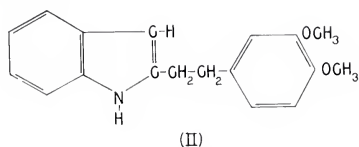
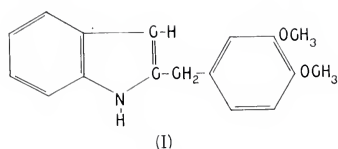


STUDIES IN THE INDOLE SERIES VII. THE COURSE OF THE FISCHER REACTION WITH KETONES OF THE TYPE $R \text{ CH}_2 \text{ CO CH}_3$. ALPHA-PROPYL AND ALPHA-HOMOVERATRYL INDOLE

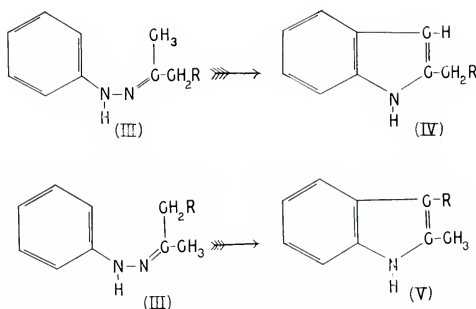
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Some time ago, in connection with work on the structures of certain Angostura alkaloids, we desired for purposes of comparison α -Veratryl Indole (I) and α -Homoveratryl Indole (II).



Despite the numerous researches on indole derivatives recorded in the literature, no methods were at that time available for securing indoles with elongated mixed aliphatic-aromatic groupings in the α -position.

The well-known Fischer reaction might be expected to yield with the ketones of the type, $R \text{ CH}_2 \text{ CO CH}_3$, a mixture of Indoles (IV) and (V), depending upon whether the methyl or methylene group supplied the requisite hydrogen for ammonia formation; and, indeed, Emil Fischer himself¹ suggested some time ago that the reaction proceeded in both directions. The yield of (IV) was, however, always negligible in comparison with that of (V), as would be expected *a priori*.

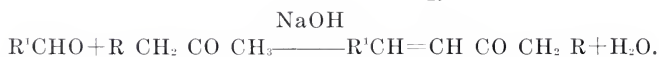
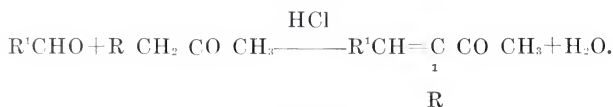


It was therefore surprising that Arbusow and Friauf² should have found that in the case of decomposition of methyl propyl ketonephenylhydrazone with cuprous chloride as catalyst, the principal product is α -propyl indole. It is conceivable that, under varying conditions and with employment of various catalysts, methyl may at one time play the role of yielding hydrogen and methylene at another time, as is the case with condensation between aldehydes and the ketones in question, acids

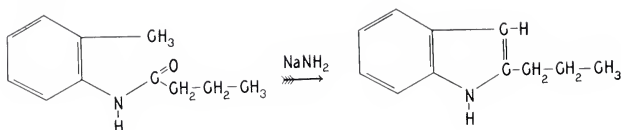
¹Fischer, E., 1886. Ann. 236:133.

²Arbusow, A. E. and Friauf, A. P., 1913. J. Russ. Phys. Chem. Soc. 45:694-696.

favoring elimination of water by means of the methylene hydrogen, and alkalis doing the same by means of the methyl hydrogen:

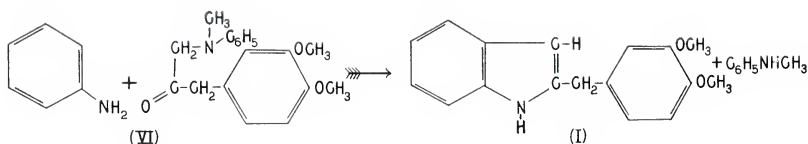


Nevertheless Arbusow gives no satisfactory proof for the structure of his α -propyl indole, and his work leaves doubt in minds of investigators in this field in view of the description by Verley and Beduwé³ twelve years later of another compound which they call α -propyl indole. Their α -propyl indole was prepared by elimination of the elements of water from the toluidide of propionic acid by means of sodamide.



Verley evidently overlooked Arbusow's work and consequently makes no comparison of his product with that of the Russian investigator.

For the preparation of alpha benzyl indoles like (I), Julian and Pikel' found it necessary to work out a new procedure based upon the reaction between appropriate α -amino-ketones, like (VI), and arylamines.



