cactus was collected near Zapotitlán on the road from Tehuacán Puebla to Huajuapan de León and from the glycosidic fraction there was obtained nearly 1% of **chichipegenin** and 0.2% of **methyl oleanolate (Vb)**.

Isolation of Triterpenes from *M. schenckii*.—A 1.54-kg. sample (dry) of cactus collected near Diaz Ordaz, Oaxaca, yielded only 55 g. of glycosidic material after alcohol extraction and ether washing. Acid hydrolysis and chromatography of the neutral fraction gave 0.052% of **stellatogenin (VIIa)**[17] (m.p. 311–314°, $[\alpha]_D$ +40°; acetate VIIb, m.p. 323–326°, $[\alpha]_D$ +49°), identified by infrared comparison with an authentic sample,[6] while methylation of the acids and chromatography led to 0.136% of **methyl oleanolate (Vb)** (m.p. 197–199°).

Lithium Aluminum Hydride Reduction of Triacetyl Methyl Myrtillogenate.—Methyl myrtillogenate (IIb) triacetate (196 mg.) was heated under reflux for 12 hours with 1 g. of lithium aluminum hydride in 100 cc. of ether and was then processed in the manner described earlier[21] for oleanolic acid lactone. The crude **Δ^{12}-oleanen-3β,16β,28,29-tetrol (IVa)** (155 mg., m.p. 275–280°) was recrystallized from methanol to yield an analytical specimen, m.p. 280–283°, $[\alpha]_D$ +101° (methanol), no infrared absorption in the carbonyl region.

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 76.00; H, 10.52.

Acetylation with acetic anhydride–pyridine and purification by alumina chromatography (elution with benzene) followed by recrystallization from methanol furnished **Δ^{12}-oleanen-3β,16β,28,29-tetrol tetraacetate (IVb)**, m.p. 182–183°, $[\alpha]_D$ +71°.

Anal. Calcd. for $C_{38}H_{58}O_8$: C, 70.99; H, 9.09. Found: C, 71.23; H, 9.47.

The difference in physical constants precluded identity with chichipegenin (and its acetate) and the infrared spectra were also different.

DETROIT, MICHIGAN
MEXICO 20, D. F.

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

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

Terpenoids. XXIX.[1] Iresin (Part 2).[2] A New Fundamental Sesquiterpene Skeleton[3,4]

BY CARL DJERASSI AND WERNER RITTEL[5]

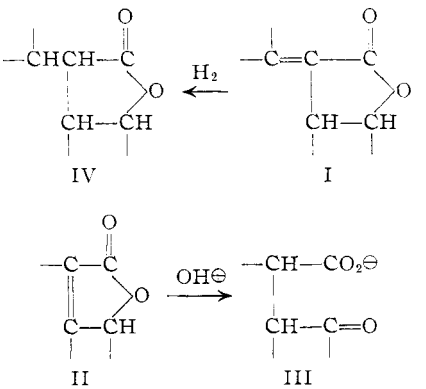
RECEIVED FEBRUARY 14, 1957

By means of various degradations, it has been shown that iresin possesses structure XXV (or the variant XXXII) based on a skeleton (XIII or XIV) which is unique among sesquiterpenes. Since this skeleton is always found in rings A, B and C of the higher (di- and tri)-terpenes, iresin represents an important link in the presently accepted biogenetic pattern of the lower and higher terpenes.

Recently,[2] there has been described the isolation and characterization of a novel sesquiterpene ($C_{15}H_{22}O_4$) which was named iresin. We should now like to record the salient experiments which led to the elucidation of the skeletal structure of this substance and which suggest that iresin occupies a unique position in terpene chemistry. Future papers will deal with various transformations of the functional groups of iresin and with its stereochemistry.

The nature of the four oxygen atoms already has been elucidated in the first paper[2] of this series and they were shown to be present as two reactive hydroxyl groups and as an α,β-unsaturated, five-membered lactone ring. The latter could, *a priori*, be of two types—the double bond being exocyclic (I) or endocyclic (II) with respect to the lactone ring—and it seemed important to differentiate between these two possibilities before initiating more drastic degradations.

Since α,β-unsaturated lactones of type II are known[6] to be convertible by base to the corresponding keto acids III, iresin was subjected to such treatment and was recovered unchanged (after acidification) even when heated with potassium *t*-butoxide. We conclude that the unsaturated lactone system of iresin is of type I and direct chemical proof for this supposition was afforded by ozonization experiments described below. The only double bond present in iresin is that conjugated with the



(1) Paper XXVIII, C. Djerassi, S. Burstein, H. Estrada, A. J. Lemin, A. E. Lippman, A. Manjarrez and H. G. Monsimer, THIS JOURNAL, **79**, 3525 (1957).

(2) Part 1, C. Djerassi, P. Sengupta, J. Herran and F. Walls, *ibid.*, **76**, 2966 (1954).

(3) Announced in part in a preliminary communication (C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, *ibid.*, **76**, 6410 (1954)).

(4) We are grateful to the Rockefeller Foundation for financial support.

(5) Ciba Ltd., Basel, Switzerland. Postdoctorate research fellow, 1953–1954.

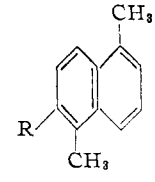
(6) *Cf.* W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941); L. C. McKean and F. S. Spring, *J. Chem. Soc.*, 1989 (1954); J. B. Stenlake and W. D. Williams, *ibid.*, 2114 (1955).

lactone system and it can be reduced readily.[2,7] The resulting dihydroiresin (IV) was found[2] to be unstable to base and after acidification yielded an isomer, isodihydroiresin. Simple opening of the lactone ring and closure with another, suitably located hydroxyl group was excluded,[2] since iresin[8] and dihydroiresin afforded the same tetrol upon lithium aluminum hydride reduction while a different tetrol was obtained from isodihydroiresin. It follows that base treatment of dihydroiresin either resulted in inversion of the enolizable α-position or that inversion accompanied by lactonization with another hydroxyl group had occurred. An unambiguous differentiation between these two alternatives was accomplished as follows.

