fied at 170° and formed a meniscus at 190–195°. The infrared spectra of the above sample and of a sample prepared by methanolysis of germine pentaacetate were identical. This material represents germine contaminated with small amounts of germine esters.

Anal. Calcd. for $C_{27}H_{43}O_9N$: C, 63.63; H, 8.50. Found: C, 63.23; H, 8.64.

In a volatile acid determination[18] 6.795 mg. consumed 0.40 ml. of 0.01 *N* NaOH; calcd. for germine monoacetate, 1.23 ml.

Methanolysis of Pentaacetylgermine.—A solution of pentaacetylgermine (109.4 mg.) in methanol (16 ml.) and water (8 ml.) was allowed to stand at room temperature for 18 hours. After removal of the solvents *in vacuo* the residue was taken up in a small amount of dry methanol and allowed to crystallize in the refrigerator. Three recrystallizations from methanol yielded material (9 mg.) which sintered at 165–170° but did not completely liquefy until at about 195°. The infrared spectrum of this material was identical with that of the material described in our earlier publication.[2]

Volatile acid determinations[18] on two independently prepared samples weighing 6.173 and 5.559 mg., respectively, yielded amounts of acid equivalent to 0.34 and 0.14 ml. of 0.01 *N* NaOH, respectively; calcd. for germine monoacetate: 1.21 and 1.09 ml., respectively.

Monoacetylneogermitrine.—Neogermitrine (32 mg.) was acetylated with acetic anhydride (1 ml.) and pyridine (1 ml.) for 15 hours at room temperature. Evaporation of the reagents *in vacuo* left a crystalline residue, which was recrystallized twice from acetone in which it is rather sparingly soluble. The thus purified product (22.9 mg.) melted at 248–249° (dec.) and had $[\alpha]^{24}\text{D}$ −88° (*c* 0.45 in pyridine).

Anal. Calcd. for $C_{35}H_{57}O_{12}N$: C, 63.41; H, 7.98. Found: C, 63.28; H, 7.95.

In a volatile acid determination[18] 14.57 mg. consumed 7.79 ml. of 0.01 *N* NaOH; calcd. for germine triacetate mono-α-methylbutyrate, 8.08 ml.

Acetylation of germidine under the above conditions yielded a product having the same properties.

Acknowledgments.—The authors are indebted to Mr. Harry Hulit and to Mrs. Anna Klingsberg for technical assistance, to Mr. Carl Sabo for the infrared spectra, to Mr. Irving Miller for some of the bioassays and to Mr. Joseph F. Alicino for the microanalyses.

NEW BRUNSWICK, NEW JERSEY

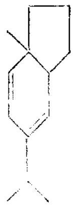
[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF HARVARD UNIVERSITY AND COLUMBIA UNIVERSITY]

Picrotoxin. II. The Skeleton of Picrotoxinin. The Total Synthesis of *dl*-Picrotoxadiene

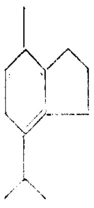
BY HAROLD CONROY[1]

Picrotoxadiene, a degradation product of picrotoxinin, has been synthesized by an unambiguous route, and shown to be *cis*-5-isopropyl-8-methylhydrin-4,6-diene. The skeleton of picrotoxinin has been shown to be that of 1,2,6,7,9-pentoxy-1,4-dicarboxy-5-isopropenyl-8-methylhydrindane. The unique relationship of picrotoxinin to the steroid family is pointed out.

Picrotoxadiene,[2] a hydrocarbon retaining the relevant features of the picrotoxin skeleton, has been obtained by a systematic, stepwise degradation of the unsaturated hydroxyketolactone, picrotoxinide,[2] in turn prepared by pyrolysis of dihydro-α-picrotoxininic acid.[3] It was shown that picrotoxadiene must have either of the structures (I) or (II), although I was favored because of the ultraviolet spectrum (λ_{max} 258 mμ, log ε 3.6; expected for I: 260 mμ, for II: 272 mμ) and because the substance offered resistance to dehydrogenation under mild conditions. Accordingly, a synthesis of 5-isopropyl-8-methylhydrin-4,6-diene was undertaken and is reported in detail herein.[4]

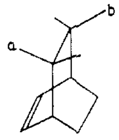


I

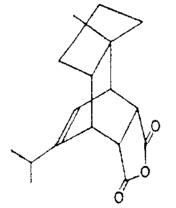


II

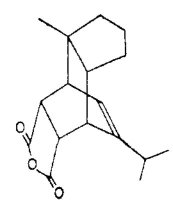
The structure (I) implies two forms differing in the configuration at the ring junction, *i.e.*, *cis* and *trans*. To decide which isomer should be the aim of synthesis, consider the following argument: *trans* groups, (a) and (b), protruding from the bicyclo[2.2.2]octene system (III) are held rigidly at opposed angles, but in the (hypothetical) adduct (IV)[5] from maleic anhydride and the *trans* form of I, *these must be joined to the same atom.* The *cis*-adduct (V)[5] is essentially strain-free. The strain



III



IV



V

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[1] National Institutes of Health Postdoctoral Fellow, 1950–1951. Present address: Department of Chemistry, Columbia University, New York City.

