[Contribution from the Department of Chemistry of the University of Wisconsin]

The Preparation of Indoles from Diazo Ketones[1]

C. E. BLADES[2] AND A. L. WILDS

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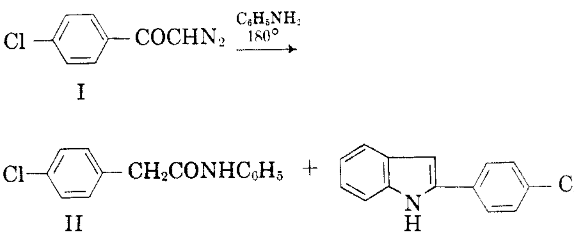
A method has been developed for the synthesis of substituted indoles from the reaction of diazo ketones with aniline salts and aniline at 180–200°. Diazo ketones derived from diazomethane and aromatic acid chlorides gave the 2-arylindole in good yields (generally 65–83%). The method also was applicable to N-alkylanilines and to aliphatic diazomethyl ketones. Diazo ketones derived from diazoethane gave the 3-methyl-2-arylindole (32–55% yield). The reaction is discussed in relation to the Bischler indole synthesis, which it parallels, and to the reaction of heterocyclic amine salts with diazo ketones reported by King and Miller.

In the course of investigations on the Wolff rearrangement, continuing the earlier studies of Wilds and Meader,[3] unusual results were encountered in several instances when the diazo ketone was heated with aniline. In addition to the anilide expected from the rearrangement, a substantial amount of another product was isolated which proved to be an indole derivative. By further study of the reaction it was possible to develop suitable conditions for making indole formation the major reaction.

The crystalline diazo ketone (I) from *p*-chlorobenzoyl chloride and diazomethane was found to undergo smooth rearrangement on heating with benzyl alcohol and γ-collidine, giving *p*-chlorophenylacetic acid in as high as 63% yield after hydrolysis. The same diazo ketone on heating with aniline, however, gave a mixture from which only small amounts of *p*-chlorophenylacetanilide (II) could be isolated together with 20–28% of a solid which proved to be 2-(*p*-chlorophenyl)indole (III). Previously Van Den Berghe[4] in this laboratory had obtained similar amounts (10–25%) of 2-*tert*-butylindole, as well as the expected β,β,β-trimethylpropionanilide, using the crude diazo ketone from trimethylacetyl chloride and diazomethane.

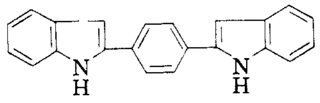
Since 2-substituted indoles are known to result when α-halo ketones are heated with aniline (the Bischler indole synthesis),[5] it seemed possible that the indoles were being formed in the present cases from chloro ketone contaminating the diazo ketone. Indeed, during the early studies on the reaction of acid chlorides with diazomethane Nierenstein[6] reported chloro ketones and other chlorine-containing compounds to be the main products. Arndt[7] and Bradley,[8] however, showed that the major products are diazo ketones when the acid chloride is added to excess diazomethane. We have observed that the crude diazo ketones prepared in this way may contain significant amounts (5–15%) of the chloro ketone, and this impurity can remain in the diazo ketone even after several recrystallizations. In the present case, however, a diazo ketone sample containing no more than 10% of the chloro ketone gave 28% of the indole III. Thus, at least part of the indole was being formed from the diazo ketone. These results suggested that aniline hydrochloride, formed from the chloro ketone or other chlorine-containing impurities, was reacting with the diazo ketone. It was found that larger amounts of the indole did result when some hydrochloric or hydrobromic acid was added to the aniline.



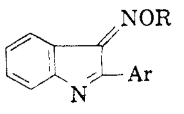
I

II

III



IV



Va, R = H
Vb, R = C_6H_5CO

By further study conditions were found whereby 2-*p*-chlorophenylindole (III) was obtained as the major product from the diazo ketone I. Two procedures were developed using aniline containing

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(1) From the Ph.D. Thesis of C. E. Blades, 1953. Presented in part at the 126th Meeting, A.C.S., New York, N.Y., Sept. 12–17, 1954, Abstracts, p. 13-O.

(2) Wisconsin Alumni Research Foundation Research Assistant, 1951–1953. Present address, Air Reduction Research Laboratories, Murray Hill, New Jersey.

(3) Wilds and Meader, *J. Org. Chem.*, **13**, 763 (1948).

(4) John Van Den Berghe, Ph.D. Thesis, Univ. of Wisconsin, 1952.

(5) See review by Julian, Meyer, and Printy, in Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N.Y., Vol. 3, p. 32.

(6) Lewis, Nierenstein, and Rich, *J. Am. Chem. Soc.*, **47**, 1728 (1925); Dale and Nierenstein, *Ber.*, **60**, 1026 (1927).

(7) Arndt, Eistert, and Partale, *Ber.*, **60**, 1364 (1927); Arndt and Amende, *Ber.*, **61**, 1122 (1928); Arndt, Eistert, and Amende, *Ber.*, **61**, 1949 (1928).

(8) Bradley and Robinson, *J. Chem. Soc.*, 1310, 1545 (1928); Bradley and Schwarzenbach, *J. Chem. Soc.*, 2904 (1928).

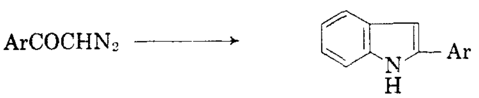
either aniline hydrobromide or an equivalent amount of boron trifluoride etherate. The highest yields (up to 82%) were obtained by heating at 180–200° for five hours. Nevertheless, most of the reaction took place very rapidly, for 65% of the indole III could be isolated after only three minutes of heating—the time during which nitrogen was evolved.