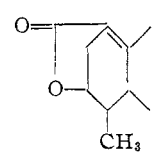
The two hydroxyl groups of iresin are not located on adjacent carbon atoms since the substance is unaffected[2] by glycol-cleaving reagents such as lead tetraacetate. On the other hand, it was now found that iresin condensed readily with benzaldehyde or acetaldehyde in the presence of zinc chloride[9] to yield highly crystalline benzylidene (XXX) or acetylidene (XXI) derivatives from which iresin could be regenerated after acid treatment. This observation not only indicated that iresin possessed a 1,3-glycol system but it also presented a means of protecting the two hydroxyl groups in an alkaline medium. Hydrogenation of benzylidene–iresin (XXX) led to benzylidene–dihydroiresin (XXXI) and alkaline treatment afforded benzylidene–isodihydroiresin, alternatively prepared from isodihydroiresin and benzaldehyde. This circle demonstrates that the two hydroxyl groups cannot be implicated in the dihydroiresin → isodihydroiresin change and that the reaction simply involves inversion at the adjacent enolizable center[10] to the more stable isomer.[11]

The gross structural features of sesquiterpenes usually can be detected[12] by dehydrogenation and identification of the resulting aromatic products. When iresin was heated with palladized charcoal catalyst near 300°, two crystalline dehydrogenation products were obtained. These were identified as 1,5-dimethylnaphthalene (Va)[13] and 1,5-dimethyl-2-naphthol (Vb)[14] and it should be noted that while both substances had been described in the literature,[13,14] neither one had ever been encountered as a characteristic sesquiterpene dehydrogenation product.[12] This constituted the first indication that iresin might represent a novel sesquiterpene type, a supposition which was shown in the sequel to be correct.

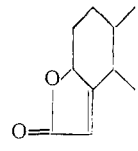
The two naphthalene derivatives (Va, Vb) account for 12 out of the 15 carbon atoms of iresin. Since angular or *gem*-substituents as well as actual or potential carboxyl groups are lost during dehydrogenations,[12] it can be assumed that the loss of three carbon atoms involved the carboxyl group of the lactone ring as well as one (ethyl or oxygenated ethyl) or two (methyl or oxygenated methyl) angular (or *gem*) alkyl groups. Obviously the more significant dehydrogenation product was the naphthol Vb since the surviving oxygen atom automatically labeled one of the three hydroxylic functions of iresin. *A priori*, the phenol could have arisen from either the two alcoholic substituents of iresin or from the hydroxyl group incorporated in the lactone ring. The latter possibility, however, could be ruled out since an α,β-unsaturated five-membered lactone moiety involving that oxygen atom (and furnishing Vb upon dehydrogenation) would lead to partial structures VI or VII. The former would violate Bredt's rule while the latter does not follow the earlier mentioned prerequisite (*cf.* I) that the double bond be exocyclic to the lactone ring.



Va, R = H
b, R = OH
c, R = C_6H_5COO



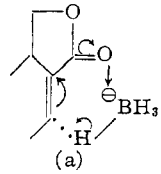
VI



VII

It follows, therefore, that the phenolic hydroxyl group of 1,5-dimethyl-2-naphthol (Vb) originated from one of the two alcoholic groups, which are very easily acylated and saponified.[2] Since this chemical behavior excludes tertiary hydroxyl functions and since they must be part of a 1,3-glycol system (condensation with aldehydes), partial structures VIII and IX (R = H or alkyl) are the only permissible ones insofar as the two hydroxyl groups are concerned. The survival of an alcohol under the drastic dehydrogenation conditions is reminiscent of the 3-hydroxy-4,4-dimethyl system of the pentacyclic triterpenes (*e.g.*, β-amyrin (X)), since dehydrogenation[15] of such compounds leads in part to phenolic products (*e.g.*, XI, XII) in which the orig-

(7) Unsaturated butenolides usually are not attacked by sodium borohydride (*cf.* R. Richter, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 76 (1954), and references cited) but iresin was found to be converted by this reagent in very good yield to dihydroiresin (XXIX) (see Experimental). While examples of the reduction of α,β-unsaturated ketones by means of sodium borohydride to the saturated alcohols are known (*e.g.*, F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chemistry & Industry*, 1482 (1954)), the sole reduction of the double bond appears unusual (*cf.* H. Schechter, D. E. Ley and E. B. Roberson, THIS JOURNAL, **78**, 4984 (1956)) and may possibly proceed through a cyclic intermediate (*cf.* R. E. Lutz and J. S. Gillespie, *ibid.*, **72**, 2002 (1950)) which would be favored by the *cisoid* unsaturated carbonyl system (a).



(a)

(8) In this case the double bond was also reduced.

(9) *Cf.* K. Freudenberg, H. Toepffer and C. C. Andersen, *Ber.*, **61**, 1758 (1928).

(10) As is to be expected on mechanistic grounds, inversion appears to occur prior to opening of the lactone ring since some isodihydroiresin can be extracted from the alkaline solution without acidification.

(11) The stereochemistry of these compounds will be discussed in a subsequent paper.

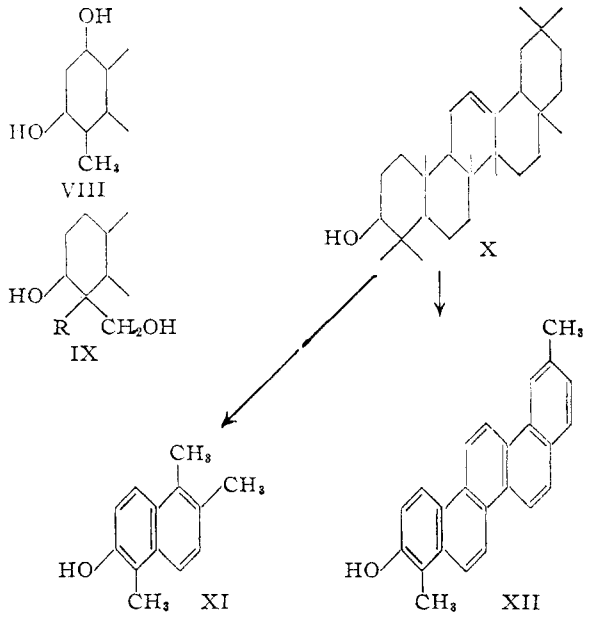
(12) *Cf.* J. Simonsen and D. H. R. Barton "The Terpenes," Vol. III, Cambridge University Press, 1952, and A. J. Haagen-Smit in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. XII, Springer, Vienna, 1955, pp. 1–43.