[2] For the first article of this series, see H. Conroy, THIS JOURNAL, **74**, 491 (1952).

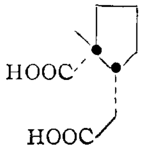
[3] P. Horrmann, *Ber.*, **46**, 2793 (1913).

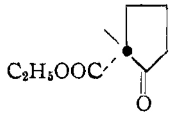
[4] First reported in a Communication to the Editor, H. Conroy, THIS JOURNAL, **73**, 1889 (1951).

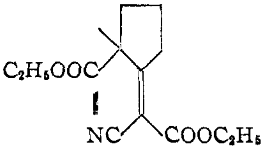
[5] Two points of stereochemistry implied in the expressions (IV) and (V) have been assumed for purposes of the discussion; although these points may be incorrectly represented, the argument is not thereby invalidated. Thus the configuration of the angular methyl group in each case has been almost arbitrarily assigned, while the anhydride grouping is shown *endo* only on the basis of the rule of Alder [K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937); K. Alder, *et al.*, *Ann.*, **514**, 1 (1934); K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938)].

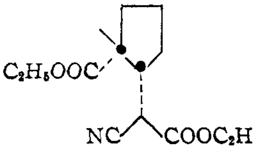
imposed by *trans* fusion of a five-membered ring to the bicyclic system of *boat* forms is far greater than that obtaining in the simple *trans*-hydrindane, in which the cyclohexane ring can assume the *chair* conformation. To the extent that strain in the adduct is mirrored in the transition state for addition, the Diels–Alder reaction with *trans*-diene would be expected to be uncommonly slow, while the equilibrium would favor the reactants rather than the product. Encouragement for the hypothesis that the diene is indeed *cis*-fused was found in the remarkable ease of addition of maleic anhydride to picrotoxadiene with formation of the adduct[2,4] in very high yield.

The synthesis of *cis*-5-isopropyl-8-methylhydrin-4,6-diene (I) was initiated with *cis*-2-methyl-2-carboxycyclopentane-1-acetic acid (VI), which has been described by Errington and Linstead.[6] The acid was prepared according to these authors, by catalytic hydrogenation of the Reformatsky product of 2-methyl-2-carbethoxycyclopentanone (VII) and ethyl bromoacetate, a method found, on repetition, to be entirely unsatisfactory for the manufacture of the relatively large amount of pure, *cis*-diacid needed in this study. Instead, 2-methyl-2-carbethoxycyclopentylidene cyanoacetic ester (VIII), which has been prepared[7] in high yield by the excellent method of Cope[8] from the keto-ester (VII), was hydrogenated in ethanol with Pd–charcoal to the saturated cyano-ester (IX). The product (IX) was readily saponified with concomitant decarboxylation to the pure *cis*-diacid (VI), identical with a sample obtained by the more tedious Linstead route. It is worthy of note that aluminum amalgam reduction of the cyano-ester (VIII) gives a saturated derivative which can be hydrolyzed to the *trans*-2-methyl-2-carboxycyclopentane-1-acetic acid.[6]

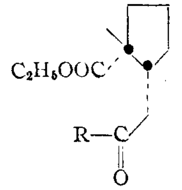

VI

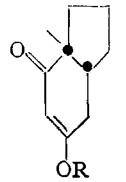

VII

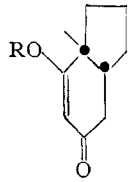

VIII


IX

The diester (X) was converted to the half-ester (XI) with one equivalent of ethanolic alkali, and thence to the acid chloride (XII). As anticipated, the infrared absorption spectrum of XII showed two characteristic carbonyl peaks, at 5.58 and 5.80 μ, due to the acid chloride and ester functions, respectively. Sodium malonic ester and XII in benzene gave the keto-triester (XIII), readily convertible by acid hydrolysis to the methyl keto-ester (XIV) in 57% over-all yield from the acid chloride. The methyl ketone (XIV) was characterized by its 2,4-dinitrophenylhydrazone, whose infrared spectrum exhibited the ester band at 5.80 μ as well as that intense peak at 6.2 μ associated with the system $C{=}N{-}N$. Cyclization of XIV with sodium hydride in benzene containing a trace of methanol afforded the crystalline *cis*-enol (XV or XVa) in 86% yield. The unusual infrared spectrum of the enol is recorded (Fig. 1). It is clear that no ambiguity arises from the (unlikely) possibility that partial hydrolysis of X gave, instead of XI, the alternative half-ester, for the latter would yield the same enol (XV or XVa) on being subjected to the sequence outlined.