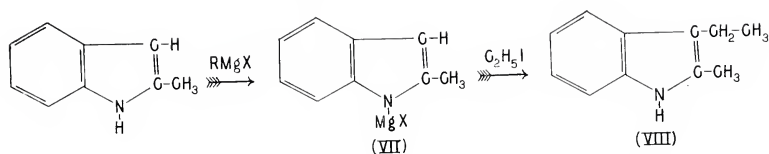
Since ketones of the type (VI) had not hitherto been known and were prepared for the first time by Julian and Pikel' with somewhat involved reactions,⁴ we naturally were interested in Arbustow's preparation of α -propyl indole, for its aromatic analogue, alpha-homoveratrylindole, might be prepared in similar fashion, a preparation which would be much simpler than the method of Julian and Pikel', since the latter method demands at the outset ketones of the type $\text{R} \text{CH}_2 \text{CH}_2 \text{CO} \text{CH}_2\text{X}$, where X is either halogen or an arylamino residue.

We therefore repeated Arbusow's work. With his so-called " α -propyl indole" in hand the next question was proof of structure. Arbusow had based his formula purely upon the observation that his compound gave the "pine-shaving reaction", characteristic of indoles substituted in the alpha or beta positions, but not of those substituted in both alpha and beta positions. Thus he reasoned that his compound

³Verley, M. A. and Beduwé, J., 1925. Bull. Soc. Chim. (iv) 37:189-191.

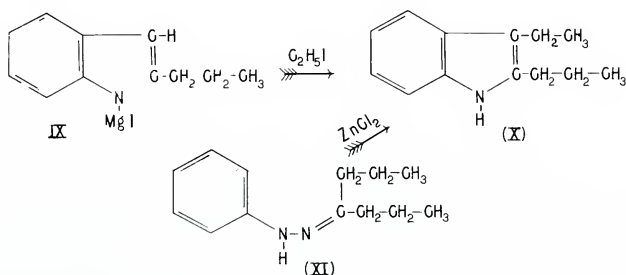
⁴Julian, P. L. and Pikel, J., 1933. J. A. C. S. 55:2105.

could not be α -methyl- β -ethylindole but must be α -propylindole. We soon found this evidence to be faulty, for when we had carefully purified his compound, it did not give the pine-shaving reaction, and we could only conclude that he secured the reaction because of impurities present in the sample tested. Indeed, we could likewise secure the reaction with all crude preparations before purification. These facts pointed to α -methyl- β -ethyl indole as representing the constitution of his product. Nevertheless more rigid proof of structure was undertaken. For this purpose we decided upon the use of the reaction between an indolylmagnesium halide and an alkyl halide, discovered some years ago by Oddo and his coworkers⁵ and employed more recently in synthetic work with much success in the laboratories of Hoshino and Majima.⁶ This reaction yields β -alkyl indoles and is illustrated by the reaction between α -methylindolylmagnesium iodide (VII) and ethyl iodide, the reaction we employed in deciding the constitution of Arbusow's " α -propyl indole".



This reaction led to an indole (VIII) identical in every respect with Arbusow's compound. His substance is therefore not α -propyl indole but α -methyl- β -ethyl indole.

This leaves as the only other compound described in the literature which might be α -propyl indole, the one prepared by Verley. That it is actually α -propyl indole we have proved in similar fashion. Thus α -propyl indolylmagnesium iodide (IX) gave on treatment with ethyl iodide α -propyl- β -ethyl indole (X). To synthesize (X) by another and unequivocal route, di-*n*-propyl ketonephenylhydrazone (XI) was prepared and subjected to the Fischer reaction, yielding a substance identical with (X) secured from Verley's α -propyl indole. Thus Verley's preparation is the only case without question where α -propyl indole has actually been synthesized.



⁵Oddo and Sanna, 1921. Gazz. Chim. Ital. (II) 51:334.

⁶Majima, R., 1924. Ber. 57:1449; Hoshino, T., 1933. Ann. 500:35.

with diazomethane, the desired chloroketone was obtained in excellent yield, and this chloroketone gave, likewise in excellent yield, the desired α -homoveratryl indole on heating with aniline.

In view of the ease with which diazomethane is now cheaply prepared in relatively large quantities in the laboratory,¹⁰ the chloromethyl ketones are readily accessible substances.

These chloroketones constitute the surest and most convenient starting material for preparation of α -substituted indoles.

Experimental Part

Arbusow's " α -Propyl Indole".

