that kynurenine as well as *o*-aminoacetophenone were formed in the alkaline solution. Irradiation of tryptophan as such or in proteins in the presence or absence of photosensitizers has also been studied.[3-7] It has been demonstrated that tryptophan is converted to 3-indoleacetic acid by the action of ultraviolet radiation.[8] However, autoxidation products other than the above three have rarely been found. Witkop, *et al.*,[9] have recently suggested that tryptophan might be oxidized to formylkynurenine in acidic (or neutral) solution.

We have studied the photoöxidation of tryptophan in slightly acidic aqueous solution in the following three cases: (1) in the absence of metal ions, (2) in the presence of ferrous ion and (3) in the presence of methylene blue as sensitizer. In every case kynurenine as well as 3-hydroxykynurenine were detected as photoöxidation products. On the contrary, only kynurenine was found in the dark autoxidation.

Experimental

L-Tryptophan (m.p. 289°) was dissolved in distilled water free of metal ions to give a 0.1% solution (*p*H 5.98). In a 20-cc. non-fluorescent test-tube, 5 cc. of the solution was exposed to sunlight (May) at 33 ± 2° for 10 hours. During the photoöxidation the *p*H of the solution increased from 5.98 to 6.67 in 10 hours. The photoöxidized solution was chromatographed on paper (developer: 4 *n*-butyl alcohol, 1 glacial acetic acid and 5 water) after 5 and 10 hours, respectively (22°). In both cases two fluorescent substances were found which gave a purple color with ninhydrin. One exhibited R_f 0.5 and the other R_f 0.45. The former fluoresced blue, the latter bluish-green under ultraviolet light (365 mμ). Both spots were respectively eluted with as little as possible warm water and the ultraviolet absorption spectrum of each was examined by means of a Beckman model DU spectrophotometer. The former had absorption maxima at 360 and 259 mμ and the latter at 273 and 235 mμ. These properties, respectively, were in accord with that of kynurenine and 3-hydroxykynurenine. The two solutions were also positive in Otani-Honda's reaction (kynurenine) and Ehrlich's diazotization reaction (3-hydroxykynurenine), respectively.

In an experiment done in the dark under the same conditions, only kynurenine was detected.

When ferrous sulfate ($FeSO_4 \cdot 7H_2O$) (10%) or methylene blue was added to the tryptophan solution and the photooxidation carried out under the above conditions, the formation of 3-hydroxykynurenine was more or less enhanced. In the methylene blue-sensitized photoöxidation a 100-watt Mazda tungsten lump can be used in place of sunlight. With ferrous sulfate, 3-hydroxykynurenine was found even in the dark. The oxidation-reduction potential in each case was measured by means of the Shimazu model K-2 potentiometer every hour at 20° during the autoxidation. The results showed that more oxidation took place under illumination than in the dark, since in the illuminated reactions much more positive oxidation-reduction potentials were observed.

Acknowledgment.—The authors are indebted to Professor R. Oda for his helpful discussions.

DEPARTMENT OF INDUSTRIAL CHEMISTRY
FACULTY OF ENGINEERING
KYOTO UNIVERSITY, KYOTO, JAPAN

(3) H. Gaffron, *Biochem. Z.*, **179**, 157 (1926).
(4) F. Lieben, *ibid.*, **184**, 453 (1927).
(5) A. W. Galston, *Science*, **111**, 619 (1950).
(6) L. Weil, W. G. Gordon and A. R. Buchert, *Arch. Biochem.*, **33**, 90 (1951).
(7) Y. Obata and S. Sakamura, *J. Chem. Soc. (Japan) Pure Chem. Section*, **73**, 811 (1952).
(8) A. Berthelot, *et al.*, *Compt. rend.*, **206**, 699 (1938).
(9) B. Witkop, *et al.*, *Experientia*, **8**, 36 (1952).

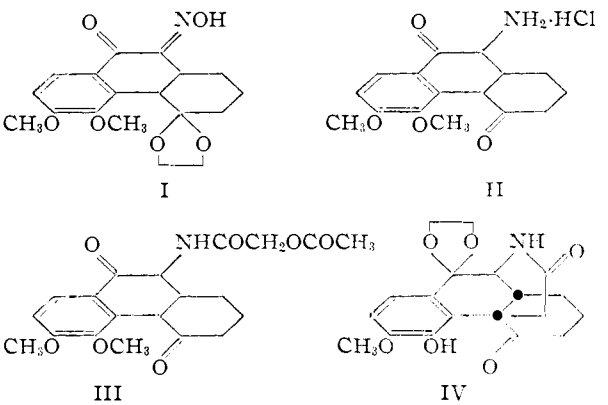
COMMUNICATIONS TO THE EDITOR

THE SYNTHESIS OF MORPHINE

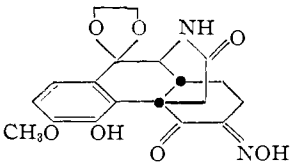
Sir:

