa.—The mercaptal VIIa (400 mg.) was heated under reflux for 2 hr. with 2.5 g. of W-2 Raney nickel in 150 cc. of acetone. Filtration of the nickel, evaporation of the acetone and recrystallization from acetone–hexane led to 164 mg. (56%) of 3-desoxyisodihydroiresin (VIIIa), m.p. 104–110°.

3-Desoxyisodihydroiresin Trityl Ether (VIIIb) by Wolff–Kishner Reduction of VI.—A mixture of 1.0 g. of the keto trityl ether VI, 110 cc. of diethylene glycol, 40 cc. of absolute ethanol and 3 cc. of 85% hydrazine hydrate was heated at 100° for 1.5 hr., 0.5 g. of potassium hydroxide was added and heating under reflux was continued for 1 hr. The condenser was removed, water was distilled out until the temperature of the vapor rose to 200° whereupon reflux was re-established for 4 hr. Dilution with water and extraction with chloroform furnished an oil which was chromatographed on 40 g. of alumina. Elution with benzene afforded the desired trityl ether which was recrystallized from chloroform–hexane (yield, 176 mg.) whereupon it exhibited m.p. 243–244° with sublimation from 225°, $[\alpha]_D$ −27°. Ether eluted a small amount of unchanged keto trityl ether VI (m.p. 270–283°).

Anal. Calcd. for $C_{34}H_{38}O_3$: C, 82.55; H, 7.74; O, 9.70. Found: C, 82.90; H, 8.38; O, 9.10.

3-Desoxyisodihydroiresin Mesylate (VIIIc).—The saturated alcohol VIIIa (265 mg.) dissolved in 5 cc. of pyridine was treated with 8 drops of methanesulfonyl chloride and left at room temperature for 2 days. Dilution with ice-water gave a solid, which was filtered and washed well with water; yield 290 mg., m.p. 118–121°. The analytical sample was obtained from acetone–hexane, whereupon it showed m.p. 123–124°, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{16}H_{26}O_5S$: C, 58.17; H, 7.93. Found: C, 58.43; H, 7.96.

When this mesylate was heated with sodium iodide in acetone solution in a bomb tube at 100 or 120° for 24 hr., only unchanged starting material was encountered. At 160°, considerable decomposition took place and no pure product could be isolated.

3-Desoxydehydroisodihydroiresin (IXa).—The oxidation of 960 mg. of the saturated alcohol VIIIa was performed with 770 mg. of chromium trioxide and 45 cc. of pyridine for 1 hr. as described above for isodihydroiresin trityl ether, and the once-crystallized aldehyde (850 mg.) was recrystallized from ethyl acetate, whereupon it melted at 207–209°, $[\alpha]_D$ −209°, $\lambda_{max}^{CHCl_3}$ 5.60 and 5.78 μ.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.21; H, 9.19.

A 140-mg. sample of the aldehyde IXa was treated with ethane dithiol and boron trifluoride exactly as described for the conversion of VI → VIIa. The intermediate mercaptal did not crystallize, but the complete disappearance of the aldehyde function was indicated by the infrared spectrum which showed a single band at 5.61 μ corresponding to the lactone moiety. Consequently, the total product was dissolved in 50 cc. of acetone and heated under reflux for 1.25 hr. with 1 g. of W-2 Raney nickel catalyst. Filtration of the catalyst and evaporation of the acetone gave the saturated lactone IXb as a wax-like solid (m.p. 65–82°), which after recrystallization from chloroform–hexane and high vacuum sublimation melted at 90–96°, $\lambda_{max}^{CHCl_3}$ 5.61 μ, $[\alpha]_D$ −71°.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24; O, 13.54. Found: C, 76.40; H, 9.61; O, 13.92.

