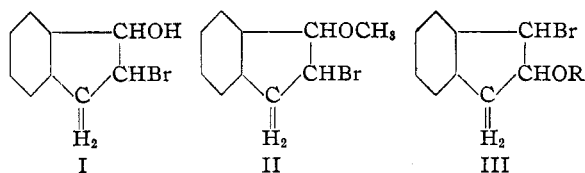


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some Bromine Derivatives of Indene and Indane¹

BY H. D. PORTER AND C. M. SUTER

It was shown by Courtot² and co-workers that the well-known indene bromohydrin has structure I since on oxidation it gives 2-bromo-1-indanone. Von Braun and Weissbach³ therefore logically assumed that the methoxybromoindane obtained from indene dibromide and methanol had structure II. On the other hand, Jacobi⁴ has presented evidence indicating that the alkoxybromoindanes prepared in this manner correspond to III.



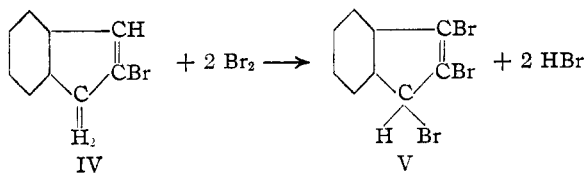
The present investigation was undertaken to explain this apparent contradiction and amplify the available information concerning other bromine derivatives of indene and indane.

Indene bromohydrin, either upon pyrolysis at 150–160° or by dehydration with phosphorus pentoxide, is converted into 2-bromoindene, m. p. 38–39°. The structure of this compound was confirmed by reaction with sodium ethoxide and hydrolysis of the resulting ethoxyindene to 2-indanone by the action of dilute acid. Thermal decomposition of indene dibromide likewise gives 2-bromoindene although the yield is somewhat lower. Jacobi⁴ reported that the compound formed in this reaction was 1-bromoindene. Apparently unknown to Jacobi, 1-bromoindene had been prepared previously⁵ by the action of cyanogen bromide upon indenylmagnesium bromide and has quite different properties from the 2-bromoindene obtained from indene dibromide. As evidence for the structure he proposed, Jacobi found that the Grignard reagent of the bromoindene gave indene-1-carboxylic acid. It would not be surprising to obtain this acid from 2-bromoindene because of the activity of the methylene hydrogens in indene toward Grignard reagents.⁶

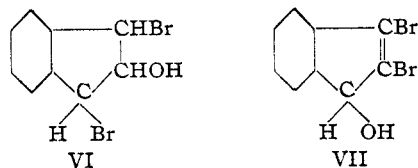
However, upon repeating Jacobi's experiment numerous times, the only product isolated was a low yield of indene-2-carboxylic acid.⁷

2-Bromoindene is inert toward boiling aqueous alkali or potassium formate in methanol. It adds hydrogen bromide in glacial acetic acid to give indene dibromide, identified by hydrolysis to the bromohydrin. Various attempts to alter the manner in which addition occurred by a change of solvent and the presence of hydroquinone or benzoyl peroxide⁸ were unsuccessful.

Bromine reacts readily with 2-bromoindene in carbon tetrachloride at room temperature with evolution of hydrogen bromide. The product obtained is apparently 1,2,3-tribromoindene as it contains only one hydrolyzable bromine and upon oxidation gives phthalic acid.



The exact mechanism of the bromination is uncertain. The "tribromoindane" obtained by Jacobi⁴ from his supposed 1-bromoindene is probably V. 1,2,3-Tribromoindane had been prepared considerably earlier⁵ by addition of bromine to 1-bromoindene. It is a solid melting at 133–134° while Jacobi's product was described as an oil. Jacobi's 1,3-dibromo-2-hydroxyindane (m. p. 90°), VI, is unexplained as the VII obtained in this investigation did not crystallize. 1,2,3-Tribromoindane, obtained from indene dibromide and bromine,⁹ was found to be unexpectedly inert toward hydrolysis and no hydroxydibromoindane could be isolated for comparison with Jacobi's product.



(1) Presented before the Organic Division of the American Chemical Society at the New York Meeting, April, 1935.

(2) Courtot, Fayet and Parant, *Compt. rend.*, **186**, 371 (1928).

