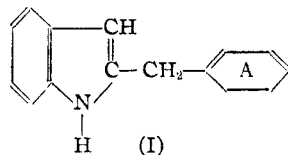


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

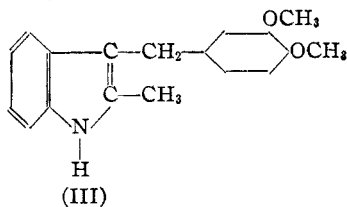
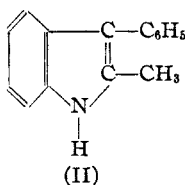
Studies in the Indole Series. I. The Synthesis of Alpha-Benzylindoles

BY PERCY L. JULIAN AND JOSEF PIKL

The present investigation was carried out for the purpose of developing a method for preparing α -benzylindole (I) and certain of its derivatives containing substituents in the phenyl group (A). These indoles are of interest to us in connection with work on the structure of certain of the *Angostura* alkaloids.



The usual methods for synthesizing alpha-substituted indoles are due to Fischer and to Madelung and Verley. The method of Fischer,¹ based on the elimination of ammonia from the phenylhydrazones of ketones is excellent for the preparation of indoles containing either a methyl or a purely aryl group in the alpha position. It is questionable, however, whether the Fischer method when applied to α -alkyl indoles other than α -methyl indoles, actually yields products of this structure.² It is certain that the Fischer synthesis when applied to the phenylhydrazone of methyl benzyl ketone, which might be expected to yield α -benzylindole (I), furnishes not the desired indole but instead α -methyl- β -phenylindole (II).³ Similarly the Fischer synthesis when applied to the phenylhydrazone of methyl-3,4-dimethoxyphenylethyl ketone, $\text{CH}_3\text{COCH}_2\text{CH}_2-\text{C}_6\text{H}_3(\text{OCH}_3)_2$, furnishes α -methyl- β -(3,4-dimethoxy)-benzylindole (III).⁴



The method of Madelung,⁵ which was modified by Verley,⁶ consists in the elimination of a molecule of water from the acyl derivatives of *o*-toluidines. This method, while satisfactory for the preparation of indoles with a purely aliphatic group in the alpha position, has been found to be inapplicable to the preparation of indoles of the type we desired.⁴

(1) Fischer and Hess, *Ber.*, **17**, 559 (1884).

(2) Hollins, "Synthesis of Nitrogen Ring Compounds," D. Van Nostrand Co., New York, 1927, p. 96.

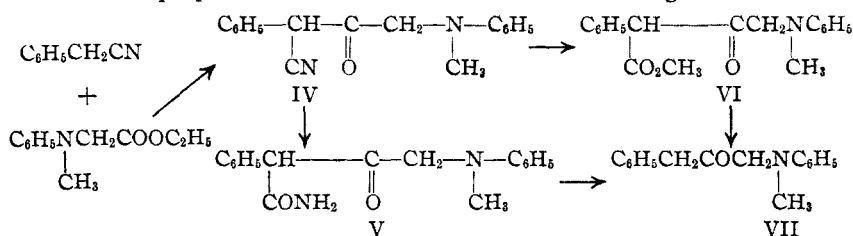
(3) Trenkler, *Ann.*, **248**, 106-113 (1888).

(4) Julian, Dissertation, Vienna, 1931.

(5) Madelung, *Ann.*, **405**, 58 (1914).(6) Verley, *Bull. soc. chim.*, [4] **35**, 1039 (1924); [4] **37**, 189 (1925).

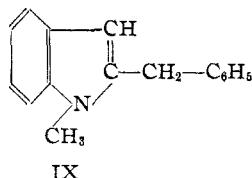
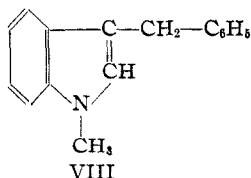
Since, then, the customary methods of synthesizing α -substituted indoles are not applicable to the preparation of α -benzylindoles, we developed a synthesis of this type of indole based on the following considerations.