Having developed two procedures for preparing 2-*p*-chlorophenylindole (III) in good yield from *p*-chloro-α-diazoacetophenone (I), it was of interest to apply these to some other α-diazomethyl ketones. The results are summarized in Table I. In seven cases the yield of 2-arylindole was good ranging from 65% for 2-(*p*-methoxyphenyl)indole to 83% for 2-(2′-naphthyl)indole. With the *p*-nitrophenyl derivative, however, only a small amount of the indole could be isolated, and then only when heating was brief. This instability of a nitro compound toward heating in aniline is not surprising. The bis-diazoketone prepared from terephthalyl chloride and diazomethane was subjected to the indole reaction, giving some *p*-bis-(2-indolyl)benzene (IV), although in low yield (10%). The method was also used to prepare another alkyl derivative, 2-*n*-propylindole. Here the low yield (23% based on acid chloride) reflected in part the greater sensitivity to decomposition and difficulty in isolating this alkylindole on a small scale, compared to the arylindoles.[9]

In each case the product was the 2-substituted indole. Where the latter had been prepared previously, melting points were in agreement. In addition the indoles were characterized by preparing the benzoyl derivative of the 3-oximinoindolenine (Vb), a derivative requiring the 1- and 3-positions to be unsubstituted. Authentic samples of 2-(1′-naphthyl)-indole and 2-(2′-naphthyl)indole were prepared for comparison from the phenylhydrazone of the corresponding acetonaphthone by the Fischer indole synthesis. Although the respective products agreed in melting point, the diazo ketone method gave better results than the Fischer synthesis in these cases. The structures of 2-(*p*-nitrophenyl)indole and *p*-bis-(2-indolyl)benzene (IV) were not proved by independent synthesis, but are assigned by analogy to the others. In no case of this type in which aniline is the amine has the alternate 3-isomer been observed either from the diazo ketone procedure or from a bromomethyl ketone by the Bischler method.[15]

TABLE I

2-Arylindoles from Diazomethyl Ketones, Aniline, and an Anilinium Salt



Ar	Anilinium Salt	Reaction time (hrs.)	Yield, %	M.P. of Purified Product, °C.	M.P., °C. (Reported)	Reference
Phenyl	BF_3	1–5	67	189.5–190	189–190	10
p-Chlorophenyl	HBr	5–10	79–81	206–207	205–206	10
p-Chlorophenyl	BF_3	5	75–82	206–207	205–206	
p-Methoxyphenyl	BF_3	1–5	61–65	230.5–231	228–229	11
p-Nitrophenyl	BF_3	0.08	3	251–252	–	–
p-Tolyl	BF_3	1	77	220.5–221	218.5–219.5	12
4-Biphenylyl	HBr	5	75	300–300.5	302–304	12
Terephthalyl[a]	BF_3	2	10	Above 360	–	–
1-Naphthyl	HBr	1	73	140–141	140.5–141	present work (Fisher method)
1-Naphthyl	BF_3	5	76	140–141	140.5–141	
2-Naphthyl	HBr	5	69	203.5–204	196	13
2-Naphthyl	BF_3	5	83	203.5–204	196	
2-*n*-Propyl	HBr	0.17	23	147–150 (picrate)	149 (picrate)	14

[a] *p*-Bis-(2-indolyl)benzene (IV).

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(9) Compare the report of Catch, Hey, Jones, and Wilson [*J. Chem. Soc.*, 276 (1948)] that they failed to obtain 2-*n*-propylindole after attempts to cyclize the related anilinomethyl *n*-propyl ketone with aniline hydrobromide and aniline.

(10) Crowther, Mann, and Purdie, *J. Chem. Soc.*, **58** (1943).

(11) Koraczynski and Kierzek, *Gazz. chim. ital.*, **55**, 361 (1925).

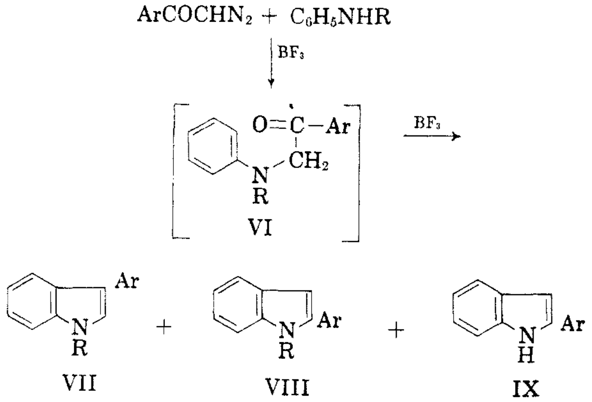
(12) Brown and Mann, *J. Chem. Soc.*, 847, 858 (1948).

(13) Brunck, *Ann.*, **272**, 201 (1893).

(14) Julian and Pikl, *Proc. Indiana Acad. Sci.*, **45**, 150 (1935).

(15) Julian, *et al.*[5] have reported cases of the Bischler synthesis in which both possible 2,3-diarylindoles were obtained when one aryl group was phenyl and the other *p*-tolyl or *p*-anisyl. While these examples are important to the mechanism of the Bischler type of reaction, they are not in conflict with the above generalization, which apparently holds for cases with only one aryl substituent available for the 2 or 3 position.

Next, representative runs were made using N-alkylanilines. In each case a mixture of three indoles resulted in which the 1-alkyl-3-arylindole (VII) predominated (see Table II). Thus, from *p*-chloro-α-diazoacetophenone and N-methylaniline, chromatographic separation of the products gave 39–40% of 3-(*p*-chlorophenyl)-1-methylindole (VII) 12–18% of 2-(*p*-chlorophenyl)-1-methylindole (VIII) and 7–8% of 2-(*p*-chlorophenyl)indole (III).



It is interesting to note that even higher yields (55–64%) of the 3-aryl-1-alkylindole resulted when N-ethylaniline was used, only traces (1–4%) of the 2-aryl-1-ethyl derivatives being formed. Thus, the transition from the 2-aryl to the 3-aryl isomer is almost complete as R changes from hydrogen to ethyl in the aniline derivative. These results suggest that the larger steric requirement with the N-alkyl group favors direct cyclization of the intermediate, presumed to be the anilino ketone (VI), rather than indirect cyclization *via* an anilino-anil (or isomeric enediamine), required to give the 2-aryl derivative.

Again the products obtained from the diazo ketones and N-alkylanilines paralleled, in general, the results in the Bischler synthesis using the bromo ketone. An apparent discrepancy is found in the work of Brown and Mann,[12] who isolated 2-aryl-1-methylindoles in two cases. Thus, they reported obtaining 2-(*p*-chlorophenyl)-1-methylindole, but not the 3-aryl isomer, from reaction of *p*-chlorophenacyl bromide with N-methylaniline. Although yields were not reported, it seems probable that in their examples the results may be attributed to a greater ease of isolation of the 2-isomer from the complex reaction mixture, rather than its predominance over the 3-isomer. In other examples they did obtain the 3-aryl-1-alkylindole.