X, R = OC$_2$H$_5$
XI, R = OH
XII, R = Cl
XIII, R = CH(COOC$_2$H$_5$)$_2$
XIV, R = CH$_3$


XV, R = H
XVI, R = C$_2$H$_5$


XVa, R = H
XVIa, R = C$_2$H$_5$

The enol (XV or XVa) was converted to its ethyl ether (XVI) by a simple acid-catalyzed esterification process in which the water formed in the equilibrium was removed by distillation with benzene. Of the two possible isomeric enol ethers which might conceivably be formed, it was assumed that XVI was actually the product, rather than XVIa, since the addition of ethanol would take place at the most accessible position. Lithium aluminum hydride reduction of the enol ether (XVI) afforded the carbinol (XVII) which when washed with cold, dilute acid gave the *cis*-hydrindenone (XIX) *sponte sua;* the hydroxy-ketone (XVIII) is undoubtedly an intermediate. The *cis*-8-methylhydrind-6-ene-5-one, obtained in 89% yield from XVI, was characterized by its 2,4-dinitrophenyl-

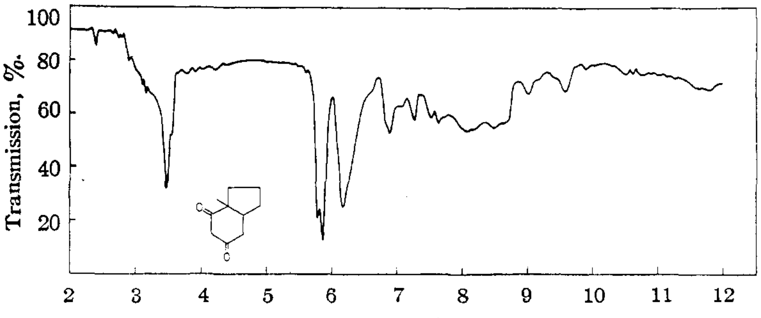


Fig. 1.—Infrared spectrum in chloroform.

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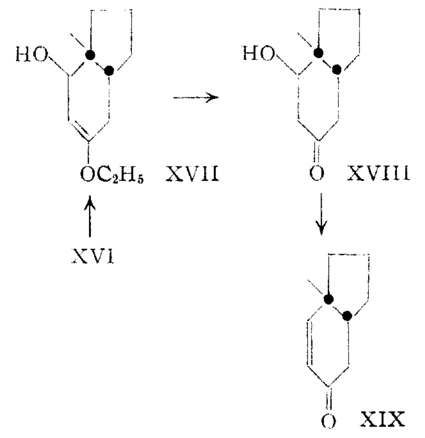
(6) K. D. Errington and R. P. Linstead, *J. Chem. Soc.*, 666 (1938).

(7) P. Bagchi and D. K. Banerjee, *J. Ind. Chem. Soc.*, **24**, 12 (1947).

(8) A. C. Cope, *et al.*, THIS JOURNAL, **63**, 3452 (1941).



hydrazone and by its reduction product, *cis*-8-methylhydrindan-5-one (XX), which gave a crystal-

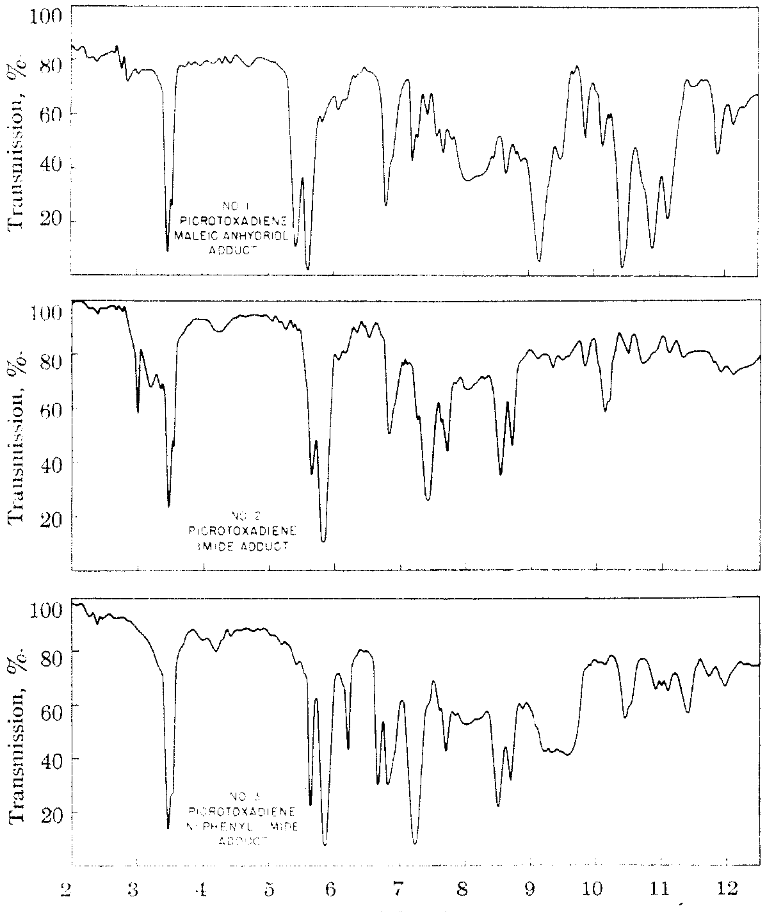
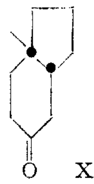
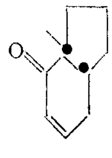