(13) A. S. Bailey, K. C. Bryant, R. A. Hancock, S. H. Morrell and J. C. Smith, *J. Inst. Petroleum*, **33**, 503 (1947).

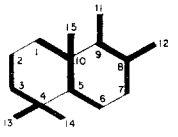
(14) L. Ruzicka and E. Rey, *Helv. Chim. Acta*, **26**, 2136 (1943).

(15) For pertinent review, see O. Jeger in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VII, Springer, Vienna, 1950, p. 16.

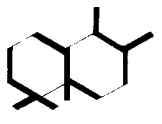
inal alcoholic group is retained. Such an analogy would tend to support partial structure IX (R = alkyl) for iresin and direct chemical proof will be described below.



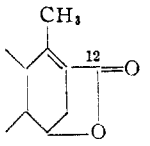
On the assumption that iresin obeys the isoprene rule, only two carbon skeletons need to be considered. The first one (XIII) ($1x$-$y2$, $2x$-$y3$)[16] follows both the isoprene and farnesol rules (head-to-tail attachments of isoprene units) and is thus suggestive of rings A, B and C of the di- and triterpenes, while structure XIV ($1x$-$x2$, $2y$-$y3$)[16] involves an irregular attachment of isoprene units. For the sake of brevity, only XIII will be used in the subsequent discussion and a numbering system is proposed which follows as closely as possible that of the steroids, di- and triterpenes. It should be remembered, however, that all of the structures discussed below could also be elaborated within the framework of XIV with the angular methyl group at C-5 instead of C-10.



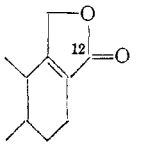
XIII


XIV

If a skeleton based on XIII or XIV is provisionally accepted for iresin, then the attachment of the lactone ring follows rigorously. The carboxyl carbon atom of the lactone ring is lost during dehydrogenation to 1,5-dimethylnaphthalene (V) and hence can only be represented by C-12, C-13 (or C-14) or C-15. Since iresin possesses a double bond which is in conjugation with the potential carboxyl group, only C-12 is left for consideration. This, *ipso facto*, also locates the hydroxyl group involved in lactone formation since of the three possible attachments of a five-membered, α,β-unsaturated lactone moiety originating at C-12 (of XIII or XIV), XV violates Bredt's rule and XVI possesses a double bond endocyclic to the lactone ring (II rather than the required I). This leaves XVII (or the variant with the angular methyl group at C-5) as the only reasonable expression for iresin, the remaining hydroxyl group occupying either position 1 (*cf.* VIII) or 13 (or 14) (*cf.* IX). Experimental proof for this structural proposal was provided by various oxidations.



XV



XVI

The key experiment proved to be the ozonolysis of iresin, which was expected to lead to rupture of the double bond and the introduction of two extra carbonyl groups ($C_{15}H_{22}O_4 \rightarrow C_{15}H_{22}O_6$). In point of fact, only one oxygen atom was added and the two hydroxyl groups originally present in iresin had disappeared. The ozonization product ($C_{15}H_{20}O_5$) gave a color with ferric chloride solution and exhibited an ultraviolet absorption maximum at 240 mμ (as compared to 224 mμ for iresin) which was shifted to 274 mμ in alkaline solution. Acetylation produced a monoacetate (subsequently shown to be XIXb) which had an ultraviolet absorption maximum at 218 mμ and which could be saponified to the original compound. These spectral properties are in excellent agreement with those predicted for an α-ketobutenolide[17] (XVIIIa) (and its enol acetate XVIIIb), which would be formed by ozonolysis of XVII. This would also explain the disappearance of the two hydroxyl groups in the ozonization product since if structure XVII (hydroxyl group at C-1 or C-13) were indeed correct, then the intermediate aldehyde XVIIIa would be perfectly located for internal acetal closure. On that basis, the final product should be represented by XIXa or XXa, depending upon the location of the second hydroxyl group (VIII or IX) in iresin and either structure is strain-free as well as fully compatible with the analytical, spectroscopic and chemical data. Complete confirmation for these views was provided by the observation that ozonolysis[18] of acetylidene iresin (XXI or XXIII)—the two hydroxyl groups now being blocked—afforded a crystalline product (XXII or XXIV) in which the presence of an α-ketobutenolide system as well as that of an aldehyde could be demonstrated. When the protecting group was removed by acid treatment, the intermediate immediately cyclized to the above described internal acetal (XIX or XX).

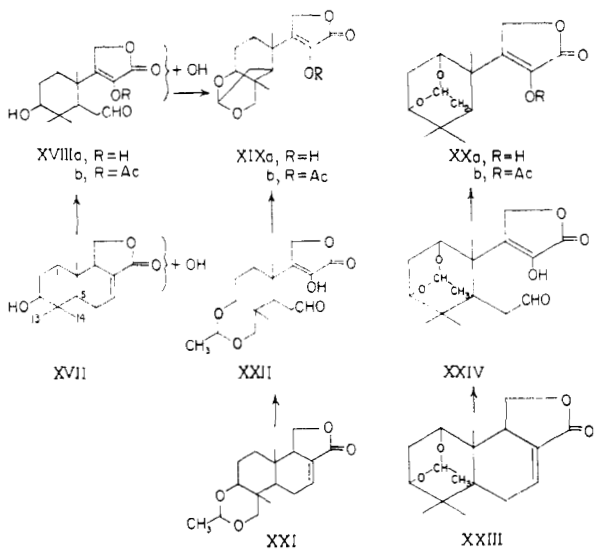
While the dehydrogenation results (formation of 1,5-dimethyl-2-naphthol (Vb)) favor locating the second hydroxyl group at C-13 or C-14 (IX) and consequently structures XIX, XXI and XXII, more conclusive evidence had to be provided concerning this important constitutional point.