TABLE II

INDOLES FROM DIAZOMETHYL KETONES AND N-ALKYLANILINES

Ar	R	Reaction Time (min.)	Yield of Indoles Isolated (%) 3-Ar-1-R	2-Ar-1-R	2-Ar-1-H
p-Chlorophenyl	Methyl	20–60	39–40	12–18	7–8
p-Chlorophenyl	Ethyl	60	55	0.3–0.5	1
p-Biphenylyl	Ethyl	60	64	4	2

The appearance in each case of a small amount of the 2-aryl-1-*H*-indole cannot be attributed to the presence of aniline in the N-alkylaniline. The N-methylaniline was specially purified and gave no test for primary amine in the Hinsberg reaction. Brown and Mann,[12] who observed a similar dealkylation in the Bischler synthesis, postulated this to arise by demethylation of N-methylanilinium bromide to aniline and methyl bromide with the latter alkylating more of the amine to give dimethylaniline. They were able to isolate some of the latter. It seems to us more probable that the methyl transfer occurs by direct nucleophilic attack of methylaniline on methylanilinium bromide at the high temperature (or possibly on the N-methylphenacylanilinium ion corresponding to VI). The lower yield of indole resulting from dealkylation in the N-ethyl series is consistent with the increased hindrance to such a nucleophilic displacement.

We were interested in the possibility of extending the indole synthesis to diazoethyl ketones, which have been made readily available by the work of Wilds and Meader.[3] If the parallel to the Bischler synthesis continued, the reaction of α-diazoethyl aryl ketones with aniline in the presence of the aniline salt would give the 3-methyl-2-arylindole.

Five diazoethyl ketones were prepared and subjected to the conditions for indole formation developed in the previous series (see Table III). The yields (32–55%) were lower than in the diazomethyl series; the products were less stable and considerably more difficult to isolate, for example, decomposing on the alumina column when chromatography was attempted. This greater tendency to decompose was observed with the crude 3-methyl-2-(2′-naphthyl)indole obtained from either the Bischler or Fischer syntheses as well as from the diazoketone. The indole from the *p*-tolyl diazoketone agreed in melting point with 3-methyl-2-(*p*-tolyl)indole as prepared by the Fischer method.[16] 3-Methyl-2-(*p*-chlorophenyl)indole and 3-methyl-2-phenylindole were also prepared from the appropriate phenyl hydrazones and agreed in melting point with the products from the diazoketones.

From the reactions of their respective diazo-

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[16] Buu-Hoï and Nguyen-Hoán, *Rec. trav. chim.*, 68, 441 (1949).

TABLE III

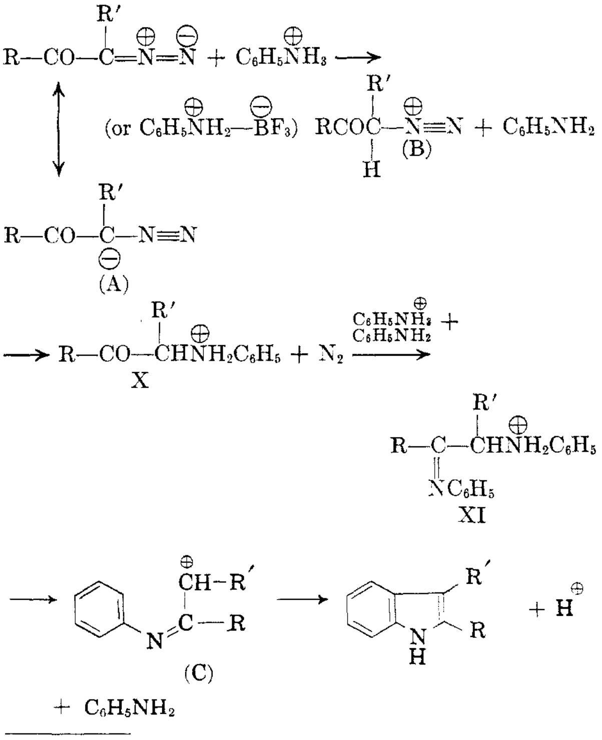
INDOLES FROM α-DIAZOETHYL KETONES AND ANILINE

Ar	Catalyst	Reaction Time (hrs.)	Yield, %	M.P. of purified sample, °C.	M.P. of TNB Derivative, °C.
p-Chlorophenyl	BF_3	5	42	175–176	131–131.5
p-Chlorophenyl	HCl	1	46	175–176	131–131.5
Phenyl	HBr	1	32	89.5–91	155–155.5
p-Tolyl	HBr	0.08	50	116–117	150–150.5
p-Biphenylyl	HBr	0.33	55	162–163.5	176–176.5
2-Naphthyl	HBr	2	—	—	197–197.5

ketones small amounts of *p*-chlorobenzanilide and benzanilide were isolated, evidently the result of some cleavage of the diazoketone by aniline at the elevated temperature. Wilds and Meader[3] observed a related hydrolytic cleavage of some diazoethyl ketones to the acid during warming with potassium hydroxide solutions. The indole synthesis was unsuccessful with the diazoethyl ketone derived from *p*-anisoyl chloride. From the crude diazo ketone the product obtained was *p*-anisanilide in 69% yield, when the aniline reaction was carried out at 190°; at 160° only 25% of the anilide was obtained but none of the indole could be isolated in this case either. Similar results were obtained with the diazoketone derived from 1-diazopropane and *p*-anisoyl chloride.

The lower yields of indoles from the diazoethyl ketones reflect the greater opportunity for side reactions with aniline in this series. The work of Baddeley, Holt, and Kenner[17] is of interest in this connection. From an attempt to carry out the rearrangement of α-diazopropiophenone to α-phenylpropionanilide using silver nitrate and aniline in ethanol solution, they isolated some β-anilinopropiophenone. Although details have not been reported by them, we have confirmed this result. This β-anilino ketone presumably arises by an elimination reaction to the vinyl ketone followed by re-addition of aniline. At the higher temperature of our indole synthesis the conditions are suitable for such an elimination with or without re-addition, as well as for polymerization of the vinyl ketone, and may account in part for the increased decomposition and lower yields which occurred in the diazoethyl series. The intermediate α-anilinium ketone ion X which Baddeley, *et al.* presumed to be involved in their elimination step is the same as that thought to be formed initially in our indole synthesis.