α -Halogenated and α -hydroxy ketones yield indoles on being heated with arylamines.⁷ According to accepted views as to the course of this reaction (Bischler, Ref. 7) one should expect to secure α -benzylindoles from ketones of the type RCH_2COCH_2X where R is a phenyl or substituted phenyl group and X is either a halogen atom or an arylamino group. Unfortunately neither of these latter two classes of ketones is known and it was necessary first to develop a method of preparing them. Such a method of preparation was worked out in the following fashion



The various stages in this synthesis go smoothly once the proper experimental conditions have been determined. It is necessary to use methyl-anilinoacetic ester rather than the simpler anilinoacetic ester itself because the latter substance does not condense with benzyl cyanide but instead undergoes self-condensation in the presence of sodium ethylate to a diketopiperazine derivative.⁸

The methylanilino ketone (VII) on heating with aniline yields as principal product α -benzylindole (I). In addition to (I) we always obtained in varying yields another substance, which proved to be N-methyl- β -benzylindole (VIII). The formation of this substance is at odds with the "rule" for the course of the reaction as proposed by Bischler⁷ and generally accepted (compare Hell and Cohen, Ref. 7) and we propose in a later communication to consider in some detail the mechanism of indole formation in this reaction.

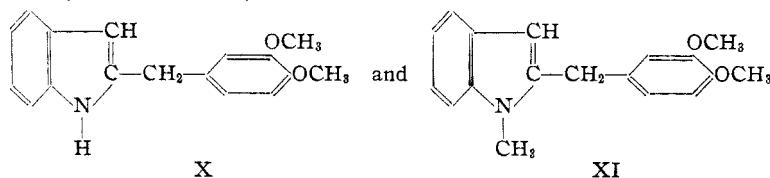


The methylanilino ketone (VII) on similar treatment with methyl-aniline yielded the N-methyl α -benzylindole (IX).

(7) Möhlau, *Ber.*, **15**, 2480 (1882); Fischer, *ibid.*, **21**, 1071, 1811 (1888); Woulff, *ibid.*, **20**, 428 (1887); Bischler, *ibid.*, **26**, 1336 (1893); Hell and Cohen, *ibid.*, **37**, 866 (1904).

(8) Vorländer, *ibid.*, **33**, 2568 (1900).

We have applied the method to the synthesis of two other derivatives of α -benzylindole, namely



To obtain the derivatives (X) and (XI) the only variant in the procedure we have outlined consists in the replacement of benzyl cyanide in the initial condensation by 3,4-dimethoxyphenylacetonitrile.

The α -benzylindoles thus prepared are all colorless crystalline solids. They show the characteristic properties of alpha-substituted indoles. Thus they develop color on exposure to light and air, they give the pine-shaving reaction and they are weak bases which yield brick-red picrates.

Experimental Part

N-Methylanilinoacetobenzyl Cyanide (IV).—A mixture of 48 g. of N-methylanilinoacetic ester and 29 g. of benzyl cyanide was added slowly to a solution of 8.5 g. of sodium in 85 cc. of absolute alcohol. The solution was heated on the water-bath for three hours and then poured into 800 cc. of cold water. The unchanged material was extracted with ether and the nitrile was precipitated by acidification with hydrochloric acid. The yield of crude nitrile melting at 115° was 55 g.; recrystallized from methyl alcohol, m. p. 121° .

Anal. Calcd. for $C_{17}H_{15}ON_2$: C, 77.27; H, 6.10. Found: C, 77.47; H, 6.14.

A solution of the nitrile in methyl alcohol is colored green with ferric chloride. The hydrochloride of the nitrile melts at 165° ; upon addition of water to its alcoholic solution, the nitrile is precipitated.

Phenyl N-Methylanilinoacetamide (V).—Attempts to convert the nitrile (IV) into the amide with concentrated hydrochloric acid were unsuccessful, the main product being a high melting substance (245°), difficultly soluble in ordinary solvents. The desired amide was obtained in satisfactory yield by the following procedure.

