dene bromohydrin produces 1-indanone in high yields. The mechanism of this reaction and its bearing upon the theory of aldehyde and ketone formation from aliphatic dibromides has been discussed.

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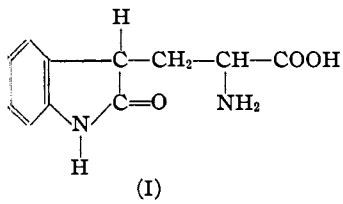
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

# Studies in the Indole Series. VI. On the Synthesis of Oxytryptophan and Further Studies of 3-Alkylation of Oxindoles[1]

BY PERCY L. JULIAN, JOSEF PIKL AND FRANK E. WANTZ

The program of investigation into the chemistry of oxindoles, undertaken some time ago in this Laboratory, centered largely in its first phase around 1,3-dimethyloxindoles since these offered convenient starting material for the synthesis of physostigmine.[2] The ease with which these 1,3-dialkyloxindoles underwent alkylation in the 3-position, led us to attempt the synthesis of oxytryptophan (I) by way of condensation reactions similar to those recently communicated.

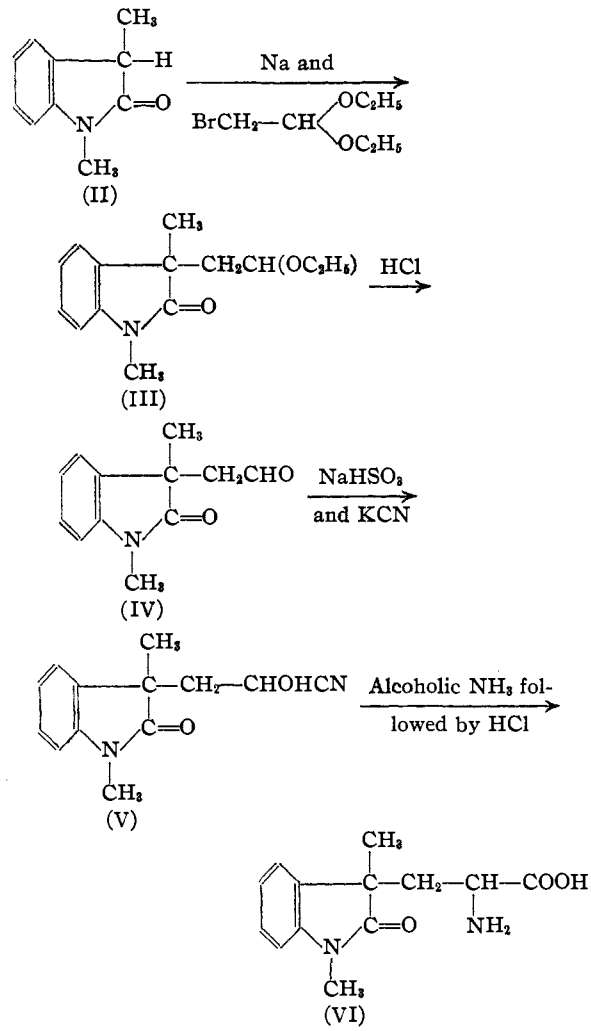


(I)

Much attention has been directed recently to this amino acid (I) since it has been indicated by Kotake[3] to be the first transformation product in the intermediary metabolism of tryptophan in the animal organism. Moreover, proof of the conversion of tryptophan into oxytryptophan, which might occur through certain oxidases, would probably explain the origin of many natural products containing the indole nucleus, among these physostigmine.[4]

In order to eliminate complications which might arise from possible enolizations of the hydrogen atoms in positions 1 and 3 of ordinary oxindole (VII), we decided to test out our proposed condensations, for introduction of the grouping $-CH_2-CH(NH_2)COOH$ into the 3-position of oxindoles, on 1,3-dimethyloxindole (II), with which we were quite familiar.