In considering the probable route by which the diazoketones are converted into indole derivatives, the parallel to results in the Bischler synthesis is significant. Indeed, it seems likely that the first step in each involves the formation of a common intermediate, the α-anilino ketone X (or its salt). In the present case the anilino ketone would arise from the aniline salt, functioning as an acid in its reaction with the diazoketone. Thus, by a mechanism paralleling that for conversion of an acid to a methyl ester with diazomethane, the diazo ketone (A) would accept a proton from the anilinium salt to form a short-lived α-diazonium ketone (B) which through nucleophilic attack by aniline leads to the salt of the anilino ketone X. The use of aniline as the solvent allows this reagent to compete favorably with bromide ion in the displacement. The succeeding steps parallel the Bischler synthesis.[18] One reasonable way in which this can be formulated is the reaction of anilinium ion with the carbonyl group to give the anilino anil; the latter in the form of its salt XI loses the original aniline to give a carbonium ion C which can cyclize with loss of a proton and shift of hydrogens to give the indole.[5,12,19]



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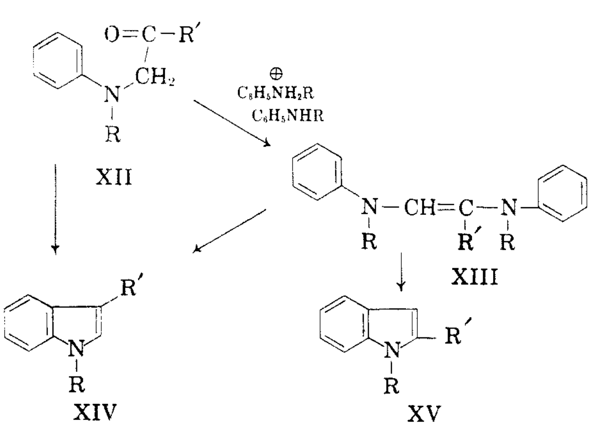
(17) Baddeley, Holt, and Kenner, *Nature*, **163**, 766 (1949).

(18) Although the details of the Bischler mechanism are not fully settled, the steps presented here seem to us in accord with the known facts. The recent experiments of Weygand and Richter [*Chem. Ber.*, **88**, 499 (1955)] with C^{14} labeled aniline leave no doubt as to the equilibrium between phenacylaniline and aniline under conditions of indole formation.

(19) Julian, Meyer, Magnani, and Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).

With an N-alkylaniline, the usual type of anilino anil XI is not possible, but the isomeric enamine XIII provides the route to the 2-substituted indole XV, while direct cyclization of the anilino ketone XII (or the alternate direction of cyclization of XIII) can lead to the favored 3-substituted indole XIV.



In an effort to support the first step in the diazo ketone reaction, efforts were made to isolate the α-anilino ketone. It was soon recognized that the conditions normally employed for the indole synthesis could not be used, since a 65% yield of the indole (III) was isolated when heating of α-diazo-p-chloroacetophenone was stopped as soon as nitrogen evolution was complete (3 minutes). Rapid conversion of anilino ketones to the indoles has been observed in Bischler cyclizations. A number of attempts were also made using lower temperatures, with or without a solvent such as ethanol, and with 1-naphthylamine replacing aniline as the primary amine. Although unstable mixtures were obtained which could be converted further to an indole, the pure anilino ketone could not be isolated. There is ample evidence in the literature[10,20–22] to indicate the unstable nature of such compounds, especially when impure, and the elevated temperature (75–100°) necessary for reaction of the diazo ketone with the aniline salt evidently favored such decomposition. It may be noted that recently Yates has succeeded in isolating some of the anilino ketone from reaction of α-diazoacetophenone with aniline in the presence of copper.[23]

That the reaction of the aniline salt takes this course is supported by the work of King and Miller with salts of tertiary heterocyclic amines.[24] They found, for example, that pyridine hydrochloride reacted with α-diazoacetophenone in ethanol solution to give an excellent yield (84%) of N-phenacylpyridinium chloride. Three of the diazo ketones used in the present work were compared in this reaction by heating with 4-picoline hydrobromide in ethanol under similar conditions. The yield of the phenacyl picolinium salt isolated was 92% from α-diazoacetophenone, 78% from p-chloro-α-diazoacetophenone, and only 37% from p-chloro-α-diazopropiophenone.

It was shown that a quaternary salt such as these could be used to prepare the indole; heating N-phenacyl-4-picolinium bromide with aniline gave 2-phenylindole in 69% yield. The over-all yield from the diazo ketone (63%) by this route approached that of the direct method (67%). The decreased yield of phenacyl salt with the diazoethyl ketone also paralleled the lower yields of indole by the direct method.

It was of interest to see if diazo ketones could be converted to phenacyl tertiary amines in one step. The two-step procedure involving first reaction with hydrobromic acid to give the bromo ketone has been used extensively. There was little reaction of α-diazoacetophenone or its p-chloro derivative with piperidine hydrobromide in boiling alcohol, in contrast to the more acidic picoline hydrobromide. In the higher boiling 2-methoxyethanol, however, α-1-piperidylacetophenone hydrobromide was formed in about 74% yield.

EXPERIMENTAL[25]

Acid chlorides. Most of these were prepared from the pure acid using thionyl chloride, as described earlier;[3] the best yields of distilled acid chloride were in the range 89–93%. p-Nitrobenzoyl chloride (m.p. 71–72°) and p-phenylbenzoyl chloride (m.p. 111.5–112.5°) were recrystallized from benzene. Terephthalyl dichloride was prepared as described by Cohen and de Pennington,[26] m.p. 82–83.5°.

Diazohydrocarbons. A distilled solution of diazomethane in ether was prepared[27] from N-nitroso-N-methylurea, and diazoethane from N-nitroso-N-ethylurethan by the method of Wilds and Meader.[3] In one run diazoethane was prepared in 37% yield from N-nitroso-N-ethylurea (obtained in 36% yield) and 1-diazopropane in 60% yield from N-nitroso-N-n-propylurea (obtained in 35% yield, m.p. 76–77°). The amount of diazohydrocarbon was determined by the benzoic acid method.[3]

Preparation of diazomethyl ketones. The usual procedure was followed in which an ethereal solution of acid chloride was added dropwise to a rapidly stirred solution of diazomethane (2.5–3.0 equivalents) at 0–5°. Analysis for chlorine in the crude diazo ketone indicated amounts of chloro ketone varying from 5 to 15%. The crude products were satisfactory for conversion to the indole. α-Diazo-2-acetonaphthone, obtained in 86% yield, was recrystallized from benzene–petroleum ether, m.p. 81–83°.