A solution of 10 g. of nitrile in 300 cc. of 90% sulfuric acid was heated for one hour at 125° . After cooling it was poured onto ice and the major portion of the sulfuric acid neutralized with sodium carbonate, whereupon 9.5 g. of the amide precipitated out. It was fairly pure and after one recrystallization from methyl alcohol melted sharply at 141° .

Anal. Calcd. for $C_{17}H_{15}O_2N_2$: C, 72.34; H, 6.43. Found: C, 72.74; H, 6.63.

α -N-Methylanilino- α' -phenylacetone (VII).—A solution of 15 g. of amide in 500 cc. of 5% hydrochloric acid was heated on the water-bath for four hours. A small quantity of oil separated, which was filtered off, the filtrate cooled, a large quantity of ether added, and neutralized with soda. About 0.5 g. of the 245° compound, described under the amide, separated. On evaporation of the ethereal solution, 11.8 g. of an oil remained which soon crystallized on standing in a cool place. On fractionating in high vacuum (0.05 mm., temp. of air-bath 180 – 190°), 10.0 g. of pure product was obtained which separated from ether-petroleum ether in long colorless prisms melting sharply at 37° .

The ketone is very sensitive toward atmospheric oxygen and in the course of a day is converted into a brown liquid if left open and exposed to air. Sealed in a vacuum, it

remained for months without the slightest deterioration even on constant exposure to light.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.33; H, 7.10. Found: C, 80.43; H, 7.08.

The oxime was prepared from equal quantities of hydroxylamine hydrochloride and ketone in alcoholic solution. After an hour's standing water was added and the oxime precipitated; recrystallized from alcohol, m. p. 119°.

Anal. Calcd. for $C_{16}H_{15}ON_2$: C, 75.59; H, 7.08; N, 11.00. Found: C, 75.48; H, 7.12; N (Micro-Pregl), 10.88.

γ -N-Methylanilino- α -phenylacetoacetic Methyl Ester (VI).—A solution of 25 g. of nitrile in 125 cc. of absolute methyl alcohol was saturated with dry hydrogen chloride at 0°. The hydrochloride of the nitrile which almost immediately separated gradually passed into solution on continued introduction of the gas. The solution was allowed to stand for ten to twelve days at room temperature, the ammonium chloride which had separated was filtered off and the filtrate allowed to evaporate slowly to dryness in a vacuum over potassium hydroxide. On taking up the resinous mass in alcohol and adding ether, 6.5 g. of the hydrochloride of the ester crystallized out; recrystallized from methyl alcohol, m. p. 158°.

Anal. Calcd. for $C_{18}H_{20}NO_2Cl$: C, 64.75; H, 6.04. Found: C, 64.75; H, 5.95.

From the alcoholic solution of the hydrochloride the free ester was precipitated with water. It melted at 73°.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 72.68; H, 6.43. Found: C, 72.55; H, 6.43.

The mother liquors were taken up in 900 cc. of 5% hydrochloric acid, heated on the water-bath for one and a half hours, and worked up in a manner similar to that employed on hydrolysis of the amide. In this way 7 g. of ketone melting at 37° was obtained along with 3.2 g. of the 245° compound already mentioned. The pure hydrochloride of the ester gave the ketone (VII) in especial purity, on hydrolysis with 5% hydrochloric acid. The constitution of our ketone is therefore well established through its production from ester and amide and its conversion into the oxime.

α -Benzylindole (I).—A mixture of 8 g. of ketone (VII), 30 g. of aniline, and 5.4 g. of aniline hydrochloride was heated to boiling for twenty minutes in a metal bath. Noticeable evolution of water took place. The mixture was cooled, treated with water and extracted with ether. The ethereal solution was shaken several times with 2.5% hydrochloric acid to remove the aniline. The residue on evaporation consisted of crystals mixed with a small quantity of oil. For purification the product was distilled in high vacuum (0.05 mm., temp. of air-bath, 170–180°). In this manner 4.8 g. of indole was obtained, which on recrystallization from petroleum ether melted sharply at 86°.