This paper reports the successful synthesis of the expected dimethyloxytryptophan (VI). 1,3-Dimethyloxindole was condensed with bromoacetal, the product (III) hydrolyzed and the aldehyde (IV) converted by way of the well-known Strecker synthesis into the amino acid (VI).



Attempts to carry out the same reactions with oxindole (VII) failed of their purpose, the initial condensation with bromoacetal presenting difficulties. That this is probably not due to enoli-

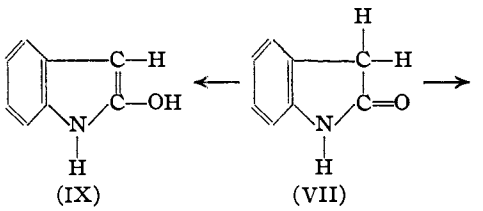
(1) Abstracted in large part from the senior research of Frank E. Wantz at DePauw University, 1934–1935.

(2) Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934); Julian and Pikl, *ibid.*, **57**, 539, 563, 755 (1935).

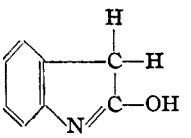
(3) Kotake, *Z. physiol. Chem.*, **195**, 158–166 (1931).

(4) Julian and Pikl, THIS JOURNAL, **57**, 755 (1935).

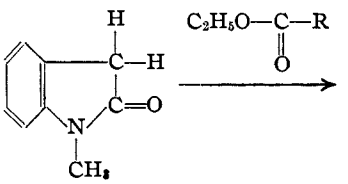
zation of (VII) in the sense represented by formula (VIII) rather than (IX) is indicated by the results obtained with (VII) in the Grignard machine. It gives two moles of gas and consumes two moles of reagent.



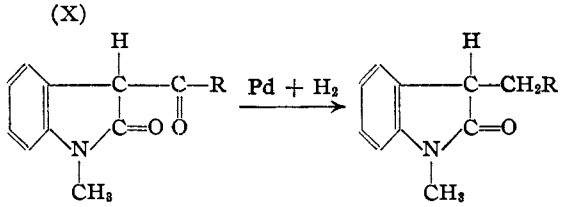
(IX) (VII)



(VIII)



(X)



(XI) (XII)

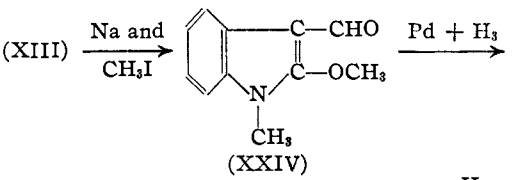
Condensation even of 1-methyloxindole (X) with bromoacetal could not be smoothly effected, despite numerous attempts.

We were therefore compelled to work out an entirely different procedure for smooth 3-alkylation of oxindoles not bearing an alkyl group in the 3-position, and the initial results with 1-methyloxindole (X) are communicated in this paper.

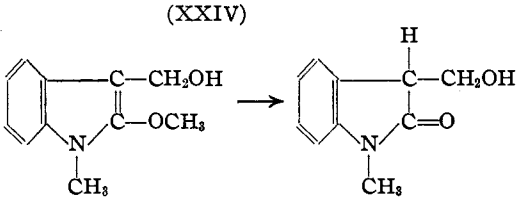
This new procedure makes use of 3-acyloxindoles (XI) which we have been able to obtain quite readily and in excellent yield through condensation of the oxindole (X) with esters. These 3-acyloxindoles, though readily cleaved by acids or bases, are cleanly hydrogenated catalytically to the corresponding 3-alkyl derivatives (XII). Table (I) shows the 3-acyloxindoles we have employed, together with the corresponding reduction products.

Compounds (XVIII) and (XIX), resulting, respectively, from condensation of the oxindole (X) with malonic ester and reduction of the product secured, are of particular interest to us in our attempts to synthesize oxytryptophan, for they point to possible successful outcome of this synthesis through condensation of oxindole with phthalimido-malonic ester, reduction of the resulting acyl derivative and hydrolytic cleavage to the amino acid (I). The results of this study will be reported in a later communication.