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(20) Bischler and Brion, *Ber.*, **25**, 2860 (1892).

(21) Verkade and Janetzky, *Rec. trav. chim.*, **62**, 763 (1943).

(22) Möhlau, *Ber.*, **14**, 171 (1881); **15**, 2466 (1882).

(23) Yates, *J. Am. Chem. Soc.*, **74**, 5376 (1952).

(24) King and Miller, *J. Am. Chem. Soc.*, **70**, 4154 (1948).

(25) All m.ps. are corrected; those designated micro were determined on a calibrated hot stage with a microscope. We are indebted to Messrs. Edward Shiner, Bennett Buell, Gerald Gilbert, John Belew, Gershen Winestock, Edmund Eisenbraun, and Sanford Aronovic for some of the microanalyses. Ultraviolet spectra were determined in 95% ethanol using a Cary spectrophotometer, and molecular extinction coefficients ϵ are reported.

(26) Cohen and de Pennington, *J. Chem. Soc.*, 61 (1918).

(27) Arndt, *Org. Syntheses*, Coll. Vol. **2**, 165 (1943).

Anal. Calc'd for $C_{12}H_8N_2O$: C, 73.4; H, 4.11. Found: C, 73.2; H, 4.14.

α-Diazo-p-phenylacetophenone was obtained in 83% yield and was recrystallized from petroleum ether, m.p. 119–120.5°.

Anal. Calc'd for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.54. Found: C, 75.8; H, 4.34.

p-Bis-(diazoacetyl)benzene, obtained in 98% yield, sintered at 180° without melting at 300°.[28] For characterization it was converted in acetone solution with 5% aqueous hydrochloric acid into *p*-bis-(chloroacetyl)benzene in 75% yield, m.p. 185–186° after recrystallization from alcohol. This melting point agrees with that reported by Ross (186°),[28] but not that of Ruggli and Gassenmeier (153°)[29] for the chlorination product of *p*-diacetylbenzene.

Anal. Calc'd for $C_{10}H_8Cl_2O_2$: C, 52.0; H, 3.49. Found: C, 51.6; H, 3.71.

Preparation of diazoethyl ketones. The procedure of Wilds and Meader was used.[3] The *p*-chloro and *p*-methyl derivatives of α-diazopropiophenone and α-diazo-2-propionaphthone were recrystallized from petroleum ether at Dry Ice temperatures. α-Diazopropiophenone and its *p*-methoxy derivative were obtained as oils and used as such. The chlorine content of the latter corresponded to a maximum of 20–25% of the chloro ketone, with less than 7% unreacted acid chloride.[30]

α-Diazo-p-phenylpropiophenone was obtained in 71% yield, m.p. 103–104.5° from petroleum ether.

Anal. Calc'd for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.12. Found: C, 76.3; H, 5.25.

Rearrangement of p-chloro-α-diazoacetophenone. (*a*). *With benzyl alcohol and γ-collidine.* Following the procedure described previously,[3] *p*-chlorophenylacetic acid was obtained in 55–63% yield after hydrolysis. (*b*). *With aniline.* A mixture of 1 g. of *p*-chloro-α-diazoacetophenone (m.p. 114–114.5°) and 5 cc. of freshly distilled aniline was immersed in a preheated oil-bath at 180°. After the vigorous reaction was over (2–3 minutes, nitrogen evolution 86–87% of theory) the mixture was cooled in an ice-water bath. The product was a mixture from which variable amounts (20–28%) of 2-(*p*-chlorophenyl)indole, m.p. 207.5–208°, were isolated and only small amounts (6% or less) of *p*-chlorophenylacetanilide. The highest amount of the latter (30%) was obtained by adding the powdered diazo ketone in portions to boiling aniline.

Rearrangement of p-nitro-α-diazoacetophenone. While the collidine-benzyl alcohol procedure gave the rearranged acid in 63% yield, the aniline procedure gave *p*-nitrophenylacetanilide in only 23% yield. After recrystallization from alcohol the anilide melted at 212–213°; reported[31] 211.7–213.2°.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.72. Found: C, 65.3; H, 4.81.

2-p-Chlorophenylindole. General procedure. After studying many of the variables, the following procedure was adopted. A mixture of 1.0 g. (5.5 mmoles) of *p*-chloro-α-diazoacetophenone and 1 g. (5.7 mmoles) of finely powdered aniline hydrobromide[32] (or as an alternative 0.9 g. of boron trifluoride etherate added after the aniline) was placed in a 50-ml. flask and 10 to 15 ml. of freshly distilled aniline was added at room temperature. The mixture was swirled and the flask, with condenser attached, was immediately immersed in a pre-heated oil bath at 175–200°. Nitrogen evolution (85–92%) was complete in 3 minutes, and heating was continued for five hours. The cooled reaction mixture was treated with an excess of a solution of sodium carbonate and steam-distilled to remove excess aniline. The solid residue was collected and recrystallized either from carbon tetrachloride or a mixture of benzene and petroleum ether, giving 0.87 g., m.p. 204–205°. The residue from the evaporated mother liquor was sublimed under reduced pressure to separate the indole from the black tars which were always present.[33] In this manner additional material melting from 195–200° to 204–206.5° was obtained to bring the total yield to 75–82%.

The purest sample melted at 206.6–207.1°; reported[10] 205–206°. Ultraviolet spectrum: maxima at 249.5 mμ (23,400), 313.5 mμ (27,200); inflection at 227 mμ (17,900); minima at 235 mμ (17,000), 270 mμ (14,300).

Nitrosation[34] by treatment in acetic acid with an aqueous solution of sodium nitrite at room temperature gave 72% of 3-oximino-2-(*p*-chlorophenyl)indolenine, which was recrystallized from acetic acid, m.p. 275.0–275.3° (dec.).