This substance was obtained according to the data of Arbusow in the yield stated by him. The crude product gave the "pine-shaving" reaction quite definitely. Accordingly, the picrate was prepared from equimolecular quantities of crude indole and picric acid in methyl alcoholic solution. Recrystallized from methyl alcohol it was obtained in dark red crystals, melting at 153°. On decomposing the pure picrate with alkali and recovering the indole in the usual way, the latter was secured pure; b.p. 159-161°, 14 mm. This product did not give the pine-shaving test.

Reaction of α -Methyl Indolylmagnesium Iodide with Ethyl Iodide.

To a Grignard solution from 10.9 g. methyl iodide and 2.4 g. magnesium in dry ether, 8.5 g. of α -methyl indole (m.p. 59-60) was added with good cooling. After evolution of methane had ceased, the mixture was heated for one hour on the water bath. The principal portion of the ether was then distilled off, iso-amyl ether was added to replace it, and to the cooled solution thus obtained 15.7 g. of ethyl iodide was added. After the little additional evolution of gas had subsided, the reaction mixture was sealed in a tube and heated for 10 hours in a boiling water bath. Considerable solid separated. The contents of the tube were taken up with water and ether, with addition of a small quantity of acid, and the ethereal solution distilled at 144-148° (9 mm.) giving the violet-red picrate of Arbusow's " α -propyl indole" and therefore identifying the latter as α -methyl- β -ethyl indole.

Verley's α -Propyl Indole.

Prepared according to the directions of Verley, this indole distilled at 160-162°, 15 mm., and on standing in the ice chest solidified; m.p. 32. The picrate, prepared from equimolecular quantities of picric acid and indole in ethereal solution, melted at 149°. In contrast to the picrate of α -methyl- β -ethyl indole, it is a light brick-red. This difference in color between picrates of α -substituted and of α , β -disubstituted indoles we have found for all cases studied. It constitutes a convenient sight method for differentiating between these two classes of indoles. Mixed with the picrate of Arbusow's indole, Verley's α -propyl- β -ethyl indole in exactly the same fashion as α -methyl indole was converted into the α -methyl- β -ethyl derivative. The product distilled at 158-162°, 11 mm. The deep red picrate, made in alcoholic solution and recrystallized from alcohol,

¹⁰Arndt, F., 1935. *Organic Syntheses*: 15:3.

melted at 116° . In order to identify it, the phenylhydrazone of di-n-propyl ketone was prepared, an oil which distilled at $162-163^{\circ}$, 11 mm. On fusion with anhydrous zinc chloride according to Fischer, α -propyl- β -ethyl indole was secured, identical with the product secured by action of ethyl iodide on the magnesium derivative of Verley's α -propyl indole. Likewise were the two picrates, m.p. 116° , identical. Thus Verley's product is actually α -propyl indole.

Preparation of α -Homoveratryl Indole.

After attempts to condense homoveratryl cyanide, prepared according to the method of Baker and Robinson¹¹ with N-methylanilino-acetic ester, had proved fruitless, the reaction of diazomethane on the acid chloride of dimethyl-dihydro-caffeic acid was studied. This acid chloride was prepared by action of thionyl chloride on the acid and distilled at 150° , 0.8 mm.

To a solution of 10.3 grams of the acid chloride dissolved in 200 c.c. absolute ether was added a diazomethane solution prepared from 30 grams of nitrosomethyl urethane. The solution was allowed to stand for 30 hours, first at low temperature and after twelve hours at room temperature. It was then concentrated at low temperature to about 250 c.c., cooled in a freezing mixture, and swept through with dry hydrogen chloride for about half an hour. After a short time nitrogen evolution began. Allowed to stand for 45 minutes, the solution was neutralized with aqueous bicarbonate, the ethereal solution dried over sodium sulphate and on concentration, beautiful crystals separated but melted on filter paper. The total residue on removal of ether was 10.5 g. Without further purification this crude chloroketone was mixed with 15 grams of aniline and heated at 120° for 20 minutes, then at 180° for 1 hour. The residue after heating was taken up in water and ether and the ethereal solution washed successively with 3% hydrochloric acid and water and vacuum distilled. The fraction boiling at $205-210^{\circ}$ (0.1 mm.) was collected, 3.6 g. A small portion of lower boiling material, $150-180^{\circ}$, and which crystallized, was discarded. Recrystallized from methyl alcohol, then from benzene petroleum ether, the 3.6 g. of material gave 2 g. of pure indole, m.p. $126-128^{\circ}$. It gave the pine shaving test.

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.83; H, 6.81

Found: C, 77.07; H, 1.94

¹¹Baker and Robinson, 1925. J. Chem. Soc. 127:1433.