Chromium trioxide oxidation of iresin in pyridine

(16) For symbolism see W. Klyne, *Chemistry & Industry*, 725 (1954).

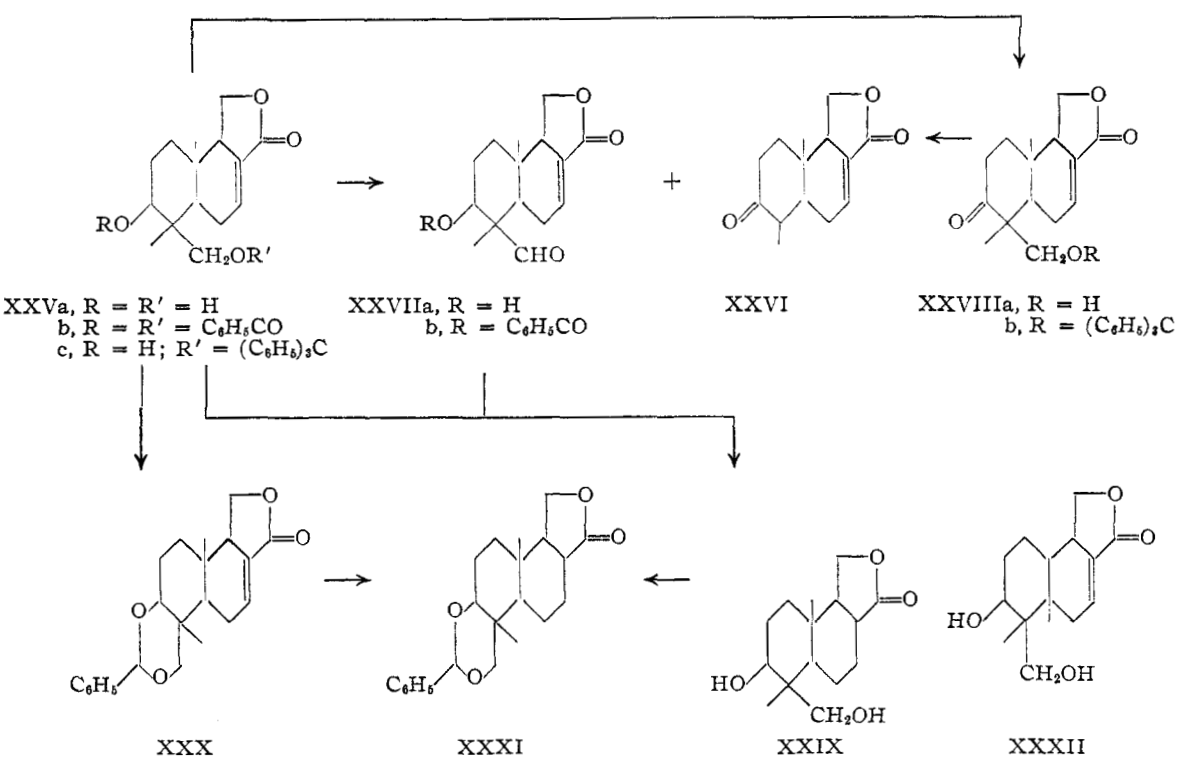
(17) *Cf.* A. Rossi and H. Schinz, *Helv. Chim. Acta*, **31**, 473 (1948); T. A. Geissman, THIS JOURNAL, **75**, 4008 (1953).

(18) This experiment was carried out by Dr. A. L. Nussbaum (see ref. 3).



solution[19] led to two products which could be separated chromatographically. The analysis of the less polar substance indicated the loss of CH_4O, which would only be compatible with a 13-nor-3-keto structure (XXVI). The presence of the unchanged α,β-unsaturated butenolide system and of an isolated keto group was demonstrated by the nor-ketone (XXVI) can be rationalized only *via* an intermediate β-keto aldehyde or β-keto acid and consequently requires the presence of a primary hydroxyl group in iresin (XXVa), thus eliminating the alternate formulation with a hydroxyl group at C-1 (VIII). The more polar product, although not giving a Tollens reaction, was shown to be the hydroxy-aldehyde XXVIIa rather than the corresponding hydroxy-ketone (XXVIIIa). The substance did not give formaldehyde upon base treatment, as would be expected[21] from the hydroxy ketone XXVIIIa upon retroaldolization, and did not form a trityl ether. On the other hand, it did yield a crystalline benzoate (XXVIIb) as well as a 2,4-dinitrophenylhydrazone, the ultraviolet absorption maximum of which was typical[20] ($\lambda_{max}^{CHCl_3}$ 354 mμ) of an aldehyde and produced dihydroiresin (XXIX) upon reduction with sodium borohydride.[7,8]

A related approach by another series of transformations[22] led to the same conclusion and involved conversion of iresin (XXVa) to its trityl ether XXVc followed by chromium trioxide–pyridine oxidation[19] to the keto-alcohol trityl ether XXVIIIb. Acid cleavage of the trityl ether was accompanied by reverse aldol condensation with formation of formaldehyde (isolated as the dimedone derivative) and the nor-ketone (XXVI).



ultraviolet and infrared spectroscopic data as well as by the formation of a yellow 2,4-dinitrophenylhydrazone ($\lambda_{max}^{CHCl_3}$ 364 mμ[20]). The formation of a

The above-described degradations are only compatible with structures XXV or XXXII for iresin, the single uncertainty being the location of the

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

(20) *Cf.* E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945); J. D. Roberts and C. Green, THIS JOURNAL, **68**, 214 (1946); C. Djerassi and E. Ryan, *ibid.*, **71**, 1000 (1949).