(3) Von Braun and Weissbach, *Ber.*, **63B**, 3052 (1930).

(4) Jacobi, *J. prakt. Chem.*, **129**, 55 (1931).

(5) Grignard, Bellet and Courtot, *Ann. chim.*, **4**, 28 (1915).

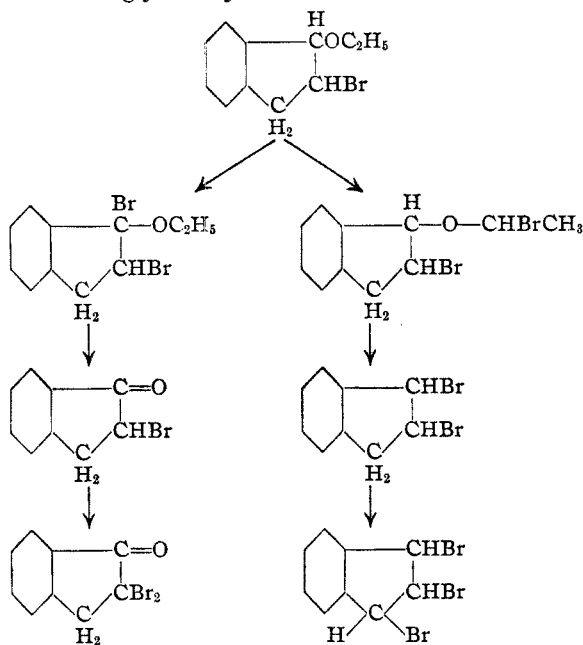
(6) Grignard and Courtot, *Compt. rend.*, **152**, 272 (1911).

(7) Perkin and Révay, *Ber.*, **26**, 2254 (1893); *J. Chem. Soc.*, **65**, 228 (1894).

(8) Kharasch and Mayo, *THIS JOURNAL*, **55**, 2468 (1933).

(9) R. Meyer and W. Meyer, *Ber.*, **51**, 1571 (1918).

Refluxing indene dibromide with ethyl alcohol gives a mixture containing 1-ethoxy-2-bromoindane, 2-bromoindene and indene dibromide. The pure ethoxy compound is obtainable by adding pyridine to the mixture to carry the alcoholysis to completion or by removal of the unchanged indene dibromide by hydrolysis to the bromohydrin or glycol. Jacobi's 3-bromoindene⁴ was



apparently a mixture of indene dibromide and ethoxybromoindane. It was noted in one preparation of the ethoxy compound that calcium chloride which was accidentally introduced into the mixture greatly increased the amount of 2-bromoindene formed. Here sodium carbonate was added to hydrolyze the unchanged indene dibromide.

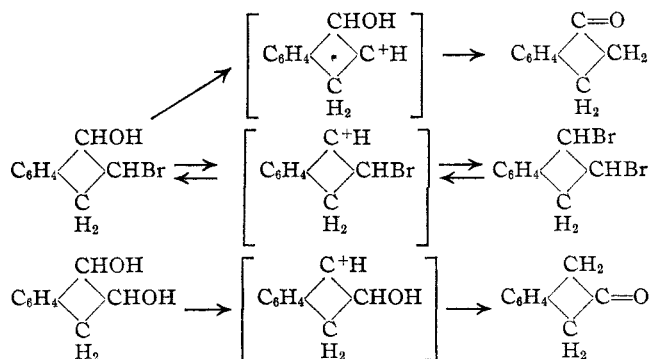
The structure of the ethoxybromoindane was established by converting it into 1-indanone through reaction with sodamide in liquid ammonia followed by acid hydrolysis of the enol ether.

The bromine in 1-ethoxy-2-bromoindane is quite unreactive, prolonged heating with aqueous sodium hydroxide or potassium acetate in glacial acetic acid having little effect. Bromination in boiling carbon tetrachloride gave a mixture of 2,2-dibromo-1-indanone and 1,2,3-tribromoindane. The formation of these products is explainable upon the basis of the behavior of α -chloro ethers toward heat.¹⁰ The reaction probably proceeds by the steps indicated above.

(10) Straus and Heinze, *Ann.*, **493**, 191 (1932).