That the enolic hydrogen atom in position 3 of the acyloxindoles is responsible for the ease with which catalytic reduction takes place is suggested by the failure to reduce 1,3-dimethyl-3-acetyloxindole (XVII) by the same procedure. This latter substance was prepared by treating the sodium salt of (XV), suspended in acetone, with methyl iodide. It is interesting to note that 1-methyl-3-formyloxindole, methylated by this same procedure, gave an O-methyl derivative (XXIV),[5] which rapidly took up hydrogen when reduced catalytically to yield (XXV), a substance which is apparently readily hydrolyzed to the oxindole alcohol (XXVI). This compound is interesting in that it is the anhydride of *o*-methylamino-tropic acid.

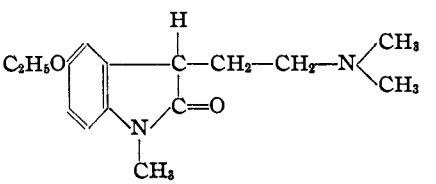


(XXIV)

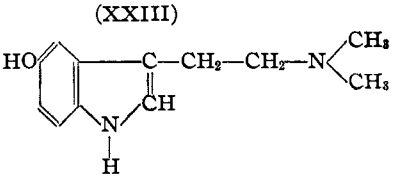


(XXV) (XXVI)

The substances (XXI) and (XXIII) were included in this study because of their close resemblance to bufotenine (XXVII), one of the toad secretions.



(XXIII)



(XXVII)

**Bufotenine**

TABLE I

| 3-Acyloxindole | Reduction product | M. p. or b. p., °C. | Acyl products on first line Reduction products, second line Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|
| 1-Methyl-3-formyloxindole[5] (XIII) | 1,3-Dimethyloxindole[5] (XIV) | | | | | |
| 1-Methyl-3-acetyloxindole (XV) | 1-Methyl-3-ethyloxindole (XVI) | 109 | 69.80 | 5.87 | 69.69 | 6.00 |
| | (Tribromo product analyzed) | 169 | 32.03 | 2.43 | 31.74 | 2.68 |
| 1,3-Dimethyl-3-acetyl-oxindole (XVII) | ..... | 79 | 70.90 | 6.45 | 71.07 | 6.70 |
| 1-Methyl-3-carboethoxy-acetyl-oxindole (XVIII) | β-1-Methyloxindolyl-propionic ester (XIX) | 67 | 64.34 | 5.79 | 64.34 | 5.88 |
| | | Liq. b. p. 160 (1 mm.) | 67.99 | 6.92 | 67.60 | 7.17 |
| 1-Methyl-3-dimethylaminoacetyl-oxindole (XX) | 1-Methyl-3-β-dimethylamino-ethyloxindole (XXI) | 219 | 67.20 | 6.94 | 67.25 | 7.15 |
| | (Picrate analyzed) m. p. 168° | Liq. b. p. 185 (16 mm.) | 50.98 | 4.74 | 51.05 | 4.86 |
| 1-Methyl-5-ethoxy-3-β-dimethyl-aminoacetyloxindole (XXII) | 1-Methyl-5-ethoxy-3-β-di-methylaminoethyloxindole | 196 | 65.17 | 7.31 | 65.00 | 7.53 |
| | (XXIII). Picrate analyzed, m. p. 157° | Liq. b. p. 221 (17 mm.) | 51.30 | 5.13 | 51.30 | 5.40 |
| 1-Methyl-2-methoxy-3-formyl-indole[5] (XXIV) | 1-Methyl-2-methoxy-indolyl-carbinol (XXV) | ... | ... | .. | ... | .. |
| | | 62 | 69.11 | 6.81 | 69.39 | 7.19 |

It has been pointed out by Jensen and Chen[6] that bufotenine has remarkable effect upon the blood pressure. Dr. Jensen (Laboratory for Endocrine Research, Johns Hopkins Medical School) has kindly undertaken investigation of (XXI) and (XXIII) for action similar to that of bufotenine in raising the blood pressure.