(21) *Cf.* D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1953).

(22) These three experiments were carried out by Dr. F. W. Donovan (see ref. 3) and will be published in part 3 of this series, together with other reactions of the glycol system of iresin.

angular methyl group[23] which could be at C-10 (XXV) or at C-5 (XXXII). Experiments are under way to settle this point but from a biogenetic standpoint, either structure would be acceptable since XXXII would almost certainly have arisen by methyl migration of a plant precursor based on structure XXV. It should be noted that iresin is the first sesquiterpene which follows an isoprene pattern found so far only among the higher terpenes (di- and triterpenes). In fact, the conspicuous absence of such a skeleton in the sesquiterpene series (prior to the isolation of iresin) led Ruzicka[24] to the plausible assumption that "this appears to indicate that the biogenesis of the steroids, diterpenes and triterpenes differs in some fundamental detail from that of the monoterpenes and sesquiterpenes." The present demonstration that iresin possesses such a structure makes this assumption unnecessary and to that extent iresin can be considered a missing link in terpene biogenesis.[25] Its importance in the terpene series has encouraged us to study its chemistry in detail and future papers will deal with additional transformations as well as with its relative[26] and absolute configuration.

Experimental[27]

Stability of Iresin toward Alkali.—A solution of 100 mg. of iresin and 0.45 g. of potassium in 20 cc. of dry *t*-butyl alcohol was heated under reflux for 16 hr. in an atmosphere of nitrogen. Dilution with water, concentration *in vacuo* and extraction with chloroform did not yield any material. Acidification of the aqueous phase followed by extraction with chloroform and recrystallization of the chloroform residue furnished 86 mg. of pure iresin. Virtually the same result was obtained when iresin was heated for 5 hr. with 20% methanolic potassium hydroxide solution.

Iresin Dibenzoate (XXVb).—A solution of 100 mg. of iresin (XXVa) in 1 cc. of pyridine was treated at 0° with 0.5 cc. of benzoyl chloride and was then left at room temperature overnight. After the addition of a small amount of methanol, the reaction mixture was worked up in the usual fashion and the dibenzoate (190 mg.) was recrystallized from acetone–ether, methanol and methanol–ether to give colorless prisms, m.p. 209.5–210.5°, $[\alpha]^{22}D$ −52° (*c* 1.07).

Anal. Calcd. for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.47; H, 6.36.

Benzylideneiresin (XXX).—A mixture of 50 mg. of iresin, 2 cc. of freshly distilled benzaldehyde and 80 mg. of powdered, freshly fused zinc chloride[9] was shaken at room temperature for 14 hours. The excess benzaldehyde was removed at 60° and 0.01 mm., and the residue was taken up in chloroform and washed well with sodium bicarbonate and water. The solid residue (66 mg.) was recrystallized successively from chloroform–petroleum ether and from acetone–ether to yield colorless needles, m.p. 242–244°, $[\alpha]D$ +70° (*c* 1.11).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.48; H, 7.52.

Cleavage of the benzylidene derivative was accomplished by heating under reflux 30 mg. of the substance with 20 cc. each of methanol and of 0.1 *N* sulfuric acid. All volatile material was removed *in vacuo* and the product was isolated by means of chloroform. Recrystallization from acetone–ether furnished 16 mg. of leaflets of iresin (m.p. 133–135°), identified by infrared comparison.

Benzylidenedihydroiresin (XXXI). (a) **From Dihydroiresin (XXIX).**—The required dihydroiresin (XXIX) could be prepared by hydrogenation[2] as well as by sodium borohydride[7] reduction of iresin in the following manner.

A solution of 40 mg. of iresin, 8 mg. of sodium borohydride and 6 cc. of 95% ethanol was kept for 6 hr. at room temperature and then acidified with dilute sulfuric acid to *p*H 3. After addition of 10 cc. of water and heating to 60° for one hr., the solution was concentrated and extracted with chloroform. The resulting crystalline residue (38 mg.) was recrystallized from acetone–ether and methanol–ether to give 30 mg. of needles of **dihydroiresin (XXIX)**, m.p. 142–145°, which was identified with an authentic sample[2] by infrared comparison and mixture melting point determination.

Conversion of 125 mg. of dihydroiresin (XXIX) into its benzylidene derivative XXXI was accomplished as described above for iresin and furnished 123 mg. of the desired product as two polymorphic forms, m.p. 188–191° (from acetone–ether) and m.p. 204–206° (from methanol), $[\alpha]D$ +19.5° (*c* 1.15).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.64; H, 8.09.

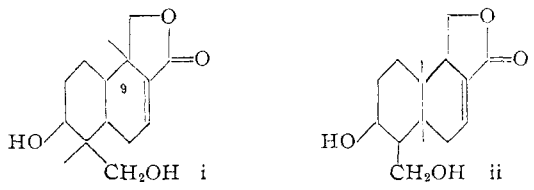
(b) **From Benzylideneiresin (XXX).**—One equivalent of hydrogen was taken up within 40 minutes when a solution of 2.66 g. of benzylideneiresin (XXX) in 250 cc. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 1.5 g. of 5% palladized charcoal. The catalyst was filtered, the solvent was removed and the crystalline residue (2.51 g.) was recrystallized from acetone–ether to yield prisms of benzylidenedihydroiresin (XXXI), identical with the material prepared according to procedure (a).

Benzylideneisodihydroiresin. (a) **From Isodihydroiresin.**[18]—Isodihydroiresin[2,28] (60 mg.) was treated in the usual fashion with benzaldehyde and zinc chloride to give 51 mg. of the benzylidene derivative, m.p. 236–239°. The analytical sample was recrystallized from methanol–acetone, m.p. 238–240°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.30; H, 7.88.