Trans indene glycol was obtained in 60–70% yields by hydrolysis of indene bromohydrin with aqueous sodium carbonate. This yield is twice that obtained by the hydrolysis method of Weissgerber¹¹ and the procedure is much simpler than the one involving the preparation and hydrolysis of indene diacetate.^{11,12} Conversion of the glycol and of indene oxide¹² to 2-indanone by boiling with dilute acid has been reported by several investigators.^{11,12,13} In the present work it was found that both indene bromohydrin and 1-ethoxy-2-bromoindane under similar treatment yield 1-indanone. Since indene bromohydrin was found to be readily obtainable from a drip oil fraction containing less than 50% indene, both indanones are now readily accessible.

The formation of 1-indanone from indene bromohydrin has considerable bearing upon the validity of the mechanism advanced by Whitmore¹⁴ to explain aldehyde and ketone formation from the hydrolysis of dibromides. According to this mechanism the hydrolysis of indene dibromide or treatment of indene bromohydrin with dilute acid should produce 2-indanone, whereas actually none of this results. As long as the bromine atom remains attached to carbon atom 2 the hydrogen joined to this carbon is apparently immobilized. This is not the case for the corresponding hydrogen in indene glycol. These reactions may be formulated thus



By analogy it seems likely that in the conversion of an aliphatic dibromide containing a tertiary bromine to an aldehyde or ketone the formation of the glycol precedes that of the carbonyl compound.

(11) Weissgerber, *Ber.*, **44**, 1436 (1911).

(12) Böseken and Van Loon, *Proc. Acad. Sci. Amsterdam*, **20**, 1181 (1918).

(13) Heusler and Schieffer, *Ber.*, **32**, 28 (1899); Walters, *J. Soc. Chem. Ind.*, **46**, 150 (1927).

(14) Whitmore, *This Journal*, **54**, 3280 (1932); Evers, Rothrock, Woodburn, Stahly and Whitmore, *ibid.*, **55**, 1136 (1933).

Practically all of the indene dibromide employed in this investigation was prepared from indene bromohydrin and hydrobromic acid. This dibromide was found to be identical with that obtained directly from indene. In view of the recent work of Bartlett¹⁵ upon the *cis* and *trans* cyclohexene chlorohydrins, it is probably that indene bromohydrin is the *trans* isomer as it yields indene oxide with great ease. Correspondingly, the indene chlorohydrin obtained in larger amount by the hydrolysis of indene dichloride² would be the *trans* isomer. The fact that 1-indanone was obtained as the final product in the action of sodium methoxide upon the other (*cis*) indene chlorohydrin tends to confirm these structures.

Experimental

Indene Bromohydrin.—Bromine water was added in successive 2-liter quantities to 165 g. of a crude indene, b. p. 176–182°, obtained by the fractionation of drip oil or crude solvent naphtha¹⁶ and the mixture stirred vigorously. The spent bromine water was siphoned off before addition of the next portion. When no more bromine reacted the pasty product was filtered and washed with benzene. The yield was 95 g. or 31%, assuming the starting material to be 100% indene. The product thus prepared melted at 126–128°. Similar preparations employing pure indene have been described previously.¹⁷

Preparation of 2-Bromoindene.—(1) A solution of 22 g. of indene bromohydrin in 150 cc. of carbon tetrachloride was refluxed with 7 g. of phosphorus pentoxide for two hours. The solution was decanted from the phosphoric acid and distilled. The fraction distilling at 123–124° (22 mm.) solidified on cooling and after recrystallizing from methanol melted at 38–39°. The yield was 11 g. or 55% of the theoretical amount.

(2) Heating 10.5 g. of indene bromohydrin in a small flask in an oil-bath at 155–160° for two hours gave 4 g. of crude 2-bromoindene, b. p. 123–128° (17 mm.). A better method was as follows. A mixture containing 25 g. of indene bromohydrin and 40 cc. of bromobenzene, b. p. 156°, was distilled very slowly, additional bromobenzene being added at the same rate through a dropping funnel. The end of the reaction was indicated by the absence of water in the distillate. Distillation of the residue gave 10.2 g. or 45% of the theoretical amount of product, boiling at 125–127° (23 mm.), which solidified upon standing. Recrystallization gave the pure 2-bromoindene, m. p. 38–39°.