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.95; H, 6.28; N, 6.76. Found: C, 87.14; H, 6.02; N, (Micro-Pregl) 6.68.

If the melted indole is slowly cooled and then again melted, it liquefies sharply at 75°. If this melt is seeded with a trace of the 86° melting material, the substance crystallizes immediately and then melts sharply at 86°. When the melt is solidified by rapid cooling, the substance remelts constantly at 86°. We have here probably a case of dimorphism.

The picrate prepared from equivalent quantities of α -benzylindole and picric acid in methyl alcohol appeared in brick-red needles, melting at 115°.

Anal. Calcd. for $C_{21}H_{15}O_7N_4$: C, 57.78; H, 3.69. Found: C, 57.78; H, 3.63.

N-Methyl- β -benzylindole (VIII).—From the mother liquors on recrystallization of the indole (I) above, we obtained 0.2 g. of a substance melting at 61°. In one experiment where the reaction was carried out at 128° instead of at 180°, the yield of 61° compound was 30% of the theoretical. Analysis of the product gave: C, 86.97; H, 7.05. Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83.

N-Methyl- β -benzylindole was synthesized as follows. A mixture of 8.5 g. of dihydrocinnamic aldehyde methyl phenylhydrazone (m. p. 52°) and 10 g. of fused zinc chloride was heated for ten minutes at 170 – 180° . The cooled mass was extracted with ether, the ethereal solution shaken first with concentrated potassium hydroxide solution, then with 5% hydrochloric acid. On evaporation 7.5 g. of oil remained which distilled in high vacuum at 170° (temp. of air-bath). The distillate was taken up in alcohol and the indole melting sharply at 61° crystallized from the solution in colorless needles. A mixed melting point with the product from aniline and the ketone (VII) showed no depression. The picrate from the equivalent quantities of the indole and picric acid in ethereal solution melted at 120 – 121° .

N-Methyl- α -benzylindole (IX).—3.5 g. of ketone (VII) was mixed with 1.5 g. of methylaniline hydrochloride and 10 g. of methylaniline, and heated for one hour at 190 – 200° . The cooled mass was treated with water, extracted with ether, and the ethereal extract shaken in portions with a total of 100 cc. of 3% hydrochloric acid. Evaporation of the ether left 3.5 g. of oil which almost completely distilled over at 170 – 180° (temp. of air-bath) and 0.05 mm., and crystallized completely on standing in a cool place; recrystallized from ether–petroleum ether, m. p. 65° .

Anal. Calcd. for $C_{18}H_{18}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.58; H, 7.25; N (Micro-Pregl), 6.66.

The picrate, which easily dissociates in alcoholic solution into the indole (IX) and picric acid, was prepared from equivalent quantities of the indole and acid in ethereal solution as brick red needles, m. p. 97° .

Anal. Calcd. for $C_{22}H_{18}O_7N_4$: C, 58.65; H, 4.03; N, 12.44. Found: C, 58.50; H, 3.96; N (Micro-Pregl), 12.49.