(b) **From Benzylidenedihydroiresin (XXXI).**—A solution of 185 mg. of benzylidenedihydroiresin in 8 cc. of 5% methanolic potassium hydroxide was kept for 24 hr. at room temperature and 2 *N* sulfuric acid was added followed by water. A precipitate separated which could be extracted only with difficulty with chloroform. Concentration of the washed and dried chloroform extract yielded colorless needles (153 mg.) which were filtered. This rather insoluble material gave an acid reaction toward litmus and its solubility increased during recrystallization attempts. It appears,

(23) Two other alternatives, which do not follow the isoprene rule (XIII or XIV) can be eliminated. The first one, involving placement of the angular methyl group at C-9 (i) can be ruled out since the ozonization product XIXa formed an enol acetate XIXb thus requiring a hydrogen atom at C-9 in iresin. The second structure (ii) can be excluded on two grounds: (a) the hydroxy-aldehyde corresponding to XXVIIa would very easily undergo dehydration and it would be expected that reaction with 2,4-dinitrophenylhydrazine would yield a derivative of an α,β-unsaturated aldehyde which was not the case. (b) In experiments in the isodihydroiresin series (to be published in part 3 of this series), it was possible to isolate a 3-keto-13-aldehyde and this did not give any color with ferric chloride which is only compatible with a β-ketoaldehyde which is completely substituted at the α-position.



(24) L. Ruzicka, *Experientia*, **9**, 357 (1953).

(25) The substance may be formed in the plant by a type of farnesol (or its equivalent) cyclization for which there exists experimental precedent (for leading references see G. Stork and A. W. Burgstahler, THIS JOURNAL, **77**, 5068 (1955)).

(26) In this connection it may be pertinent to mention that the formation of the cyclic acetal XIX is of considerable significance since this requires that the C-3 hydroxyl group, the carbon atom bearing the primary hydroxyl function and the 5–6 bond must all be *cis*.

(27) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform solution in 1 dcm. tubes. The microanalyses were carried out by Geller Laboratories (Hackensack, N. J.) and by Mr. Joseph F. Alicino (Metuchen, N. J.).

(28) Mr. Sumner Burstein has observed that when the alkaline isomerization of dihydoiresin is conducted in the earlier described manner (ref. 2) approximately 10–15% of isodihydroiresin can be extracted from the alkaline solution prior to acidification (*cf.* ref. 10).

therefore, that this was the open hydroxy acid which relactonized slowly. Crystallization from ethanol–ether furnished two fractions, a low melting material (50 mg., m.p. 183–200°) probably representing impure starting material, and 40 mg. of a more soluble substance. After one more recrystallization, this latter substance melted at 235–238°, undepressed upon admixture with benzylideneisodihydroiresin prepared according to (a). The infrared spectra of the two samples were identical.

Dehydrogenation of Iresin.—An intimate mixture of 1.04 g. of iresin and 2.0 g. of 5% palladized charcoal was heated for 2 hr. at 280–300° in an atmosphere of nitrogen. After cooling, the reaction mixture was extracted first with hot petroleum ether and then with ether and each extract was washed with sodium carbonate solution and with 20% sodium hydroxide solution. From the petroleum ether fraction there was obtained 118 mg. of neutral oil, no carbonate-soluble material and 45 mg. of phenolic solid (after acidification and ether extraction of the sodium hydroxide washings) with m.p. 150–164°. Similar examination of the ether fraction produced 90 mg. of hydrocarbon and 150 mg. of phenolic solid, m.p. 158–165°.

The two phenolic fractions were pooled, recrystallized twice from chloroform and then sublimed at 125° and 14 mm., whereupon a m.p. of 163.5–164.5° was observed. Identity was established by mixture melting point determination and infrared comparison with a specimen (m.p. 164–165°) of **1,5-dimethyl-2-naphthol (Vb)**[14] which was prepared by saponification of a sample of authentic benzoate Vc kindly furnished by Prof. O. Jeger, E.T.H., Zurich.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.74, 83.63; H, 7.00, 7.01.

A 31-mg. sample of the phenol Vb was benzoylated in the manner described above for iresin dibenzoate (XXXVb) and purified by chromatography on neutral alumina.[29] The crystals (20 mg.) eluted with hexane–benzene (4:1) were recrystallized from methanol to afford prisms of the **benzoate Vc**, m.p. 152–153°, undepressed upon admixture with an authentic specimen[14] of the same m.p. The infrared spectra were identical.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.29; H, 5.99.

The neutral oils from the original petroleum ether and ether extracts were pooled and distilled at 80–100° and 16 mm. The colorless distillate (122 mg.) was dissolved in 2 cc. of ethanol and treated with a hot ethanolic solution of 150 mg. of trinitrobenzene. The resulting yellow needles melted at 120–150° after recrystallization from ethanol, but could not be purified effectively by further recrystallization and the complex was decomposed, therefore, by passing a hot pentane solution of it through alumina. The regenerated hydrocarbon was partially crystalline and several recrystallizations from methanol and from pentane at −80° gave 6 mg. of colorless leaflets of **1,5-dimethylnaphthalene (Va)**, m.p. 77–79°. The undepressed (78–81°) mixture melting point with authentic[13] 1,5-dimethylnaphthalene (m.p. 81–81.5°), kindly provided by Dr. A. S. Bailey (Dyson Perrins Laboratory, Oxford University), and the coincidence of the infrared and ultraviolet absorption spectra established the identity of the dehydrogenation product.

Ozonolysis of Iresin.—A stream of dry oxygen containing 1.5% of ozone (flow rate *ca.* 180 cc./minute) was passed at −80° through a solution of 490 mg. of iresin dissolved in 60 cc. of ethyl acetate. A faint blue color appeared after 20 minutes and ozonization was continued for an additional 10 minutes. The excess ozone was removed *in vacuo*, 2 g. of 5% palladium–calcium carbonate catalyst was added and the mixture was shaken in an atmosphere of hydrogen for 15 minutes whereupon no more hydrogen was consumed and a starch–iodide test was found to be negative. The catalyst was filtered, the ethyl acetate solution was washed with sodium carbonate solution, dried, evaporated and crystallized (acetone–ether) yielding 160 mg. (31%)[30] of solid, m.p. 210–220°. Recrystallization from acetone–ether and from methanol–ether furnished colorless prisms of the **acetal XIXa** showing the following properties: m.p. 230–233°, $[\alpha]_D$ −26° (*c* 0.56); $\lambda_{max}^{CHCl_3}$ 2.82, 3.00, 5.69 and 5.95 μ; λ_{max}^{EtOH} 240 mμ, log ϵ 3.90; $\lambda_{max}^{0.01\ N\ KOH}$ 274 mμ, log ϵ 4.03; bluish-gray color with alcoholic ferric chloride solution, negative Tollens (room temperature) and Schiff reactions.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; mol. wt., 280. Found: C, 64.08, 64.22; H, 7.38, 7.06; neut. equiv. (titration with 0.1 *N* sodium hydroxide), 263.