The authors are grateful for a grant from the Rosenwald Fund, which is defraying some of the expenses of this and other investigations. They also wish to renew their expressions of appreciation to Dean W. M. Blanchard, Head of the Department, for his untiring labor in making this research program possible.

## Experimental Part

### A. Synthesis of β-1,3-Dimethyloxindolylalanine (VI)

**1,3-Dimethyloxindolylacetal (III).**—To a cooled solution of 6.9 g. of sodium in 90 cc. of absolute alcohol, a mixture of 49 g. of 1,3-dimethyloxindole and 55 g. of bromoacetal was added. After heating on the water-bath (gently at first) for one hour under reflux, the mixture was poured into water, taken up with ether, the ethereal extract washed with water and distilled. At 11 mm., 56 g. of material boiling at 170–185° was collected. For analysis the portion boiling at 182.5–183.5° (11 mm.) was collected.

*Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.26; H, 8.36. Found: C, 69.65; H, 8.33.

**1,3-Dimethyloxindolylacetaldehyde (IV).**—43.2 grams of the acetal (III) was covered with 300 cc. of 5% hydrochloric acid and shaken frequently. Solution occurs after about two hours. Allowed to stand overnight, it was then made alkaline with a generous excess of sodium carbonate and extracted with ether. The ethereal extract on distillation gave a quantitative yield of aldehyde (IV), b. p. 177–178° (12 mm.).

*Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.93; H, 6.40. Found: C, 70.66; H, 6.80.

The semicarbazone, prepared in the usual manner, melts at 206°, recrystallized from dilute alcohol.

*Anal.* Calcd. for $C_{13}H_{16}O_2N_4$: C, 59.98; H, 6.19. Found: C, 59.82; H, 6.42.

**1,3-Dimethyloxindolylacetaldehydecyanhydrin (V).**—To a well-stirred mixture of 64 g. of aldehyde (IV), 35 g. of sodium bisulfite, 50 cc. of water and 100 cc. of ether, a mixture of 25 g. of potassium cyanide and 30 cc. of water was added. The beautifully crystalline cyanhydrin which separated was filtered and washed generously with water and then a little ether; yield 50 g.; recrystallized from ether–petroleum ether, m. p. 142°.

*Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.82; H, 6.09. Found: C, 67.80; H, 6.33.

**β-1,3-Dimethyloxindolylalanine (VI).**—Twenty grams of cyanhydrin (V) was warmed for seven hours at about 60° with 16 cc. of 12% absolute alcoholic ammonia. The reaction product was poured into 50 cc. of 10% hydrochloric acid, whereby all went into solution. When sufficient water was added to bring the acid concentration down to about 3%, a precipitate was formed which was removed by shaking with ether. The aqueous solution was evaporated on the water-bath almost to dryness, and 10 cc. of concentrated hydrochloric acid added. This mixture was then heated on the water-bath for eight hours, after which the whole mass was taken up in 300 cc. of alcohol and alcoholic ammonia added until no more precipitate formed. The precipitate, consisting mainly of ammonium chloride, was filtered off, and ether added to the filtrate to precipitate the amino acid; 10.5 g. of product was obtained. After several recrystallizations from

(5) Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).
(6) Jensen and Chen, *Ber.*, **65**, 1310 (1932).

80% alcohol it was fairly pure, m. p. 188° with decomposition, colorless, thin rhombic flakes. It still contained traces of ammonium chloride, very difficult to remove by this procedure.

*Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.88; H, 6.49. Found: C, 62.26; H, 6.60.

Heated above its melting point in a sublimation tube in vacuum, the acid loses carbon dioxide and pure 1,3-dimethyloxindolylethylamine[7] distils over, yielding a picrate, m. p. 186°, identical with that described in an earlier communication.

