[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF HARVARD UNIVERSITY AND IOWA STATE COLLEGE]

O-Alkylation of 3-Acyloxindoles

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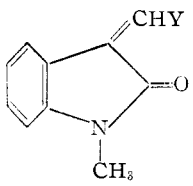
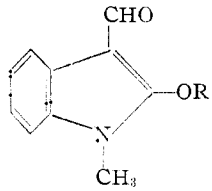
By the use of infrared and ultraviolet spectra, the previously proposed structure of the O-methylation product of 1-methyl-3-hydroxymethyleneoxindole is shown to be incorrect. The actual structure of this compound and of its reaction products is presented, and new structural formulations for various O-alkylated 3-acyloxindoles are proposed.

In preliminary experiments, which laid the groundwork for the subsequent elegant synthesis of physostigmine[1] and attempted synthesis of oxytryptophan,[2] Julian and co-workers had the occasion to alkylate 1-methyl-3-formyloxindole (Ib).[2,3] Since this compound possesses a β-dicarbonyl system,[4] alkylation might be expected at any one of three centers—the central carbon atom or either of the two oxygen atoms. When the reaction was carried out by refluxing the sodio salt of Ib with an alkyl halide in acetone—conditions generally favoring O-alkylation—one product was obtained almost exclusively. Julian assigned structure II to this compound mainly on the basis of its ability to form a bisulfite addition product and a positive Tollens test. However, in all analogous cases of O-alkylation of unsymmetrical β-dicarbonyl compounds containing as one of the carbonyl linkages a formyl residue, the introduction of the alkyl group takes place on the formyl oxygen atom. Consequently the compound expected from O-methylation of 1-methyl-3-hydroxymethyleneoxindole (Ib) should be 1-methyl-3-methoxymethyleneoxindole (Ic). Furthermore, the latter formulation does not conflict with an interpretation of the qualitative tests on the methylated compound. Thus since it is able to yield a crystalline complex with sodium iodide,[3] it might be expected to complex also with sodium bisulfite and perhaps other inorganic salts.[5] Likewise, the positive Tollens test must be due to oxidation at the site of the methoxymethylene group, or due to prior hydrolysis in the ammoniacal medium followed by oxidation of the thus-liberated hydroxymethylene group.



I

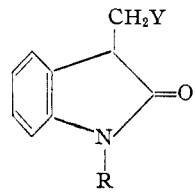
a, Y = H
b, Y = OH
c, Y = OMe
d, Y = OEt



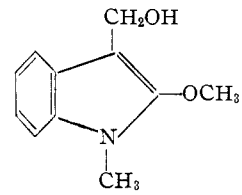
II

a, R = H
b, R = Me
c, R = Et

On the basis of formula IIb for the O-methylated product, Julian proposed IV as the structure of its hydrogenation product.[2] If, however, the methylation product be assumed to be Ic, its dihydro derivative must be 1-methyl-3-methoxymethyloxindole (IIIc).



III



IV

a, Y = H, R = CH_3
b, Y = OH, R = CH_3
c, Y = OMe, R = CH_3
d, Y = NMe_2, R = H

This hydrogenated compound was found to be hydrolyzable although no conditions of hydrolysis or chemical and physical properties of the hydrolyzed product were reported.[6] The proposed structure IIIb for this hydrolysate[3] is questionable since such a compound might undergo β-elimination of its hydroxyl group easily so as to yield 1-methyl-3-methyleneoxindole (Ia) which, in turn, would dimerize, polymerize or interact with IIIb in a Michael addition. This series of reactions is totally analogous to the recently reported attempts to synthesize oxygramine (IIId).[7-9] When oxindole is treated with formaldehyde and dimethylamine in an acetic acid solution, no Mannich base (IIId) is isolated but instead the dimethylamino group is eliminated and the resultant 3-methyleneoxindole either polymerizes, dimerizes or combines with unreacted oxindole.

The hydrolyzability of the hydrogenation product can be explained also on the basis of formula IIIc since one would expect the β-methoxyl group to be eliminated in either an acidic or basic medium and the thus-produced 3-methylene product (Ia) to react further in a fashion indicated above.