Isodihydroiresin Dimesylate (Vf) and Reaction with Sodium Iodide.—Isodihydroiresin (2.38 g.), 15 cc. of pyridine and 1.8 cc. of methanesulfonyl chloride were mixed at 0° and then left at room temperature for 2 days. After pouring into ice-water, extracting with chloroform, evaporating and crystallizing from chloroform–hexane, there was obtained 2.89 g. (77%) of dimesylate Vf, m.p. 173–176° dec. The analytical specimen was recrystallized from acetone–ether and from ethanol, m.p. 182–184° dec., $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{17}H_{28}O_8S_2$: C, 48.10; H, 6.65. Found: C, 48.34; H, 6.58.

A solution of 1.8 g. of the dimesylate in 60 cc. of acetone was heated in a sealed tube with 4.5 g. of sodium iodide at 100° for 30 hr. After cooling, 1.22 g. of sodium methanesulfonate was filtered, the filtrate was concentrated, diluted with chloroform and washed well with thiosulfate solution. Evaporation of the chloroform left 8.53 g. of oil containing considerable quantities of acetone self-condensation products (odor of mesityl oxide and phorone) and the product XIV was most effectively separated by taking advantage of of the presence of the lactone ring. For this purpose, the oil was stirred with a 5% solution of sodium hydroxide for 1 hr. on the steam-bath, extracted with ether and the extract was discarded. The aqueous layer was acidified to *p*H 5 and the resulting amorphous lactone (0.88 g.) was extracted with ether. Distillation at 100–150° and 0.1 mm. yielded a yellowish oil (0.8 g.) which crystallized on cooling; m.p. 63–74°. Two recrystallizations from hexane raised the m.p. of the colorless crystals (105 mg.) to

(26) E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945); J. D. Roberts and C. Green, THIS JOURNAL, **68**, 214 (1946).

78–86°, $[\alpha]_D$ −24°, λ_{max}^{EtOH} 222 mμ, log ε 3.78[27]; orange-yellow color with tetranitromethane.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.33; H, 8.70; O, 13.62.

The wide melting point range indicated that the product was not pure,[28] but the presence of the double bond was demonstrated by quantitative microhydrogenation in ethanol solution with 10% palladized charcoal which resulted in the consumption of 1.08 equivalents of hydrogen. Recrystallization from aqueous ethanol afforded crystals, m.p. 54–76°, which presumably represent a contaminated[28] sample of the saturated cyclopropane derivative XV.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.15; H, 9.78.

The unsaturated alcohol Xb was converted to the mesylate Xd in the conventional manner, but the product could only be obtained as an amorphous powder in spite of repeated attempts at crystallization. When this mesylate Xd was treated with sodium iodide in acetone solution as described above for the dimesylate Vf, there were obtained colorless crystals (m.p. 59–78°) of the supposed unsaturated cyclopropane XIV, whose infrared spectrum was identical with that of the solid isolated in the dimesylate–sodium iodide reaction.

DETROIT, MICHIGAN

(27) The ultraviolet absorption spectrum appears to be compatible with the unsaturated cyclopropane formulation XIV as indicated by the few relevant data listed in the literature (ref. 21).

(28) For possible side reactions see ref. 21.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

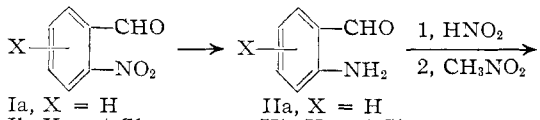
Cinnolines. III. Synthesis of *bz*-Substituted 3-Nitro- and 3-Aminocinnolines[1,2]

BY HENRY E. BAUMGARTEN, DONALD L. PEDERSEN AND MACK W. HUNT

RECEIVED NOVEMBER 8, 1957

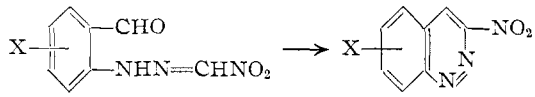
The synthesis of three new *bz*-substituted 3-nitrocinnolines by the cyclization of nitroformaldehyde *o*-formylphenylhydrazones (III) is described as well as an alternative route for proceeding from the usual starting material, an *o*-nitrobenzaldehyde, to the cinnoline. Two of the 3-nitrocinnolines have been reduced to the corresponding 3-aminocinnolines.