Anal. Calcd. for C_9H_7Br : Br, 41.02. Found: Br, 40.9.

2-Indanone from 2-Bromoindene.—Two grams of 2-bromoindene was added to 10 cc. of 100% ethyl alcohol

in which 0.5 g. of sodium had been dissolved. The mixture was refluxed for three hours, poured into excess 10% sulfuric acid and steam distilled. After removal of the alcohol a small amount of an oil came over. Upon crystallization from petroleum ether this melted at 57–58°. This was identified as 2-indanone¹⁸ by conversion to the oxime, m. p. 152°.

Refluxing 2-bromoindene with 2 *N* sodium hydroxide for two hours gave negative results, as did refluxing with potassium formate in methanol for sixteen hours.

Indene-2-carboxylic Acid.—Four grams of 2-bromoindene was treated with 0.5 g. of magnesium in 25 cc. of dry ether. The reaction was started by using a few drops of an ethylmagnesium bromide solution. After refluxing for two hours the solution was cooled and carbon dioxide introduced. After working up the product in the usual manner there was obtained 0.5 g. of indene-2-carboxylic acid, m. p. 228–229°. The only other product noted was indene. Various modifications of this procedure gave substantially the same results.

2-Bromoindene and Hydrogen Bromide.—A solution containing 0.5 g. of 2-bromoindene in 5 cc. of 37% hydrogen bromide in glacial acetic acid was allowed to stand for a day. The oil obtained, n_D^{25} 1.6285, gave upon refluxing in an acetone–water mixture for two hours and cooling, crystals of indene bromohydrin, m. p. 128°. This result was not affected by the addition of a small amount of either benzoyl peroxide or hydroquinone to the acetic acid solution.

The reaction between hydrogen bromide and 2-bromoindene in benzene in the presence of benzoyl peroxide was incomplete after two days. The only reaction product found was again indene dibromide. When the benzoyl peroxide was replaced by hydroquinone the 2-bromoindene remained practically unchanged after two days. Warming the reaction mixture on the steam-bath, however, again gave a trace of indene dibromide.

Bromination of 2-Bromoindene.—To 7.4 g. of 2-bromoindene dissolved in carbon tetrachloride was added bromine in the same solvent until the color persisted. During the course of the reaction hydrogen bromide was evolved copiously. The solution was washed with aqueous sodium bisulfite, dried, and the solvent allowed to evaporate. The product was an oil, n_D^{25} 1.6615, d_4^{25} 2.12. It could not be distilled but judging by its analysis and behavior it was a pure substance. The yield was 13 g. or 97% of the theoretical amount.

Anal. Calcd. for $C_9H_5Br_2$: Br, 68.05. Found: Br, 67.8.

Oxidation with aqueous potassium permanganate gave phthalic acid, m. p. 184–186°, which upon heating above its melting point gave the anhydride, m. p. 128°.

Hydrolysis of 1,2,3-Tribromoindene.—The tribromoindene decomposed to a tar when treated with aqueous alkali. Hydrolysis by boiling in acetone–water solution over calcium carbonate followed by steam distillation gave a few drops of an oil, n_D^{25} 1.6350, which analyzed for a dibromoindenol.

Anal. Calcd. for $C_9H_6OBr_2$: Br, 55.3. Found: Br, 54.9.

Indene Dibromide from Indene Bromohydrin.—A mixture of 38 g. of indene bromohydrin and 130 cc. of

(15) Bartlett, *This Journal*, **57**, 224 (1935).

(16) This material was supplied through the courtesy of Mr. R. B. Harper, Vice-President, and Mr. E. F. Pohlmann, Chief Testing Engineer, of the Peoples Gas Light and Coke Company of Chicago, to whom we wish to express our appreciation.

(17) Pope and Read, *J. Chem. Soc.*, **99**, 2071 (1911); **101**, 760 (1912).

(18) Schad, *Ber.*, **26**, 222 (1893), first prepared this compound.