Since the differences in interpretation of Julian's experimental results arise mainly from the uncertainty of the structure of the O-alkylation products

(1) P. L. Julian and J. Pikl, THIS JOURNAL, **57**, 755 (1935).
(2) P. L. Julian, J. Pikl and F. E. Wentz, *ibid.*, **57**, 2026 (1935).
(3) P. L. Julian, J. Pikl and D. Boggess, *ibid.*, **56**, 1797 (1934).
(4) Schwarzenbach has demonstrated clearly that compounds of this type have a large enol content in solution [*cf.* G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1044, 1701 (1944)]. Consequently 1-methyl-3-formyloxindole, represented in the enol form by Ib, will be called 1-methyl-3-hydroxymethyleneoxindole henceforth.
(5) Instead of a complex salt the bisulfite product could be considered to be the adduct of bisulfite ion at the β-carbon of the α,β-unsaturated carbonyl system in Ic. This possibility, however, is doubtful since Ic can be regenerated from the bisulfite adduct by treatment with sodium carbonate solution—a hydrolytic condition which could cause β-elimination of either the bisulfite or the methoxy group and consequently produce Ib at least to some extent.
(6) If IV had been actually the structure of the dihydro compound, it should have been inert to basic hydrolysis since only acid would cleave the enol ether linkage.
(7) E. Wenkert, private observation.
(8) P. L. Julian, E. W. Meier and H. C. Printy in "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, p. 172.
(9) H. Hellmann and E. Renz, *Chem. Ber.*, **84**, 901 (1951).

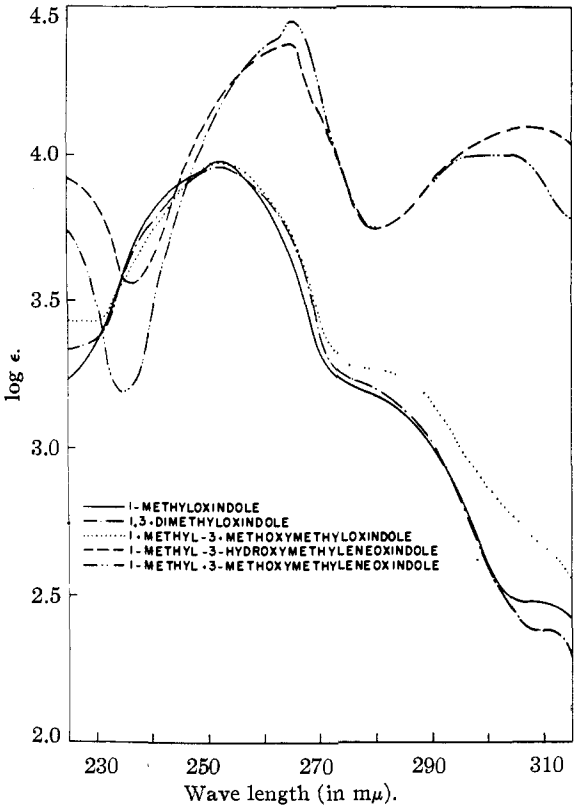


Fig. 1.—Ultraviolet spectra of: —, 1-methyloxindole; —.—, 1,3-dimethyloxindole; ....., 1-methyl-3-methoxymethyloxindole; — — — — —, 1-methyl-3-hydroxymethyleneoxindole; —..—, 1-methyl-3-methoxymethyleneoxindole. (The ultraviolet spectra were run on 95% alcohol solutions on a Carey spectrophotometer).

of 3-acyloxindoles—they being either 2-alkoxyindoles (structures II and IV) or 3-substituted oxindoles (structures I and III)—it would appear that a study of their spectra might resolve this difficulty most easily.[10]

N-Methyloxindole absorbs strongly at 252.5 mμ (log ε 3.98) (*cf.* Fig. 1), as has been observed already by Ramart-Lucas,[11,12] and shows a strong