Anal. Calc'd for $C_{14}H_9ClN_2O$: C, 65.5; H, 3.53. Found: C, 65.4; H, 3.83.

The crude oximino derivative was shaken with benzoyl chloride and 10% sodium hydroxide solution, and the product was recrystallized from benzene or acetone to give 3-benzoyloximino-2-(*p*-chlorophenyl)indolenine as orange needles, m.p. 169–170°. (See Table IV.)

In the formation of the indole somewhat lower yields resulted when the time was reduced, although even from a run heated for only 3 minutes (aniline hydrobromide procedure) 65% of the indole was isolated. Use of aqueous hydrobromic or hydrochloric acids gave lower yields, while aniline hydrogen sulfate or the hydriodide was unsatisfactory.

Preparation of 2-substituted indoles from diazomethyl ketones. The general procedure described above for 2-(*p*-chlorophenyl)indole was followed, using 1.0 g. of the diazo ketone, an equimolar amount of the acidic catalyst (boron trifluoride etherate or aniline hydrobromide), and 10 ml. of freshly distilled aniline. After heating at 175–200° for one to five hours, aniline was removed from the cooled reaction mixture either by making basic and steam-distilling or by partitioning between benzene or ether and 10% hydrochloric acid. The product then was purified by recrystallization. The centrifuge filter tube described recently by Blades and Schöniger[35] simplified recrystallizations of the air-sensitive indoles under a nitrogen atmosphere and with minimum loss. The results on the series of indoles prepared from diazomethyl ketones are recorded in Tables I and IV. In most cases a 3-benzoyloximinoindolenine derivative was prepared as indicated above.[34]

2-(1-Naphthyl)indole was also prepared using the procedure of Crowther, *et al.*[10] for the Fischer synthesis. From 0.5 g. of 1-acetonaphthone, 0.35 g. of phenylhydrazine, and 3 g. of freshly fused zinc chloride, heating at 125° for 45 minutes, 7% of the indole was obtained after recrystallization from ethanol. This product melted at 140.5–141° and showed no lowering in m.p. when mixed with 2-(1-naphthyl)-indole obtained from α-diazo-1-acetonaphthone.

2-(2′-Naphthyl)indole was prepared in 20% yield from 2-acetonaphthone phenylhydrazone with boron trifluoride as the catalyst by the method of Snyder.[37] The melting point alone or mixed with a sample of the indole obtained from α-diazo-2-acetonaphthone was 203.5–204°. Ultra-

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[28] Ross, *J. Chem. Soc.*, 752 (1950).

[29] Ruggli and Gassenmeier, *Helv. Chim. Acta*, **22**, 501 (1939).

[30] Total chlorine was determined by a modified Stepanow procedure [Bacon, *J. Am. Chem. Soc.*, **31**, 49 (1909)] and acid chloride content by a selective methanolysis method developed by Van Den Berghe.[4]

[31] Ward and Jenkins, *J. Org. Chem.*, **10**, 373 (1945).

[32] The salt was crystallized from 95% ethanol and dried *in vacuo* over calcium chloride.

[33] From the lower-boiling fraction diphenylamine was isolated, m.p. 54.7–55.4°, benzene sulfonamide derivative, m.p. 127.5–128.2°, mixture m.ps. undepressed.

[34] Spica and Angelico, *Gazz. chim. ital.*, **29**, 49 (1899).

[35] Blades and Schöniger, *Anal. Chem.*, **26**, 1256 (1954).

[36] Campbell and Cooper, *J. Chem. Soc.*, 1208 (1935).

[37] Snyder and Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943).

TABLE IV

2-SUBSTITUTED INDOLES AND THEIR BENZOYLOXIMINO DERIVATIVES

		Indole				3-Benzoyloximino Derivative				
		Carbon		Hydrogen		M.p.,	Carbon		Hydrogen	
2-Substituent	Formula	Calc'd	Found	Calc'd	Found	°C.	Calc'd	Found	Calc'd	Found
Phenyl[a]	—	—	—	—	—	152–153[i]	—	—	—	—
p-Chlorophenyl[b]	$C_{14}H_{10}ClN$	73.9	74.2	4.43	4.42	169–170[e]	69.9	70.1	3.63	3.70
p-Methoxyphenyl[a]	$C_{15}H_{13}NO$	80.7	80.9	5.87	6.12	159.5–160.5[g]	74.1	73.6	4.32	4.32
p-Nitrophenyl[c]	$C_{14}H_{10}N_2O_2$	70.6	70.2	4.23	4.46	—	—	—	—	—
p-Tolyl[a]	$C_{15}H_{13}N$	86.9	86.7	6.32	6.33	134–134.5[f]	77.6	77.9	4.74	4.75
p-Biphenyly[d]	$C_{20}H_{15}N$	89.2	89.2	5.61	5.59	157.5–158.5[e]	80.6	80.4	4.51	4.22
Terephthalyl[e,h]	$C_{22}H_{16}N_2$	85.6	85.2	5.23	5.07	—	—	—	—	—
1-Naphthyl[a]	$C_{18}H_{13}N$	88.9	88.9	5.38	5.46	171.5–172.5[f]	79.8	79.4	4.29	4.31
2-Naphthyl[a]	$C_{18}H_{13}N$	88.9	88.6	5.38	5.52	211–212.5[e]	79.8	80.2	4.29	4.55

[a] Recrystallized from 95% alcohol. [b] From carbon tetrachloride. [c] From benzene. [d] From 2-methoxyethanol. [e] From acetone. [f] From acetone-methanol. [g] From chloroform-methanol. [h] *p*-Bis-(2-indolyl)benzene. [i] Reported, m.p. 153°.[36]

violet spectrum of 2-(2-naphthyl)indole: maxima at 241 mμ (30,000), 277 mμ (16,500), 286 mμ (21,100), 324 mμ (19,300); minima at 270 mμ (15,500), 280 mμ (15,400), 293 mμ (12,000). This indole was previously prepared by Brunck,[13] by the Fischer method with zinc chloride, in 32% yield from an acetylated naphthalene mixture, but was incorrectly assigned the structure of 2-(1-naphthyl)indole.