47% hydrobromic acid was stirred on the steam-bath for three hours. The oily layer was separated, dried with calcium chloride and distilled at 1 mm. The main fraction, b. p. 100–105°, was indene dibromide, n_D^{25} 1.6290, d_4^{25} 1.747. The yield was 31 g. or 61% of the theoretical amount. The product distilling at 77–100° (1 mm.), which came over as a forerun, solidified upon cooling and proved to be 2-bromoindene, m. p. 38–39°. Some difficulty was encountered at first in inducing the indene dibromide to crystallize. Satisfactory results were finally obtained by cooling its petroleum ether solution to a low temperature. The product, m. p. 32°, was found to be identical with that obtained from indene. No other dibromide could be isolated.

Pyrolysis of Indene Dibromide.—(1) Upon heating 25.6 g. of indene dibromide in a flask in an oil-bath at 200–210° for one hour hydrogen bromide was evolved and the residue distilled at 113–115° (13 mm.). It solidified upon cooling and after recrystallization from alcohol melted at 38–39°. A mixed melting point with 2-bromoindene gave the same value. The yield was 3.3 g. or 16% of the theoretical amount.

(2) Refluxing 19 g. of indene dibromide in 30 cc. of dry tetralin (b. p. 205–210°) as long as hydrogen bromide was evolved (four hours) gave 4.8 g. or 36% of the theoretical amount of 2-bromoindene.

Preparation of 1-Ethoxy-2-bromoindane.—(1) A mixture of 40 cc. of 100% ethyl alcohol and 20 g. of indene dibromide was refluxed for four hours. During the third hour a total of 6.5 g. of pyridine was added slowly. Water was then added and the oily layer separated, washed, dried and distilled. There was obtained 6.7 g. of product, b. p. 144–148° (19 mm.), which is 38% of the theoretical amount. A portion, b. p. 147–148° (19 mm.), n_D^{25} 1.5515, d_4^{25} 1.344, was analyzed.

Anal. Calcd. for $C_{11}H_{13}OBr$: Br, 33.15. Found: Br, 33.2.

In similar experiments in which pyridine was not added the product always contained unchanged dibromide, besides a trace of 2-bromoindene.

(2) In another experiment, after refluxing 40 g. of indene dibromide with 105 cc. of alcohol containing about 5 g. of calcium chloride for five and one-half hours, 20 cc. of water and enough saturated sodium carbonate solution were added to make the mixture alkaline. This was then stirred on the steam-bath for four hours. More water was added and the product separated and dried. There was obtained 13.4 g. of material, b. p. 143.5–144.5° (17 mm.), which is 38% of the theoretical amount. A forerun of 9 g. of 2-bromoindene, b. p. 132–136°, was also recovered.

Proof of Structure of 1-Ethoxy-2-bromoindane.—A solution of sodamide in liquid ammonia was prepared by treating 0.24 g. of sodium with 50 cc. of the solvent in the presence of a trace of ferric oxide. To this solution was added 2.5 g. of the ethoxy compound. The residue remaining after the gradual evaporation of the ammonia was extracted with ether and the oil thus obtained was steam distilled from 10% sulfuric acid. From the oil in the distillate there was obtained through treatment with hydroxylamine hydrochloride and sodium acetate in methanol followed by dilution with water, crystals of 1-

indanone oxime,¹⁹ m. p. 143–144°. This was identified by a mixed m. p. with an authentic sample.

Bromination of 1-Ethoxy-2-bromoindane.—A boiling solution of 2.5 g. of the ethoxy compound in 25 cc. of carbon tetrachloride was treated with bromine as long as reaction occurred. The solvent was removed and the residue recrystallized from petroleum ether. This was a mixture, m. p. 100–106°, in which two types of crystals were evident. Those with a needle-like appearance were separated mechanically and after recrystallization from methanol melted at 133–134°. A mixed melting point indicated the substance to be 1,2,3-tribromoindane.⁹ Fractional crystallization of the original mixture from ether or ether-benzene gave rhombic crystals likewise melting at 133–134°. These were found to be 2,2-dibromo-1-indanone¹⁹ through comparison with a sample of this substance prepared from 1-indanone.