Fig. 2.—Infrared spectra in chloroform.

line, yellow α,α'-dibenzylidene derivative (λ_{max} 322 mμ, log ϵ 4.45; compare 2,6-dibenzylidene-3-methylcyclohexanone[9] at λ_{max} 328 mμ, log ϵ 4.54). Had the enol ether (XVIa) been subjected to lithium aluminum hydride reduction, the isomeric hydrindenone (XIXa) would have emerged, and this upon hydrogenation would have yielded a saturated ketone with only one active methylene group. The formation of the dibenzylidene deriv-



XX



XIXa

ative presents an unequivocal demonstration of the structures of the enol ether (*i.e.*, XVI) and the hydrindenone (XIX).

The addition of isopropyllithium[10] to the ketone (XIX) was expected to provide the diene (I), but proved to be rather complex. No unchanged hydrindenone was present in the reaction mixture when an excess of the lithium reagent was used, for the crude product gave an infrared spectrum lacking any trace of absorption at 6.0 μ, while XIX shows an intense peak at this wave length, due to the conjugated carbonyl. However the strong band at 5.82 μ in the spectrum of the product suggested the presence of a considerable proportion of *saturated* ketone, apparently formed by 1,4-addition to the conjugated system. Treatment of the crude product with excess acidic 2,4-dinitrophenylhydrazine gave an amorphous brown mass which was chromatographed on alumina, whence 59% of crystalline 7-isopropyl-8-methylhydrindan-5-one 2,4-dinitrophenylhydrazone as well as 23% of a fragrant liquid *hydrocarbon* were obtained. The hydrocarbon was superficially very similar to picrotoxadiene, but on treatment with maleic anhydride it was recovered unchanged without the formation of any detectable trace of adduct under the same mild conditions previously used for picrotoxadiene.

However an adduct formed readily when the synthetic hydrocarbon was treated with maleic anhydride and a catalytic quantity of sulfuric acid, and this adduct possessed an infrared absorption spectrum identical with that of picrotoxadiene–maleic anhydride. The spectrum is reproduced in Fig. 2 (curve 1).

The product of dehydration of the intermediate tertiary carbinol (XXI) is clearly the isomeric diene (XXII), which cannot react with maleic anhydride.[11]

In the presence of acid, XXII should be reversibly convertible to I, which can add the dienophile,

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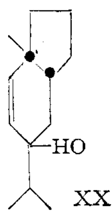
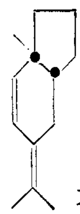
(9) H. S. French and M. E. T. Holden, THIS JOURNAL, **67**, 1240 (1945).

(10) H. Gilman, F. W. Moore and O. Baine, *ibid.*, **63**, 2480 (1941).

(11) The adduct which might so form would violate Bredt's rule (J. Bredt, *Ann.*, **437**, 1 (1924)) as extended to the bicyclo[3.3.1]-nonane system. The work of Prelog [V. Prelog, L. Ruzicka, P. Barman and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948); V. Prelog, P. Barman and M. Zimmerman, *ibid.*, **32**, 1284 (1949)] has shown that the minimum ring size permitting the inclusion of a double bond at the bridgehead is the bicyclo[5.3.1]system. The Diels–Alder reaction has been used repeatedly as a diagnostic method to distinguish those dienes capable of assuming the *s-cis* configuration ("Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 25).



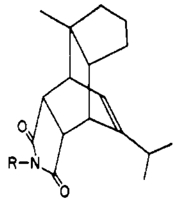
XXI



XXII

with consequent displacement of the equilibrium to the side of the adduct of I. The situation recalls the classical case of abietic acid, which reacts with maleic anhydride only at high temperatures, and then yields an adduct identical with that formed from the isomeric levopimaric acid in the cold.[12]

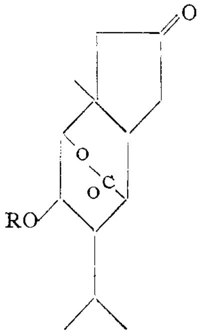
The synthetic, racemic *cis*-5-isopropyl-8-methylhydrin-4,6-diene–maleic anhydride adduct has not been obtained crystalline but has been transformed into the crystalline imide (XXIII) with ammonium carbonate and into the crystalline N-phenyl imide (XXIV) with aniline. The corresponding optically active imides were obtained from the picrotoxadiene adduct, and each of these gave an infrared spectrum (Fig. 2, curves 2 and 3) identical with that from the appropriate synthetic compound. The X-ray diffraction powder patterns of the racemic and optically active N-phenyl imides (XXIV) were found to be identical.[13]