Indoles from diazomethyl ketones and N-alkylanilines. A mixture of 2.0 g. of the diazomethyl ketone, an equimolar quantity of boron trifluoride etherate and 10 ml. of freshly distilled N-alkylaniline[38] in a 50-ml. flask was immersed in a pre-heated oil bath at 175° for the period of the reaction (20 minutes to 1 hour). The cooled reaction mixture in ether was extracted with 10% hydrochloric acid, and water, and dried over potassium carbonate. The ethereal solution was evaporated to dryness and the residue, which consisted of a mixture of three indoles, was sublimed under reduced pressure and fractionally crystallized[35] from petroleum ether. Thus it was possible to obtain the predominant indole in a relatively pure state. The mixed fractions were separated by chromatography on activated alumina. (See Table II.)

p-Chloro-α-diazoacetophenone and N-methylaniline. The sublimate (82–83%) was fractionally crystallized from petroleum ether (60–68°) to give 8% of 2-(*p*-chlorophenyl)-indole, m.p. 202.5–204°, and 26% of 3-(*p*-chlorophenyl)-1-methylindole, m.p. 90–96°. Chromatography of the mother liquors yielded an additional 14% of 3-(*p*-chlorophenyl)-1-methylindole, m.p. 93–98°, 12% of 2-(*p*-chlorophenyl)-1-methylindole, m.p. 118–121° and 6% of a mixed fraction, m.p. 72–105°. In a duplicate run the respective indoles were obtained in 36, 17, and 7% yields, as well as 14% of a mixed fraction, m.p. 78–87°. Recrystallization from petroleum ether raised the melting point of 2-(*p*-chlorophenyl)-1-methylindole to 120.7–121.3° (reported[12] 119–120°) and of 3-(*p*-chlorophenyl)-1-methylindole to 96.6–97.0° (reported[12] 96°). Ultraviolet spectrum for 3-(*p*-chlorophenyl)-1-methylindole: maxima at 227.5 mμ (27,800), 273.5 mμ (16,100), 292.5 mμ (16,200); minima at 249.5 mμ (6000), 281.5 mμ (15,400); for 2-(*p*-chlorophenyl)-1-methylindole: maxima at 225 mμ (27,800), 242.5 mμ (20,000), 298.5 mμ (20,900); minima at 236.5 mμ (18,900), 262 mμ (10,800).

p-Chloro-α-diazoacetophenone and N-ethylaniline. Fractional crystallization of the sublimate of the reaction mixture (85% yield) gave 44% of 3-(*p*-chlorophenyl)-1-ethylindole, m.p. 73.5–79.5°. The remaining material was nitrosated by treating a solution in 30 cc. of acetic acid with 0.035 g. of sodium nitrite in 0.5 cc. of water. After 2 hours the product was isolated by extraction and chromatographed to give an additional 11% of 3-(*p*-chlorophenyl)-1-ethylindole and less than 1% each of 3-nitroso-2-(*p*-chlorophenyl)-1-ethylindole, m.p. 136.5–137.5° (reported[10] 138–139°), and 3-oximino-2-(*p*-chlorophenyl)indolenine, m.p. 259–261°. In another run separated by chromatography only, 0.5% of 2-(*p*-chlorophenyl)-1-ethylindole, m.p. 86–87° (reported[10] 86–87°) and 1% of 2-(*p*-chlorophenyl)indole, m.p. 202–206.5°, were isolated along with the major product.

A purified sample of *3-(p-chlorophenyl)-1-ethylindole*, after recrystallization from petroleum ether (60–68°), melted at 80–80.5°; reported[12] 79–80°.

Anal. Calc'd for $C_{16}H_{14}ClN$: C, 75.1; H, 5.52. Found: C, 75.2; H, 5.68.

α-Diazo-p-phenylacetophenone and N-ethylaniline. The unsublimed product (91% yield) was fractionally crystallized from 95% ethanol giving 37% of 3-(*p*-biphenylyl)-1-ethylindole, m.p. 105–110°. Chromatography of the mother liquors after removal of solvent gave an additional 27% yield of this indole, as well as 2% of 2-(*p*-biphenylyl)indole, m.p. 296.5–297.5° and 4% of 2-(*p*-biphenylyl)-1-ethylindole, m.p. 133.5–135°. Recrystallization of 3-(*p*-biphenylyl)-1-ethylindole from 95% ethanol raised the melting point to 111.5–112° (reported 109–111°).[12]

Anal. Calc'd for $C_{22}H_{19}N$: C, 88.9; H, 6.44. Found: C, 88.5; H, 6.30.

Recrystallization of 2-(*p*-biphenylyl)-1-ethylindole from a mixture of petroleum ether (60–68°) and acetone raised the melting point to 135.1–135.7° (reported 133–134.5°).[12]

Anal. Calc'd for $C_{22}H_{19}N$: C, 88.9; H, 6.44. Found: C, 88.9; H, 6.68.

Indoles from α-diazoethyl ketones and aniline. The same general procedure used with diazomethyl ketones was followed, except the period of heating was usually shorter. The product was isolated by extraction with ether, washing successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. The crude material was purified either by sublimation or crystallization from a suitable solvent. The results are summarized in Table III.

2-(p-Chlorophenyl)-3-methylindole (m.p. 172–176°) was obtained from *p*-chloro-α-diazopropiophenone in 42 and 46% yields using boron trifluoride and aniline hydrochloride, respectively, as acid catalysts. Repeated recrystallization of the indole from methanol and finally from petroleum ether (60–68°) gave colorless, transparent prisms, m.p. 175–176°. Ultraviolet spectrum: maxima at 228.5 mμ (22,900), 244.5 mμ (22,700), 310.5 mμ (22,900); minima at 236.5 mμ (20,800), 273 mμ (12,700).

An authentic sample of 2-(*p*-chlorophenyl)-3-methylindole was prepared by the Fischer method from *p*-chloropropiophenone phenylhydrazone using boron trifluoride etherate as the catalyst in acetic acid, boiling for 30 minutes. The indole was isolated in 24% yield, m.p. 175–176° alone

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(38) N-Methylaniline was purified through the addition product with cuprous chloride by the method of Jones and Kenner [*J. Chem. Soc.*, 711 (1932)]. The Hinsberg test for primary amine was negative.

or when mixed with the indole obtained from *p*-chloro-α-diazopropiophenone.

Anal. Calc'd for $C_{15}H_{12}ClN$: C 74.5; H, 5.01. Found: C, 74.6; H, 5.00.