### B. Preparation and Catalytic Reduction of 3-Acyloxindoles

**Preparation of the 3-Acyloxindoles.**—The general procedure was to add a mixture of 1 mole of oxindole (X) and 1.2 moles of ester to a 10% solution of sodium ethylate containing 1.3 moles of sodium. In most cases the sodium salt separated, was filtered off and decomposed with dilute hydrochloric acid.

In the case of the condensation of (X) with malonic ester the procedure above gave a difficultly soluble substance, m. p. 225°, doubtless the trimolecular condensation product. When from two to three moles of ester was employed and the oxindole dropped into the mixture of ethylate and ester, the product consisted almost entirely of the dimolecular condensation product, m. p. 67°, recrystallized from ether–petroleum ether.

The isolation of the condensation product between oxindole and dimethylaminoacetic ester called for further modification of the procedure since this product behaves like an amino acid. The sodium salt of the condensation product was decomposed with excess 10% hydrochloric acid in the cold, then sodium bicarbonate was added rapidly and the free amine extracted with chloroform. The chloroform extract was concentrated and upon addition of ether to the hot solution the acyl amines (XX) and (XXII) snowed out. Recrystallized from chloroform and ether.

For preparation of (XXII) two new oxindoles were prepared, which have not hitherto been described, namely, 1-methyl-5-hydroxyoxindole and 1-methyl-5-ethoxy-oxindole. These were prepared from chloroacetyl chloride and N-methylphenetidine in the same manner as described for the 3-methyl analog.[8] 1-Methyl-5-hydroxy-oxindole melts at 187° recrystallized from alcohol.

*Anal.* Calcd. for $C_9H_9O_2N$: C, 66.23; H, 5.56. Found: C, 66.20; H, 5.55.

(7) Julian and Pikl, THIS JOURNAL, **57**, 539 (1935).

(8) Julian and Pikl, *ibid.*, **57**, 563 (1935).

1-Methyl-5-ethoxy-oxindole melts at 92°, recrystallized from ether–petroleum ether.

*Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.07; H, 6.86. Found: C, 68.76; H, 7.14.

**Catalytic Reduction of the 3-Acyloxindoles.**—For the first four and the last acyl oxindole listed in Table I, the procedure was to dissolve the oxindole in alcohol and reduce at about 1.5 atmospheres' pressure with from 0.05 to 0.1 its weight of Adams palladium oxide catalyst. The product after filtration was extracted with ether, the ether solution washed with sodium hydroxide to remove unchanged material and distilled. The yields were from 50 to 70% of the theoretical.

The acyloxindoles (XX) and (XXII) (Table I) were suspended in ten times their weight of absolute alcohol, about one-tenth this quantity of glacial acetic acid was added, and about 0.2 as much catalyst as oxindole employed. It was necessary to heat the mixture in the hydrogenation vessel to about 50° and maintain this temperature for reduction to proceed smoothly. The products were filtered, the alcohol removed in vacuum, the residue taken up in 3% hydrochloric acid and separated from an appreciable quantity of non-basic material by extraction with ether. The aqueous solution was made alkaline with sodium hydroxide, extracted with ether, and the ethereal extracts distilled under diminished pressure.

## Summary

1. 1,3-Dimethyloxindole is smoothly condensed with bromoacetal, in presence of sodium ethylate, to yield 1,3-dimethyloxindolylacetal. The aldehyde resulting from hydrolysis yields by the Strecker synthesis the expected dimethyloxytryptophan.

2. Condensation of oxindole and 1-methyloxindole with bromoacetal by the same procedure could not be effected.

3. Several 3-acyloxindoles have been easily reduced catalytically to 3-alkyloxindoles, and it is hoped to employ the appropriate acyloxindole for the synthesis of oxytryptophan.

4. Substances related to bufotenine have been prepared by catalytic reduction of the appropriate acyloxindoles, particularly the ethyl ether of 1-methyl-2-oxybufotenine.

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