We wish to report the synthesis of dihydrothebainone and its resolution to the optically active base. This synthesis is equivalent to that of morphine since the steps involved in the conversion of dihydrothebainone to morphine have been accomplished by other investigators.[1]

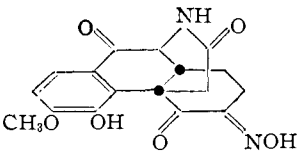
The 4-ethylene glycol ketal of 1,2,3,4,4a,9,10,10a-octahydro-4,9-dioxo-5,6-dimethoxy-10-hydroxyiminophenanthrene (I)[2] was reduced catalytically to give the amine hydrochloride, II, m.p. 210–212° (dec.), found C, 58.0; H, 6.2; Cl, 10.9. Treatment with acetylglycolyl chloride in chloroform containing pyridine afforded the amide, III, m.p. 169–171°, found C, 61.8; H, 5.8; N, 3.6. This was cyclized under conditions similar to those described for the unmethoxylated analog,[2] to yield the lactam, IV, m.p. 244–246°, found C, 63.2; H, 5.7, N, 4.0; active hydrogen, 1.7. Demethylation of the C_5 methoxyl group occurs during the cyclization. Treatment with *n*-amyl nitrite in the presence of sodium ethoxide gave the hydroxyimino derivative, V,[3] m.p. 265–266° (dec.), found C, 58.6; H, 5.2; N, 7.1. Removal of the ketal blocking group with dilute acid afforded the mono-oxime diketone, VI, m.p. 212–214° (dec.), found C, 59.3; H, 4.5; N, 7.9.



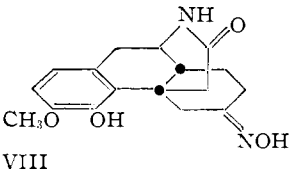
(1) M. Gates and G. Tschudi, THIS JOURNAL, **74**, 1109 (1952); C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930); H. Rapoport, C. H. Lovell and B. M. Tolbert, THIS JOURNAL, **73**, 5900 (1951).
(2) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1624 (1953)
(3) *Cf.* D. Elad and D. Ginsburg, *J. Chem. Soc.*, 2664 (1953).



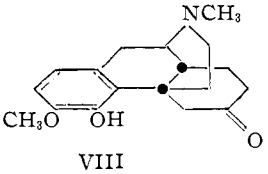
V



VI



VIII



VIII

Modified Huang-Minlon reduction of VI removed the two free carbonyl groups and yielded the oxime-lactam, VII, m.p. 210–213°, which depresses the m.p. of VI. Acid treatment hydrolyzed the oxime to the ketone which was obtained as a viscous oil. Lithium aluminum hydride reduction in tetrahydrofuran gave an oily mixture of epimeric *des*-N-methyl-dihydrothebainols which was methylated by means of formaldehyde–formic acid to a mixture of epimeric dihydrothebainols. Oxidation with potassium *t*-butoxide in the presence of benzophenone afforded racemic dihydrothebainone (VIII) whose infrared spectrum was indistinguishable from that of *l*-dihydrothebainone. Treatment of the racemate in acetone solution with one-half molar equivalent of D-tartaric acid gave *l*-dihydrothebainone D-tartrate, found C, 58.2; H, 6.2; $[\alpha]_D^{21}$ + 18.2° (*c* 1.1 water). Generation of the free base with ammonium hydroxide gave *l*-dihydrothebainone hydrate, m.p. 121–151°, $[\alpha]_D^{21}$ −75° (*c* 0.77 alc.).[4]

(4) C. Schöpf and L. Winterhalder, *Ann.*, **452**, 232 (1927), report $[\alpha]_D^{18}$ −72.5° (abs. alc.); A. Skita, *et al.*, *Ber.*, **54**, 1560 (1921), report $[\alpha]_D^{20}$ −80.12° (alc.).

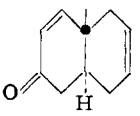
DANIEL SIEFF RESEARCH INSTITUTE
WEIZMANN INSTITUTE OF SCIENCE DOV ELAD
REHOVOT, ISRAEL DAVID GINSBURG

RECEIVED NOVEMBER 23, 1953

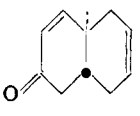
A DIRECT STEREOCHEMICAL CORRELATION OF A SESQUITERPENE ALCOHOL WITH THE STEROIDS

Sir:

The availability of the pure enantiomeric ketones (I) and (II), and the conversion of the *levorotatory*