Acetylation with acetic anhydride–pyridine and recrystallization from acetone–ether and from methanol–ether gave needles of the **enol acetate XIXb**, m.p. 149–151°, $[\alpha]_D$ −20° (*c* 0.53), λ_{max}^{EtOH} 218 mμ, log ϵ 4.02, no free hydroxyl absorption in the infrared.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; acetyl, 13.35. Found: C, 63.46; H, 6.72; acetyl, 13.75.

A 40-mg. sample of the above enol acetate dissolved in 5 cc. of 80% aqueous methanol containing 50 mg. of potassium bicarbonate was kept at room temperature for 4 days. The methanol was removed under reduced pressure and the remaining aqueous phase was extracted with chloroform. Evaporation of the washed and dried chloroform extract left 36 mg. of crystals which melted at 232–234° after recrystallization from methanol–ether and were shown to be identical with the acetal XIXa by the usual criteria.

Acetylideneiresin (XXI).—A mixture of 2.66 g. of iresin, 100 cc. of acetaldehyde and 2.5 g. of freshly fused zinc chloride was set aside at room temperature overnight. During this time, large, well-formed prisms separated which were filtered (1.74 g., m.p. 272–275°) and washed with ether. The filtrate was evaporated to dryness, the residue was taken up in ethyl acetate, washed, dried, evaporated and recrystallized to yield an additional 0.5 g. of satisfactory material. Recrystallization from methanol, chloroform–ethyl acetate and from acetone afforded large prisms, m.p. 283° (with variable, earlier sintering), $[\alpha]_D$ + 64° (*c* 1.0).

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.96; H, 8.25.

The relative insolubility of the acetylidene derivative and the ease with which it crystallizes would recommend it for the isolation of iresin from crude concentrates or mother liquors.

Ozonolysis of Acetylideneiresin (XXI).[18]—The ozonolysis of 825 mg. of the acetylidene derivative was carried out as described above for iresin itself except that a mixture of 50 cc. of chloroform and 250 cc. of ethyl acetate was used and the reaction extended over a 1.5-hr. period. The crude, semi-crystalline product (m.p. 140–210°) obtained upon concentration of the reaction mixture (after filtration of the palladium catalyst) was recrystallized from ethyl acetate–acetone and from acetone–methanol to give 275 mg. of colorless crystals of the **aldehyde XXII**, m.p. 222–225°, λ_{max}^{Nujol} 5.72–5.75 μ, λ_{max}^{EtOH} 233 mμ, log ϵ 3.92; $\lambda_{max}^{0.01\ N\ KOH}$ 272 mμ, log ϵ 3.72; positive Tollens and ferric chloride reactions.

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.76; H, 7.47.

A 53-mg. sample of the acetylidenealdehyde XXII was heated on the steam-bath for 3 hr. with 30 cc. of dioxane and 10 cc. of 0.2 *N* sulfuric acid, neutralized with barium carbonate and filtered. Evaporation to dryness and isolation with chloroform furnished 50 mg. of a crystalline residue which yielded 22 mg. of prisms, m.p. 230–234° after recrystallization from ethyl acetate–ether. The m.p. was depressed to 195–210° when this substance was mixed with the starting aldehyde XXII but remained unchanged when the compound was mixed with the cyclic acetal XIXa. Infrared spectral examination confirmed the identity.

Chromium Trioxide–Pyridine Oxidation of Iresin.—Iresin (3.8 g.) was added at 0° to the complex[19] derived from 4.0 g. of chromium trioxide and 100 cc. of pyridine and the mixture was kept at room temperature for 6 hr. whereupon 15 cc. of methanol was added. After 3 hr., the mixture was evaporated to dryness at 40° and 1 mm. and the dark red residue was extracted with ethyl acetate. The latter was

(29) All of the alumina used in this work was freed of alkali and reactivated (*cf.* J. v. Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1292 (1944)) in the following manner. Commercially available alumina (Alcoa, grade F-20), which showed a strongly alkaline reaction, was heated under reflux for 24 hr. with ethyl acetate, filtered and dried at 110°. The alumina was then washed continuously (Soxhlet extractor) for 48 hr. with hot water and then for 24 hr. with methanol. After drying at 110°, the alumina was reactivated at 180–190° for 30 minutes whereupon it exhibited activity I–II (H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941)) and was found to be neutral.

(30) On a larger scale (*e.g.*, 2.90 g. of iresin), the yield was reduced to 22%.

washed with dilute sulfuric acid, 10% sodium bicarbonate solution, water, dried and evaporated. The resulting gum (2.76 g.) was chromatographed on 85 g. of alumina[29] and led to two crystalline products.

Elution with benzene produced 350 mg. of solid (m.p. 127–137°) which was recrystallized successively from methanol, benzene–ether and ethanol to give colorless plates of the **13-nor-3-ketone XXVI**, m.p. 146–148°, $[\alpha]D$ +74° (*c* 0.43); λ_{max}^{EtOH} 224 mμ, log ε 4.11; $\lambda_{max}^{CHCl_3}$ 5.65 (lactone), 5.82 (ketone) and 5.90 μ (double bond[2]).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.71, 71.87; H, 7.74, 7.76.