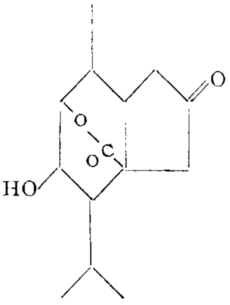


XXIII, R = H XXIV, R = phenyl

Perhaps the infrared spectra (Fig. 2) deserve special comment. That of the maleic anhydride adduct (curve 1) exhibits two sharp, characteristic peaks at 5.42 and 5.61 μ, caused by the cyclic anhydride grouping, while the imide (XXIII) (curve 2) generates two similar bands at longer wave lengths, *i.e.*, at 5.63 and 5.82 μ, in addition to the band at 3.00 μ, associated with the N–H stretching vibration. The N-phenyl imide (XXIV) (curve 3) gives two carbonyl bands almost identical with those from XXIII, but of course in XXIV the N–H vibration is missing, while a new band at 6.20 μ reflects the presence of the benzene ring.

Picrotoxadiene is clearly an optically active form of *cis*-5-isopropyl-8-methylhydrin-4,6-diene (I). Since it has been shown previously that an expression[2] for dihydropicrotoxinide (its progenitor) is limited to the two possibilities (XXV) and (XXVI) the study reported above now makes XXV the only acceptable formulation

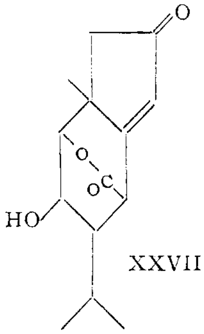




XXV, R = H
XXVIII, R = benzoyl

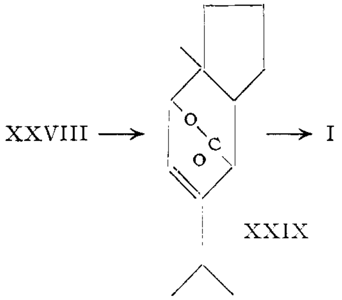
XXVI

for that substance, hence it follows that picrotoxinide can be represented only by XXVII.



XXVII

We can now deduce a plausible course for the unusual pyrolytic reaction from which picrotoxadiene was originally obtained. The first phase, elimination of benzoic acid from tetrahydrodesoxypicrotoxinide benzoate (XXVIII), leads to the unsaturated intermediate (XXIX) whose decomposition to



carbon dioxide and I is not unexpected.[13a] *The success of this reaction provides support for the con-*

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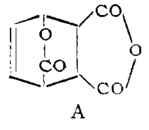
[12] L. Ruzicka, P. J. Ankersmit and B. Frank, *Helv. Chim. Acta*, **15**, 1289 (1932); L. Ruzicka and R. G. R. Bacon, *ibid.*, **20**, 1542 (1937); H. Wienhaus and W. Sandermann, *Ber.*, **69**, 2202 (1936); W. Sandermann and R. Höhn, *ibid.*, **76B**, 1257 (1942).

[13] Identity of the X-ray diffraction patterns is clear proof of the chemical identity of the samples, but the converse is untrue, *i.e.*, racemic and optically active samples of the same substance may give different X-ray patterns, since the pattern is a function of the crystallographic properties as well as the chemical structure. Thus the pattern of the *dl*-imide (XXIII) was sensibly similar to, but not identical with that of the optically active modification. More explicitly, the racemates in the two cases appear to be of different types. Since the m.p. (158–159°) of the racemic imide (XXIII) is higher than that (147–148°) of the corresponding *l*-form, this racemate can only be a *racemic compound*, which may well possess a different crystal structure from that of the active modification, but in the case of the N-phenyl imides, the racemic has a m.p. (151–152°) lower than that (178°) of the levorotatory, so the possibility that the racemate is simply a mechanical mixture of *d*- and *l*-crystals is not excluded. Obviously, if this is the fact, the X-ray method cannot distinguish between the various modifications.

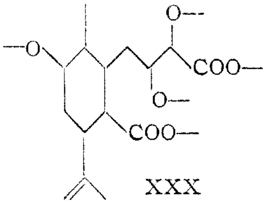
[13a] Thus the analogously constituted adduct (A) from α-pyrone and maleic anhydride, on gentle warming, readily yields the corresponding dihydrophthalic anhydride. *Cf.* O. Diels and K. Alder, *Ann.*, **490**, 257 (1931); B. Landau, Ph.D. Thesis, Harvard University, 1950.