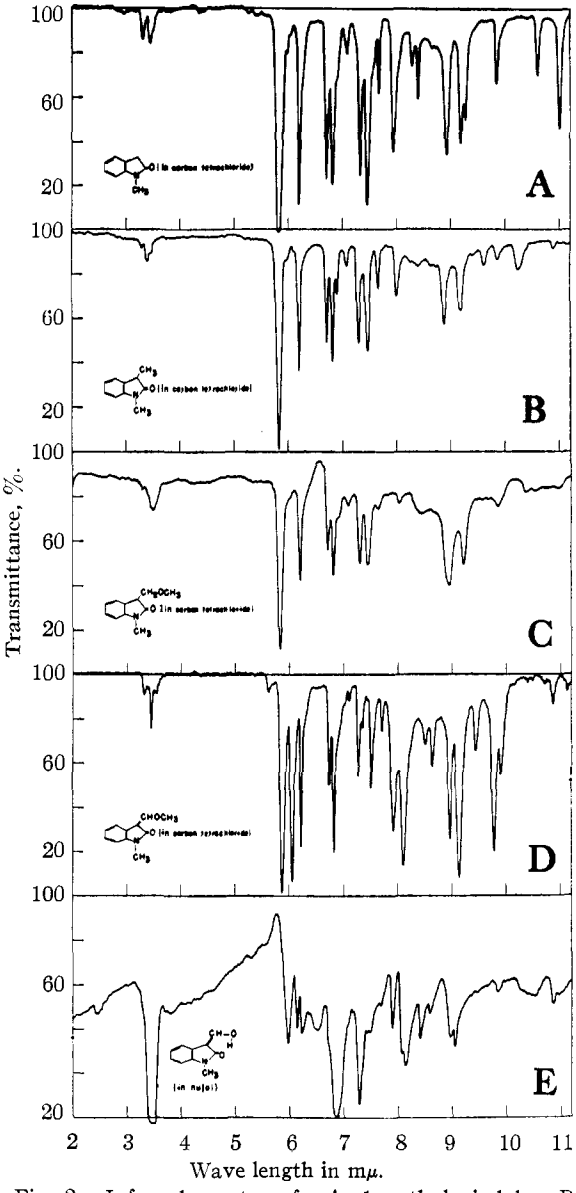


Fig. 2.—Infrared spectra of: A, 1-methyloxindole; B, 1,3-dimethyloxindole; C, 1-methyl-3-methoxymethyloxindole; D, 1-methyl-3-hydroxymethyleneoxindole; E, 1-methyl-3-methoxymethyleneoxindole. A–D were run in carbon tetrachloride and E in Nujol.

carbonyl band in the infrared at 5.82 μ (*cf.* Fig. 2).[13] Its 3-hydroxymethylene derivative shows much more intense, and longer wave length absorption, indicative of a chromophore more conjugated than a simple acylaniline grouping. Its maxima (*cf.* Fig. 1) appear at 265 mμ (log ε 4.38) and 308 mμ (log ε 4.10). The infrared spectra (Fig. 2) is void in the OH region, greatly suggesting intramolecular hydrogen bonding. The internal chelation is substantiated by the apparent shift of the oxindole carbonyl band to 5.97 μ and the appearance of a new peak at 6.13 μ, characteristic of the C=C and/or C=O bond in the chelate.[14]

(10) Prior to the spectral work the methylation product of 1-methyl-3-hydroxymethyleneoxindole was ozonized yielding in small quantity N-methylisatin, identified by m.p., mixed m.p. and comparison of its infrared spectra with that of an authentic sample. Whereas this result establishes Ic as the structure of the methylation product, N-methylisatin might have been produced conceivably by a deep-seated rearrangement of the ozonolysis product of the compound IIa. Although the latter possibility is almost non-existent, B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3855, 3861 (1952), have presented several cases of rearrangements of substituted indole ozonolysis products.

(11) P. Ramart-Lucas and D. Biquard, *Bull. soc. chim., France*, [5] **2**, 1383 (1935).

(12) All oxindoles, unsubstituted on the benzene ring, have their ultraviolet absorption maxima at 248–253 mμ (log ε *ca.* 4.0; in 95% ethanol), *cf.* ref. 8, and J. W. Cornforth, C. E. Dagliesh and A. Neuberger, *Biochem. J.*, **48**, 598 (1951). Gelsemine, an alkaloid containing the oxindole moiety, and its derivatives also show similar absorption; *cf.* M.-M. Janot and A. Berton, *Compt. rend.*, **216**, 564 (1943); M. Kates and L. Marion, *Can. J. Chem.*, **29**, 37 (1951); R. Goutarel, M.-M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta*, **34**, 1139 (1951); R. Goutarel, M.-M. Janot, V. Prelog and R. P. A. Sneeden, *ibid.*, **34**, 1962 (1951). It is interesting to note that N-alkyl oxindoles can be distinguished from the N-unsubstituted compounds by the ultraviolet spectra since the latter possess a second absorption peak at 282–285 mμ (log ε 3.2–3.4; in 95% ethanol) while the N-alkyl compounds have merely a shoulder in that general region. *Cf.* also M. Tomita, S. Uyeo and R. Yamamoto, *J. Pharm. Soc. Japan*, **64**, 164 (1944).

(13) The 5.81–5.82μ peak is characteristic of oxindoles; *cf.* ref. 12; M. Kates and L. Marion, THIS JOURNAL, **72**, 2308 (1950); L. Marion, D. A. Ramsay and R. N. Jones, *ibid.*, **73**, 305 (1951); and B. Witkop and A. Ek, *ibid.*, **73**, 5664 (1951).

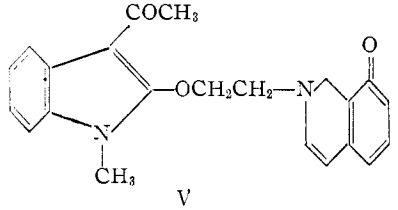
(14) *Cf.* N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Peterson, *ibid.*, **74**, 4070 (1952).