Preparation of Trans Indene Glycol.—The following procedure was found to be more convenient than those in the literature.^{11,12} A mixture of 350 cc. of saturated aqueous sodium carbonate and 17 g. of indene bromohydrin was stirred on the steam-bath for three hours. After cooling, the mixture was filtered and the product treated with hot water to separate the glycol from an insoluble tarry material. Cooling the water solution gave 6.8 g. of *trans* indene glycol, m. p. 159°, which is 60% of the theoretical amount. The water-insoluble material (4.7 g.) upon treatment with methanol left a residue which melted above 285°. Treatment of 1-indanone with aqueous sodium carbonate gave a similar product while the glycol was unaffected by long heating with the carbonate. It seems probable that 1-indanone is the precursor of this by-product.

Preparation of 1-Indanone.—A mixture of 400 cc. of 7% (by volume) sulfuric acid and 20 g. of indene bromohydrin was refluxed for ten hours. Steam distillation gave an oil, b. p. 117–118° (15 mm.), which solidified upon cooling and melted at 42° after crystallizing from petroleum ether. The yield was 10 g. or 80.6% of the theoretical amount. The oxime melted at 145–146°.

Preparation of 2-Indanone.—Refluxing 4 g. of *trans* indene glycol with 7% (by volume) sulfuric acid for one hour gave 2.5 g. or 71% of 2-indanone, m. p. 58–59°.

1-Indanone from 1-Ethoxy-2-bromoindane.—A mixture of 20 cc. of 10% (by volume) sulfuric acid and 1.1 g. of the ethoxy compound was refluxed for eight hours. Steam distillation gave 0.32 g. or 53% of an oil, identified as 1-indanone by conversion to the oxime, m. p. 143–144°.

Summary

1. 2-Bromoindene has been obtained by pyrolysis or dehydration of indene bromohydrin, pyrolysis of indene dibromide and as a by-product in other reactions. Its structure is evident from its mode of preparation and its reactions.

2. Reaction of indene dibromide with ethyl alcohol gives 1-ethoxy-2-bromoindane. Various reactions of this compound have been investigated.

3. The action of dilute sulfuric acid upon in-

(19) Kipping, *J. Chem. Soc.*, **65**, 480 (1894).

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.

EVANSTON, ILLINOIS

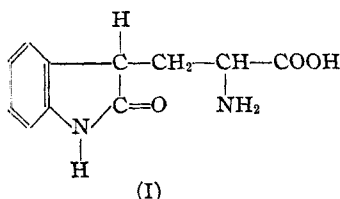
RECEIVED JULY 11, 1935

[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 Oxindoles¹

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.

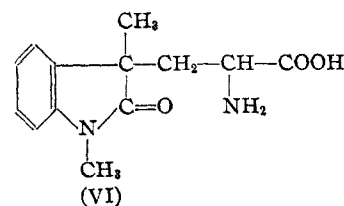
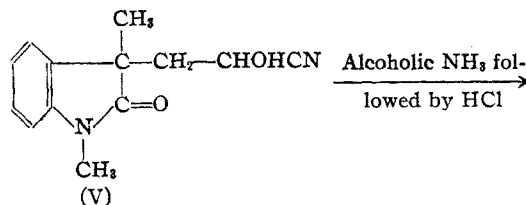
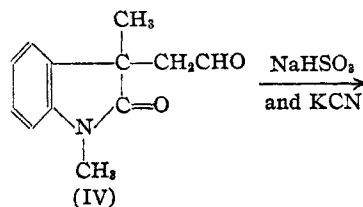
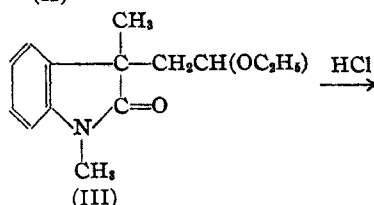
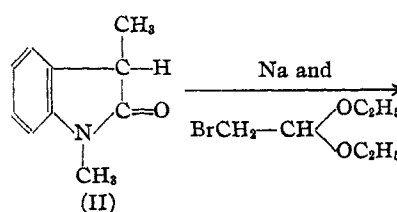


Much attention has been directed recently to this amino acid (I) since it has been indicated by Kotake³ to be the first transformation product in the intermediary metabolism of tryptophan in the animal organism. Moreover, proof of the conversion of tryptophan into oxytryptophan, which might occur through 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 $-\text{CH}_2-\text{CH}(\text{NH}_2)\text{COOH}$ 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).