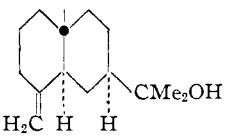


I

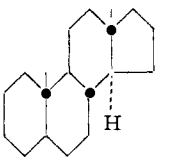


II

isomer into natural steroids,[1] provides an opportunity for effecting the direct stereochemical correlation of the steroids with other groups of natural products. We wish to record the results of such a study in the case of the sesquiterpene alcohol β-eudesmol (III).[2]

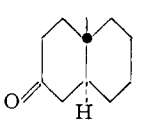


III

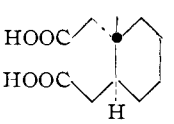


IV

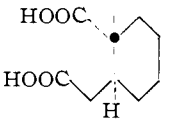
If it be accepted that the absolute configuration of the natural steroid nucleus is correctly represented by (IV),[3] the levorotatory bicyclic ketone [m.p. −3.7°, b.p. 74–78° (1 mm.), $[\alpha]^{25}D$ −239° (*c* 2.0, $CHCl_3$); $\lambda_{max.}$ 226 mμ (ε = 9600) must be (I)]. This ketone has now been converted into three further reference compounds: the *trans*-9-methyl-3-decalone (V), and the diacids (VI) and (VII). Hydrogenation of (I) in methanol over Pd-$CaCO_3$



V



VI

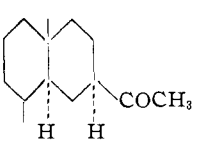


VII

leads to (V) [b.p. 123–125° (10 mm.), $[\alpha]D$ +33° (*c* 1.14, $CHCl_3$), calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.27; H, 10.76], characterized further as the *dinitrophenylhydrazone* [m.p. 144–144.5° (from EtOH), $[\alpha]D$ +24° (*c* 0.83, $CHCl_3$), calcd. for $C_{17}H_{22}O_4N_4$: C, 58.94; H, 6.40. Found: C, 58.97, H, 6.51]. Oxidation of (V) by boiling concentrated nitric acid gave (VI) [m.p. 194–195.5° (from Me_2CO/hexane), $[\alpha]D$ −31° (*c* 1.14, Me_2CO), calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.44; H, 8.62]. Treatment of (V) with bromine in acetic acid gave the *2-bromoketone* [m.p. 136.5–138°, $[\alpha]D$ +29° (*c* 4.5, $CHCl_3$), calcd. for $C_{11}H_{17}OBr$: C, 53.89; H, 6.99; Br, 32.59. Found: C, 53.69; H, 7.19; Br, 33.44], which was converted to 9-methyl-Δ^1-octalone-3 *dinitrophenylhydrazone* [m.p. 193–194.7°, calcd. for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.39; H, 5.87; N, 16.74, $\lambda\lambda_{max.}$ 256.5 mμ (ε = 17,000) and 383 mμ (ε = 29,000)], or less satisfactorily, to the corresponding *semicarbazone* [m.p. 174–176°, calcd. for $C_{12}H_{19}ON_3$: C, 65.13; H, 8.65; N, 18.99. Found: C, 64.95; H, 8.67; N, 19.15]. The free octalone, on oxidation with potassium permanganate, gave the diacid (VII)[4] [m.p. 146–147°, $[\alpha]D$ −11° (*c* 1.0, Me_2CO), calcd. for $C_{10}H_{16}O_4$: C,

(1) The preparation of these ketones and conversion of the levorotatory isomer into natural steroids, through methods based on those developed earlier with racemic intermediates [Woodward, Sondheimer, Taub, Heusler and McLamore, THIS JOURNAL, **74**, 4223 (1952); *cf.*, also, Barkley, Farrar, Knowles and Raffelson, *ibid.*, **75**, 4110 (1953)], was carried out in the laboratories of the Monsanto Chemical Company in St. Louis. We are deeply indebted to Dr. Oliver Weinkauff and his associates for communicating their results to us privately, and for providing us with generous samples of the levorotatory ketone.

(2) As to relative configurational relationships: for *trans* locking of rings, *cf.* D. H. R. Barton, *Chem. and Ind.*, 664 (1953), and W. Klyne, *J. Chem. Soc.*, 3072 (1953); the placing of the α-hydroxy*iso*propyl group in the equatorial position is based upon the configurational stability of the ketone i [$[\alpha]D$ +3° (*c* 1.95, $CHCl_3$), dinitrophenylhydrazone, m.p. 141–142°]; the ketone is reconverted to dihydroeudesmol with methylmagnesium iodide [*cf. Helv. Chim. Acta*, **14**, 1132 (1931)], and on treatment with 10% alcoholic potash at 210° gives an alcohol [m.p. 65°, $[\alpha]D$ +24° (*c* 0.50, $CHCl_3$)] which is reoxidized to (i) by chromic acid.



i

(3) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953).

(4) The use of this acid in establishing other stereochemical correlations will be reported in further communications.