The methylation product of 1-methyl-3-hydroxymethyleneoxindole shows similar ultraviolet absorption characteristics to those of its precursor (*cf.* Fig. 1), maxima: 265 mμ (log ε 4.45) and 301 mμ (log ε 4.00). Thus it appears that the methoxy compound must possess the same chromophore and consequently structure as the hydroxy compound. Since the latter is best represented by formula Ib,[4] the most logical assignment of structure for the methylation product would be Ic. The infrared spectra corroborate this suggestion. The only difference in the double bond region from the infrared of N-methyloxindole is a new band at 6.03 μ, characteristic of the enol ether linkage. Whereas the latter is part of either structure Ic or IIb, the fact that the 5.83 μ oxindole band is still apparent would disallow formulation IIb, since in this structure the unsaturated aldehyde group would be expected to absorb close to 6 μ.

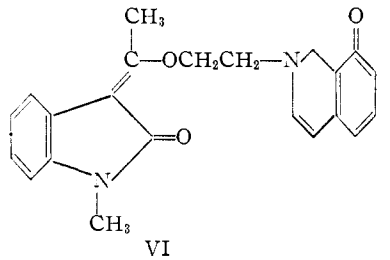
The most unambiguous results were obtained from the hydrogenation experiments. In repeated attempts to reduce catalytically the methylation product with palladium oxide catalyst,[3] the only identifiable compound isolated was 1,3-dimethyloxindole (ultraviolet and infrared spectra in Figs. 1 and 2). This fact alone establishes the structure of the methylation product as Ic, since IIb cannot possibly accommodate the formation of the dimethyloxindole on hydrogenation. In his recent review on oxindole chemistry[15] Julian states that the hydrogenation had been carried out with palladized barium carbonate. When this procedure was followed, a mixture of products was obtained, of which one component was again 1,3-dimethyloxindole. Since the latter was an obvious product of reduction, β-elimination of a methoxyl group, and further reduction of Ic, and since the elimination must have been due to the basicity of the catalysts' surface, it became apparent that only the least alkaline hydrogenation catalyst would yield Julian's dihydro compound. When finally the reduction was carried out in the presence of palladium–barium sulfate, the dihydro product actually was isolated, although still admixed with a small amount of the dimethyl compound. Its ultraviolet and infrared spectra showed conclusively that it was 1-methyl-3-methoxymethyloxindole (IIIc) and not IV as proposed by Julian. Thus its ultraviolet spectra was almost superposable on that of N-methyl- and 1,3-dimethyloxindole (Fig. 1), while its infrared showed no OH peak (required by formula IV) but double bond bands entirely analogous to those of the simple oxindoles (Fig. 2).

With the structures of the methylation product of 1-methyl-3-hydroxymethyleneoxindole and its derivatives clearly defined, any structure assignments of O-alkylated 3-acyloxindoles, based on analogy with Julian's original formulations, now require revision. Thus, for instance, the product of transetherification of 1-methyl-3-methoxymethyleneoxindole with ethanol, reported to be IIc,[3] must be actually Id.

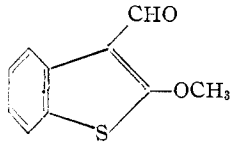
In similar alkylations involving 1-methyl-3-acetyloxindole an O-alkylated product V was isolated.[16,17] It possesses most likely also an isatylidene structure VI.



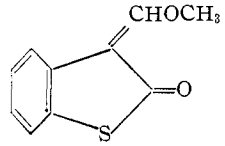
V



VI



VII



VIII

Most recently Mann[18] reported the diazomethane methylation of 3-hydroxymethylenethioöxindole, and suggested VII as the preferred structure of the product over VIII, on the basis of analogy with Julian's experiments. Whereas this formulation is now in doubt, it is impossible to assign VIII as the correct structure, since methylation by diazomethane need not be comparable at all to methylation with methyl iodide.[19]

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AMES, IOWA

(15) Reference 9, p. 155.

(16) P. L. Julian, A. Magnani, J. Pikl and W. J. Karpel, THIS JOURNAL, **70**, 174 (1948).

(17) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).

(18) R. H. Glavert and F. G. Mann, *J. Chem. Soc.*, 2127 (1952).

(19) NOTE ADDED IN PROOF.—Most recently Niemann [H. Rinderknecht, H. Koechlin and C. Niemann, *J. Org. Chem.*, **18**, 971 (1953)] reports attempted condensations of the O-methylation product of 1-methyl-3-hydroxymethyleneoxindole with hippuric acid, hydantoin, diketopiperazine, and diethyl malonate and the attempted conversion of the dihydro derivative of the O-methyl compound to a chloride. These reactions were carried out on starting materials assumed to have Julian's structural assignments. Consequently the lack of reactivity of the latter is not surprising on the basis of their reinterpreted structures.