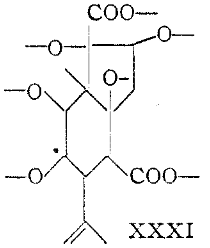


A

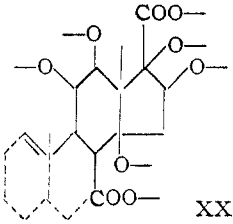
tention that the benzoyloxy and isopropyl functions in XXVIII are trans, since such pyrolytic elimination reactions proceed readily only if the groups to be split out can assume the *cis* configuration.[14,15]

Picrotoxinide retains the carbon–carbon bond missing[2] in the partial carbon skeleton (XXX), which has been proposed by Robertson, *et al.*,[16] in order to account for the formation of the substances picrotic acid and picrotonol, first obtained by Angelico[17] and Oglialoro[18] in the acid-catalyzed degradation reactions of picrotoxinin. The formation of picrotoxinide makes possible the modification of the carbon skeleton to that depicted in XXXI, and indeed, *this expression alone will serve satisfactorily to explain the variety of known transformations of picrotoxinin.* Thus alternative proposals may be considered to account for some of the acidic degradative sequences, or even for the formation of picrotoxinide, but these will not allow the elucidation of the third class of transformation products, *i.e.*, those isolated by Sutter and Schlittler.[19] It has already been shown[2,4] that the skeleton (XXXI) is entirely consistent with the formation of these substances.


XXX


XXXI

Although discussion of the evidence leading to a specific formula for picrotoxinin will be reserved at present, it is desirable at this juncture to point out the unique position of picrotoxinin in relation to the class of naturally occurring substances. The system (XXXI) has obvious terpenoid character: ten of its fifteen carbon atoms are present as a *p*-menthane unit, and yet it does not conform to the isoprene rule, even in the general sense. If, however, the skeleton is rewritten, as in XXXII, a connection with the *steroid* family becomes immediately evident, and provides grounds for speculation as to the biogenesis of picrotoxinin. It is not impossible, for example, that picrotoxinin represents an intermediate stage in phytosterol synthesis *in vivo*, or perhaps better, that it originates from a steroid by some kind of biological oxidative process. In any case, picrotoxinin is apparently the first example of a natural product bearing strong resemblance to the steroid class, but not retaining intact the steroidal carbon framework.


XXXII

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Experimental[20]

***cis*-2-Methyl-2-carboxycyclopentane-1-acetic Acid (VI).**—Ethyl 2-methyl-2-carbethoxycyclopentylidene cyanoacetate[7] (VIII) (115 g.) in 100 ml. of ethanol with 2 g. of 10% Pd–charcoal was hydrogenated in a low pressure shaker. When the correct amount of hydrogen had been absorbed, the catalyst was removed by filtration and the solution combined with that from another identical run. The oil left upon evaporation of the solvent was refluxed with 2100 ml. of 6 *N* hydrochloric acid for 12 hours. The hot acidic solution was filtered through charcoal and then allowed to cool slowly. The solid was recrystallized from hot water; the yield was 103 g., m.p. 110.1–110.5° (64%). A mixed m.p. with a sample prepared by the method of Errington and Linstead[6] was not depressed. **The diethyl ester** (X) b.p. 140 (5 mm.) was prepared in 93% yield according to the usual procedure with ethanol and concentrated sulfuric acid.

***cis*-2-Methyl-2-carbethoxycyclopentane-1-acetyl Chloride (XII).**—The diester (X) (197.8 g.) was refluxed for 15 minutes with a solution of 32.7 g. of sodium hydroxide in ethanol and enough water to give a homogeneous solution. The mixture was evaporated *in vacuo* to a thick sirup, which was taken up in water. The aqueous solution was washed with ether, acidified and the oily **half-ester** (XI) was extracted with ether. The residue left upon evaporation of the ether was dried by distillation with 300 ml. of benzene with a constant water separator. Thionyl chloride (120 g.) was added to the benzene solution and the mixture refluxed for two hours, when gases were no longer evolved. The solvent and excess thionyl chloride were removed and the acid chloride distilled *in vacuo;* yield 158 g. (81%) of material with b.p. 82° (0.15 mm.).

***cis*-2-Methyl-2-carbethoxycyclopentane-1-acetone (XIV).**—The acid chloride (XII) (135 g.) was added to a suspension made from 232 g. of ethyl malonate and 34.8 g. of sodium hydride in two liters of dry benzene. The mixture was refluxed with stirring for two hours, and then washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water. The benzene and the excess malonic ester were removed by distillation *in vacuo*, and the residue boiled with 300 cc. of 8 *N* sulfuric acid until the gas evolution stopped (6–7 hours). The oil was washed with sodium bicarbonate and then with water. The low boiling fraction obtained on vacuum distillation was fractionally redistilled. The yield was 70.0 g. (57%) of methyl ketone, b.p. 79° (0.15 mm.). **The 2,4-dinitrophenylhydrazone**, recrystallized from ethanol, formed golden yellow leaflets, m.p. 78.5–80.0°.