TABLE I

Further products by method described	Formula	Yield, %	Corr. m. p., $^\circ C.$	Analyses	
				Calcd.	Found
N-Methylanilinoacetyl-3,4-dimethoxyphenylacetoneitrile	$C_{19}H_{20}O_3N_2$	69	110	C, 70.40	70.18
				H, 6.20	5.98
				N, 8.64 (Micro-Pregl)	8.60
α -N-Methylanilinoacetyl- α' -3,4-dimethoxyphenylacetamide ^a	$C_{19}H_{22}O_4N_2$	50	156	C, 66.66	66.39
				H, 6.40	6.25
				N, 8.20 (Micro-Pregl)	8.20
α -N-Methylanilino- α' -3,4-dimethoxyphenylacetone	$C_{18}H_{21}O_3N$	79	79.5	N, 4.67 (Micro-Pregl)	4.68
				C, 68.77	68.87
α -N-Methylanilino- α' -3,4-dimethoxyphenylacetoxime	$C_{18}H_{22}O_3N_2$	120		H, 7.06	6.76
				N, 8.91 (Micro-Pregl)	9.17
				C, 76.38	76.45
α -3,4-Dimethoxyphenylmethylindole (X)	$C_{17}H_{17}O_2N$	80	146	H, 6.41	6.55
				N, 5.24 (Micro-Pregl)	5.29
Picrate of (X)	$C_{23}H_{20}O_9N_4$		101		
N-Methyl- α -3,4-dimethoxymethylindole (XI)	$C_{18}H_{19}O_2N$	90	96	C, 76.66	76.45
				H, 6.86	7.08
				N, 4.98 (Micro-Pregl)	5.02
Picrate of (XI)	$C_{24}H_{22}O_9N_4$		97		

^a This amide was prepared from 5 g. of the nitrile by leaving it to stand for twenty-four hours at room temperature with 60 cc. of concentrated hydrochloric acid and 20 cc. of glacial acetic acid. Along with the amide there was obtained about 1 g. of high melting material (214°).

Summary

1. Four α -benzylindoles have been synthesized by a method based upon the reaction between α -arylamino ketones and arylamines.

2. In this connection a new type of ketone has been synthesized.

WASHINGTON, D. C.

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Sterically Hindered Tertiary Carbinols. 2,4,6-Tribromotriphenylcarbinol¹

BY AVERY A. MORTON AND LAWSON V. PEAKES, JR.

Only a little work² has been done on tertiary carbinols which have substituents in the 2,6 positions of one of the phenyl groups. Yet these compounds offer an interesting field, not only in the phenomenon of steric hindrance, but also in the chemistry of free radicals for which they are intermediates. We have determined the conditions for preparing 2,4,6-tribromotriphenylcarbinol. In so doing our study has developed two interesting points: namely, the addition of the Grignard reagent to the sterically hindered ester is far better if carried out in a mixture of chlorobenzene and ether as a solvent than in ether alone; and the yield of tertiary carbinol by the Grignard reaction is better through the addition of the Grignard reagent to the ester than to the ketone, although it would be possible to expect that the ketone is an intermediate phase of the reaction. Of further interest is the fact that a steric hindrance effect was not carried over into the behavior of the free radical, for a solution of 2,4,6-tribromotriphenylmethyl in benzene lost its color readily on exposure to air and changed its intensity of color on heating or cooling.

In view of the work of Boyd and Hatt,³ reporting that the ketone was an intermediate step in the preparation of a tertiary carbinol from an ester, we had expected that better yields would be obtained if we started with the ketone, a compound obtained more easily than the ester. This expectation was not realized.⁴ With 2,4,6-tribromobenzophenone only a trace of

(1) From a portion of the thesis of Lawson V. Peakes, Jr., presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1932.

(2) Lund, *THIS JOURNAL*, **49**, 1346 (1927), prepared several diorthomethoxy derivatives but could obtain no crystalline chloride from them. Reich, *Bull. soc. chim.*, [4] **21**, 219 (1917), prepared 2,6-dichlorotriphenylcarbinol in 6.3% yield from the diortho ester and phenylmagnesium bromide. We were unsuccessful in repeating Reich's experiment but believe that this may be due to using the methyl instead of the ethyl ester.

(3) Boyd and Hatt, *J. Chem. Soc.*, 898 (1927).

(4) Lund² found that the yield of carbinol from methylbenzoate and 2,4-dimethoxymagnesium iodide was better than that obtained by Kauffmann and Kieser, *Ber.*, **45**, 2335 (1912), who used the same Grignard reagent with the corresponding ketone. No other instance was found where a tertiary aromatic carbinol had been prepared by both methods in a yield sufficiently low to indicate that real difficulty with the reaction was encountered.