The 2,4-dinitrophenylhydrazone of the nor-ketone XXVI, prepared by the acetic acid method,[31] was purified by chromatography on alumina and eluted with benzene–chloroform (1:1). Recrystallization from acetic acid and from ethanol gave fine yellow needles, m.p. 188–191°, $[\alpha]D$ +178° (*c* 0.80); $\lambda_{max}^{CHCl_3}$ 364 mμ,[20] log ε 4.34; $\lambda_{max}^{CHCl_3}$ 3.00 (NH), 5.67 (lactone) and 5.90 μ (double bond[2]).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.93; H, 5.34; N, 13.48.

The later benzene and benzene–chloroform (9:1) eluates from the original chromatogram furnished 725 mg. of crystals (m.p. 150–160°) which were subjected to recrystallization from acetone–ether, methanol and finally acetone. The resulting small prisms of the **hydroxy-aldehyde XVIIa** exhibited m.p. 164–166°, $[\alpha]D$ +39° (*c* 0.79); λ_{max}^{EtOH} 224 mμ, log ε 3.90; $\lambda_{max}^{CHCl_3}$ 2.82, 5.65, 5.82 and 5.90 μ, did not give a Tollens reaction at room temperature and did not form a trityl ether under conditions where iresin readily forms a monotrityl ether (XXVc).[22] No formaldehyde was produced under the basic conditions employed successfully with icterogenin,[21] thus excluding structure XXVIIIa.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.74; H, 7.73.

A small sample (21 mg.) of the hydroxy-aldehyde XXVIIa was treated with 4 mg. of sodium borohydride[7] in ethanol solution and was then processed as described above in the reduction of iresin. Recrystallization from acetone–ether led to 16 mg. of dihydroiresin (XXIX),[2] m.p. 142–146°, diacetate,[2] m.p. 208–210°.

The presence of the alcoholic function in the hydroxy-aldehyde XXVIIa was demonstrated by the formation of the **benzoate XXVIIb**, which was recrystallized from methanol and from acetone–ether, m.p. 193–195°, $[\alpha]^{16}D$ −45° (*c* 0.96).

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.95; H, 6.53.

The hydroxy aldehyde was converted into the **2,4-dinitrophenylhydrazone** by the acetic acid procedure[31] and crystallized from ethanol as orange-yellow prisms, m.p. 274–278° dec., $[\alpha]D$ +19° (*c* 0.95), $\lambda_{max}^{CHCl_3}$ 354 mμ,[20] log ε 4.12, $\lambda_{max}^{CHCl_3}$ 3.00, 5.67 and 5.90 μ.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.74; H, 5.44; N, 12.61. Found: C, 56.76; H, 5.59; N, 12.86.

DETROIT, MICHIGAN

(31) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF S. B. PENICK AND CO. AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Constitution of Samidin, Dihydrosamidin and Visnadin[1]

BY ERIC SMITH, NORMAN HOSANSKY, W. G. BYWATER AND EUGENE E. VAN TAMELEN

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Analytical and degradative evidence have been obtained which indicate the structure XIII for samidin (R = —CH=C-$(CH_3)_2$), dihydrosamidin (R = —$CH_2CH(CH_3)_2$) and visnadin (R = $CH(CH_3)CH_2CH_3$), potent vasodilatory agents isolated from the "visnagan" fraction of *Ammi visnaga*.

Ammi visnaga L. (bishop's weed), a plant indigenous to the Mediterranean regions, has been used in Egypt for centuries as a home remedy and spasmolytic. That the seeds contain biologically active substances other than the chromones khellin and visnagin[2] has been shown by Samaan,[3] whose "visnagan" fraction (the oil remaining after removal of all crystalline material) evidenced considerable vasodilatory activity. Visnagan was subsequently investigated by Cavallito and Rockwell,[4] who obtained, through chromatography on silica, a glassy solid to which the formula $C_{22}H_{26}O_7$ was ascribed. In repeating the chromatographic procedure, Smith, Pucci and Bywater[5] were able to secure two crystalline substances, designated as RI-778 (visamminol)[6] and RI-832. More recently,[5b] refined chromatographic techniques allowed isolation from the visnagan fraction of six crystalline components, of which RI-860, the so-called "yellow body," and visamminol did not possess biological activity in the test employed. The three remaining substances, all colorless and optically active, were strongly vasodilatory and consequently chemical investigations were initiated.

Elemental analyses indicated the molecular formula $C_{21}H_{22}O_7$ for substance RI-870 (m.p. 134–5°), which has been given the name *samidin*. RI-832 (m.p. 85–8°), called *visnadin*, and dihydro-RI-870 (m.p. 111–13°) are isomers possessing the formula $C_{21}H_{24}O_7$. The relationship between samidin and dihydro-RI-870 is more than empirical: the former substance absorbed one mole of hydrogen over platinum, giving rise to the latter. Therefore, dihydro-RI-870 may be properly designated *dihydrosamidin*.

The ultraviolet absorption spectra of all three substances (Table I) coincide at the maximum 323–324 mμ and at the minimum 264 mμ and are otherwise similar except that samidin absorbs strongly at lower wave lengths.

Comparison of ultraviolet curves with those of authentic chromones and coumarins provided at the outset strong evidence for the presence of a 7-oxygenated coumarin chromophore, an assignment

(1) Described preliminarily in *Chemistry & Industry*, 718 (1956).

(2) E. Spaeth and W. Gruber, *Ber.*, **71B**, 106 (1938); **74**, 1549 (1941).

(3) K. Samaan, *Quart. J. Pharm. Pharmacol.*, **4**, 14 (1931); **6**, 12 (1933); **18**, 83 (1945).

(4) C. G. Cavallito and H. E. Rockwell, *J. Org. Chem.*, **15**, 820 (1950).

(5) (a) E. Smith, L. A. Pucci and W. G. Bywater, *Science*, **115**, 520 (1952); (b) E. Smith, N. Hosansky and W. G. Bywater, Abstracts of the Medicinal Division, 24N, 126th Meeting of the American Chemical Society, New York, N. Y., September, 1954.

(6) W. Benzce and H. Schmid, *Experientia*, **10**, 12 (1954).