Anal. Calcd. for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16. Found: C, 54.96; H, 6.08.

Enol of *cis*-8-Methylhydrindan-5,7-dione (XV or XVa).—The methyl ketoester (XIV) (68 g.), 15.4 g. of sodium hy-

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[14] D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).

[15] This position receives strength from the additional fact that *ionic* dehydration of tetrahydrodesoxypicrotoxinide apparently cannot be accomplished. Thus, the latter was refluxed with phosphorus oxychloride in pyridine for ten hours and thereby converted merely to a water-soluble phosphoric ester; no trace of dehydration or decarboxylation product was formed.

[16] J. C. Harland and A. Robertson, *J. Chem. Soc.*, 937 (1939); D. Mercer, A. Robertson and R. S. Cahn, *ibid.*, 997 (1935).

[17] F. Angelico, *Gazz. chim. ital.*, **41**,i i, 337 (1911).

[18] A. Oglialoro, *ibid.*, **21**, ii, 213 (1891).

[19] M. Sutter and E. Schlittler, *Helv. Chim. Acta*, **30**, 403 (1947); **30**, 2102 (1947); **32**, 1855 (1949); **32**, 1860 (1949).

[20] All melting points are corrected.

dride, 300 ml. of dry benzene and 0.5 ml. of ethanol were refluxed with stirring. The hydrogen evolution was initially slow, but after about one-half hour a vigorous reaction began and a light yellow precipitate separated. The mixture was refluxed for two hours thereafter, then cooled and acidified, when the colorless enol crystallized immediately in long needles. The solid (50 g.) was recrystallized from dioxane–water, whence 46 g. (86.3%) of product, m.p. 145°, was obtained. For analysis a sample was recrystallized from ethanol–water: colorless needles, m.p. 146.3–146.5°. The substance was insoluble in aqueous bicarbonate but readily soluble in potassium carbonate solution. Its infrared spectrum is recorded in Fig. 1.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.11; H, 8.57.

***cis*-5-Ethoxy-8-methylhydrind-5-ene-7-one (XVI).**—A mixture of 45.0 g. of the enol (XV or XVa), 60 ml. of ethanol and 1.5 ml. of concentrated sulfuric acid in 150 ml. of benzene was refluxed with a constant water separator for ten hours, when no more water was formed. Some of the benzene was distilled off and the solution remaining was washed thoroughly with cold potassium carbonate solution, then with water. Acidification of the aqueous extracts gave 9.2 g. of unchanged enol. The benzene layer was evaporated and the residue distilled. Thirty-five grams of colorless liquid, b.p. 85° (0.08 mm.) was obtained; this represents an 84% yield based upon unrecovered enol. For analysis a sample was distilled, and gave $n^{25}\text{D}$ 1.5094.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.51; H, 9.52.

***cis*-8-Methylhydrind-6-ene-5-one (XIX).**—Thirty-two grams of the enol ether (XVI) was dropped into four grams of lithium aluminum hydride in 200 ml. of ether over a period of ten minutes, without cooling. The mixture was stirred for one-half hour, then poured into ice and acidified. The ether extract was washed with water, the solvent removed, and the oil distilled, whence 22 g. (89%) of fragrant ketone with the b.p. 50° (0.1 mm.) was obtained. For analysis a sample was redistilled, and gave $n^{25}\text{D}$ 1.5003.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.36; H, 9.46.

The 2,4-dinitrophenylhydrazone formed fiery orange-red leaflets from ethanol and gave the m.p. 138.3–139.2°.

Anal. Calcd. for $C_{16}H_{18}O_4N_4$: C, 58.16; H, 5.49. Found: C, 57.93; H, 5.41.

***cis*-8-Methylhydrindan-5-one (XX).**—Two grams of the hydrindenone (XIX) in 30 ml. of methanol was hydrogenated with platinum oxide at atmospheric pressure. The theoretical amount of hydrogen was absorbed in 45 minutes. The solution was filtered and the filtrate divided into two portions. One portion was used for the preparation of the **2,4-dinitrophenylhydrazone**, which formed orange-yellow needles and was recrystallized from ethanol. It had the m.p. 126–128°.

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 58.08; H, 6.17.

A sample of the ketone was distilled for analysis, and gave the b.p. 57° (1 mm.), $n^{25}\text{D}$ 1.4794.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.80; H, 10.70.

The remaining portion of the ketone was treated with excess benzaldehyde in the presence of a small amount of alcoholic potassium hydroxide. After one week at room temperature, the excess benzaldehyde was removed and the yellow **4,6-dibenzylidene-8-methylhydrindan-5-one** was recrystallized from aqueous methanol. The yellow needles had the m.p. 118.5–119.5° and λ_{max} 322 mμ, log *E* 4.45 (methanol).