Of the ten to twelve syntheses of the cinnoline ring described in the literature, only three procedures (the Richter, Widman–Stoermer and Borsche syntheses) appear to be of established generality.[3] In the first paper of this series[4] a new synthesis (I → IV) of cinnolines was described involving cyclization of nitroformaldehyde *o*-acylphenylhydrazones (such as III) to 3-nitrocinnolines. The present communication describes our further exploration of the generality of this synthesis as applied to *o*-nitrobenzaldehydes as starting materials.



Ia, X = H
Ib, X = 4-Cl
Ic, X = 5-Cl
Id, X = 4,5-OCH_2O

IIa, X = H
IIb, X = 4-Cl
IIc, X = 5-Cl
IId, X = 4,5-OCH_2O

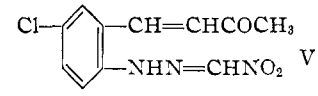


IIIa, X = H
IIIb, X = 4-Cl
IIIc, X = 5-Cl
IIId, X = 4,5-OCH_2O

IVa, X = H
IVb, X = 7-Cl
IVc, X = 6-Cl
IVd, X = 6,7-OCH_2O

For the present work three of the more accessible *o*-nitrobenzaldehydes, 4-chloro-2-nitrobenzaldehyde (Ib), 5-chloro-2-nitrobenzaldehyde (Ic) and 6-nitropiperonal (Id), were employed. The *o*-nitrobenzaldehydes were reduced to the corresponding *o*-aminobenzaldehydes (II). Without purification the *o*-aminobenzaldehydes were diazotized and coupled with nitromethane to give the nitroformaldehyde *o*-formylphenylhydrazones (III), and the latter were cyclized by treatment with dilute aqueous potassium hydroxide without intermediate purification, giving 7-chloro-3-nitrocinnoline (IVb), 6-chloro-3-nitrocinnoline (IVc) and 6,7-methylenedioxy-3-nitrocinnoline (IVd) in 10–15, 12–17 and 10% yields, respectively, based on I.

Only in the case of IVb was there any deviation from the expected behavior. In all experiments at the 0.04-mole level, IVb was obtained in 10–15% yield. However, in several experiments at the 0.20-mole level, using various concentrations of base, times of reaction and temperatures, the reaction was erratic and little IVb was formed. On recrystallizing the crude apparent product from acetone the only material isolated in quantity (about 10–26%) appeared to be nitroformaldehyde 5-chloro-2-(3-oxo-1-butenyl)-phenylhydrazone (V),



V

based on its analysis and infrared spectrum. This material apparently arose from the reaction of the uncyclized intermediate IIIb with acetone during the recrystallization. Thus, the use of acetone as a solvent during the cyclization or purification steps appears to be contraindicated.

The principal apparent limitation to the generality of the present synthesis is the relative inaccessibility of derivatives of II.[5] Various de-

(1) This work was supported in part by grant G-1090 of the National Science Foundation.

(2) Paper II, THIS JOURNAL, **77**, 5109 (1955).

(3) The cyclization of *o*-hydrazinomandelic acids (Neber–Bossel synthesis, E. J. Alford and K. Schofield, *J. Chem. Soc.*, 2102 (1952)) appears to be a potentially general synthesis also; however, as will be borne out by results to be reported shortly from this Laboratory, the use of presently published procedures may lead to the isomeric N-aminodioxindoles rather than cinnoline derivatives.

(4) H. E. Baumgarten and M. R. DeBrunner, THIS JOURNAL, **76**, 3489 (1954).

(5) According to our count (D. L. Pedersen, M.S. thesis, University of Nebraska, June, 1956) at least 30 monosubstituted and 80 di- and trisubstituted *o*-nitrobenzaldehydes (I) are mentioned in the literature but only approximately 8 monosubstituted and 14 di- and trisubstituted *o*-aminobenzaldehydes have been described. The disparity in these figures is to some extent a measure of the difficulty of reduction of I and its derivatives and the instability of II and its derivatives.