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 87.82; H, 7.42.

***cis*-5-Isopropylidene-8-methylhydrind-6-ene (XXII).**—To a solution of isopropyllithium[10] prepared under hydrogen from 1.1 g. of finely cut lithium and four g. of isopropyl chloride in 50 ml. of dry, unsaturate-free 30–60° petroleum ether, was added 3.8 g. of the hydrindenone (XIX). A vigorous reaction ensued, and after ten minutes the product was poured into water. The organic layer was washed with dilute acid, then with water, and evaporated. The infrared spectrum of the residual oil indicated the presence of a considerable amount of a saturated ketone. The oil was taken up in ethanol and treated at the reflux temperature with five g. of 2,4-dinitrophenylhydrazine and one drop of concentrated hydrochloric acid for one hour. The solvent was removed, finally *in vacuo*, and the amorphous brown residue remaining was taken up in petroleum ether–benzene and chromatographed on 150 g. of alumina. The fractions eluted with petroleum ether totaled 1.33 g. (23%) of a colorless liquid which showed no carbonyl absorption in the infrared and which was characterized by its reaction with maleic anhydride (*vide infra*). The principal dinitrophenylhydrazone fraction, eluted with benzene, crystallized readily in yellow needles; yield 7.3 g. (59%). For analysis a sample was recrystallized from ethanol and had the m.p. 140.5–144.5°. It is apparently **7-isopropyl-8-methylhydrindan-5-one 2,4-dinitrophenylhydrazone.**

Anal. Calcd. for $C_{19}H_{26}O_4N_4$: C, 60.95; H, 7.00. Found: C, 60.97; H, 7.04.

***cis*-5-Isopropyl-8-methylhydrin-4,6-diene-maleic Anhydride.**—The hydrocarbon (XXII) was treated with maleic anhydride under the same conditions used previously for picrotoxadiene,[2] but after removal of the unreacted maleic anhydride, the hydrocarbon was recovered. However, when the reaction was repeated with the addition of a trace of concentrated sulfuric acid an adduct was formed in good yield. Although the adduct could not be induced to crystallize, it was converted to the crystalline *dl*-imides (XXIII) and (XXIV) as described below. The infrared spectrum of the adduct (Fig. 2, curve 1) was identical with that of picrotoxadiene–maleic anhydride.

Natural and Racemic Imides (XXIII).—Recrystallized picrotoxadiene-maleic anhydride[2] (V) (200 mg.) was intimately ground with 4 g. of ammonium carbonate and the solid mixture heated at 130° until all the carbonate had vaporized. The residue was taken up in chloroform, another four g. of ammonium carbonate was added to the chloroform solution, and, after the chloroform had been removed the solid was again heated at 130° until the carbonate had vaporized. The residue was again dissolved in chloroform and the process repeated a third time. After filtration the chloroform solution of the residue was evaporated to dryness and the substance was triturated with petroleum ether, when the imide was obtained crystalline. The yield of crude solid imide was 160 mg. For analysis a sample was recrystallized from ethanol–water. The fine needles had the m.p. 147.6–148.3°, $[\alpha]^{20}\text{D}$ −78° (chloroform, *c* 3.1).

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.63; H, 8.55; N, 5.28.

The synthetic, racemic maleic anhydride adduct obtained above was treated with ammonium carbonate in exactly the same manner. The imide consisted of leaflets, recrystallized from ethanol–water, with the m.p. 158.2–159.0°.

Anal. Found: C, 74.59; H, 8.36; N, 5.11.

The infrared absorption spectra (Fig. 2, curve 2) of these imides were identical. The X-ray diffraction powder patterns were not identical.[13] A mixed m.p. gave the range 147–158°.

Natural and Racemic N-Phenylimides (XXIV).—Recrystallized picrotoxadiene-maleic anhydride (V) (200 mg.) was warmed with one cc. of aniline on the steam-bath for 15 minutes. The semi-solid product was triturated with dilute hydrochloric acid, whence the N-phenylimide crystallized shortly. For analysis a sample was recrystallized from ethanol–water. The fine needles had the m.p. 177.8–178.1°, $[\alpha]^{20}\text{D}$ −42° (chloroform, *c* 2.5).

Anal. Calcd. for $C_{23}H_{27}O_2N$: C, 79.04; H, 7.79; N, 4.01. Found: C, 79.57; H, 7.80.

The racemic N-phenylimide was obtained in the same way from the synthetic adduct described above. For analysis a sample was recrystallized from ethanol–water. The fine needles had the m.p. 151–152°.

Anal. Found: C, 79.04; H, 7.83; N, 3.88.

The infrared absorption spectra (Fig. 2, curve 3) of these N-phenylimides were identical. The X-ray diffraction powder patterns were identical. A mixed m.p. gave the range 151–175°.

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