The *s-trinitrobenzene derivative* was prepared and recrystallized from 95% ethanol as fine red needles, m.p. 131–131.5°.

Anal. Calc'd for $C_{15}H_{12}ClN \cdot 2C_6H_3N_3O_6$: C, 48.6; H, 2.72; N, 14.7. Found: C, 49.0; H, 2.81; N, 14.7.

2-(p-Biphenylyl)-3-methylindole was obtained from α-diazo-*p*-phenylpropiophenone in 52% yield (m.p. 159–164° from benzene–petroleum ether) using aniline hydrobromide and heating in an oil-bath at 200° for 20 minutes (nitrogen evolution 89%). A sample was recrystallized from 95% ethanol as colorless plates, micro m.p. 162.5–164°.

Anal. Calc'd for $C_{21}H_{17}N$: C, 89.0; H, 6.05. Found: C, 88.9; H, 6.25.

An additional 3% of 2-(*p*-biphenylyl)-3-methylindole was obtained by sublimation and recrystallization of the residue.[39]

The *s-trinitrobenzene derivative of 2-(p-biphenylyl)-3-methylindole* was prepared and recrystallized from 95% ethanol as deep red needles, m.p. 176–177°.

Anal. Calc'd for $C_{21}H_{17}N \cdot 2C_6H_3N_3O_6$: C, 55.7; H, 3.27. Found: C, 55.8; H, 3.28.

3-Methyl-2-phenylindole was obtained in 32% yield (m.p. 86–87.5°) from a crude sample of α-diazopropiophenone. Further purification of this sample by recrystallization failed, although it was readily purified as the *s-trinitrobenzene* derivative, fine red needles from alcohol, m.p. 155.0–155.5°.

Anal. Calc'd for $C_{15}N_{13}N \cdot C_6H_3N_3O_6$: C, 60.0; H, 3.84. Found: C, 60.0; H, 3.74.

Ultraviolet spectrum of 3-methyl-2-phenylindole: maxima at 228.5 mμ (23,700); 307.5 mμ (20,800); inflection at 237.5 mμ (22,400); minimum at 270.5 mμ (6200).

A small amount of colorless crystals of an unknown compound, m.p. 118–121°, was also isolated from the neutral fraction of the reaction mixture. Mixed with 3-methyl-2-phenylindole, the melting point of this material was depressed to 79–85°. Ultraviolet spectrum: maxima at 239 mμ (12,600 based on m.w. 200), 314 mμ (9700); inflections at 234 mμ (12,000), 245 mμ (11,500); minimum at 262 mμ (8500). The quantity was too small for further purification.

This indole was also prepared by the modification of Buu-Hoï and Nguyen-Hoán[16] for the Fischer synthesis, using a saturated solution of anhydrous hydrogen chloride in glacial acetic acid as the catalyst. Thus, crude propiophenone phenylhydrazone was converted into 3-methyl-2-phenylindole, b.p. 171–186° (0.5 mm.), m.p. 90–92°, in 88% over-all yield from the ketone. Recrystallization from methanol and petroleum ether (40–60°) gave a total recovery of 92% of the indole, m.p. 92–95°; reported 94–95°.[19]

3-Methyl-2-(p-tolyl)indole was obtained from a purified sample of α-diazo-*p*-methylpropiophenone (m.p. 43–47°) in 50% yield (m.p. 108–115°) using aniline hydrobromide as the catalyst. The total product was resublimed at 120° (0.07 mm.) to give a 46% yield of 3-methyl-2-(*p*-tolyl)indole, m.p. 116–117° (reported 119°).[16] Fine red needles of the *s-trinitrobenzene* derivative melted at 150.0–150.5°.

Anal. Calc'd for $C_{16}H_{15}N \cdot C_6H_3N_3O_6$: C, 60.8; H, 4.18. Found: C, 60.5; H, 4.14.

3-Methyl-2-(2'-naphthyl)indole. Attempts to convert α-diazo-2-propionaphthone to 3-methyl-2-(2'-naphthyl)indole failed; only traces of solids could be obtained after chromatography of the crude reaction product. 2-Propionaphthone phenylhydrazone was converted to 3-methyl-2-(2-naphthyl)-indole, m.p. 123–124.5°, in 75% yield by the boron trifluoride procedure.

The indole was also prepared from α-bromopropionaphthone by the Bischler method in 46% yield (1.5 hours' heating). Sublimation of 0.37 g. of this product under reduced pressure gave 0.31 g. of material, m.p. 126.5–127.5°, which partially decomposed on recrystallization from petroleum ether, m.p. 119.5–121.5°. The sublimed material was analyzed.

Anal. Calc'd for $C_{19}H_{15}N$: C, 88.6; H, 5.88. Found: C, 89.0; H, 5.76.

Ultraviolet spectrum: maxima at 239 mμ (40,800), 278 mμ (15,800), 287 mμ (18,200), 322 mμ (24,400); minima at 272 mμ (13,900), 281 mμ (15,400), 294 mμ (12,400).

The *s-trinitrobenzene derivative* of this indole was prepared and recrystallized from 95% ethanol as red needles, m.p. 197.0–197.5°.

Anal. Calc'd for $C_{19}H_{15}N \cdot 2C_6H_3N_3O_3O_6$: C, 54.5; H, 3.10. Found: C, 54.6; H, 3.28.

Attempt to prepare 2-(p-methoxyphenyl)-3-methylindole. The crude, oily α-diazo-*p*-methoxypropiophenone was triturated with petroleum ether (40–60°) and the petroleum ether-soluble extract thus obtained was evaporated to dryness at 0° to give a yellow oil which was used in the indole reaction. With 1 g. of aniline hydrobromide in 10 ml. of freshly distilled aniline, 1 g. of this oil was heated at 200° for 20 minutes during which time a vigorous evolution of nitrogen was observed. The only crystalline product isolated from this mixture, however, was 0.82 g. (65%) of *p*-anisanilide, m.p. 168–174°; after further recrystallization from 95% alcohol the m.p. was 173.5–174.5° and undepressed on admixture with an authentic sample.

A freshly prepared, total crude sample of α-diazo-*p*-methoxypropiophenone was subsequently analyzed as follows:[4] (i) Total chlorine content indicated that 25–30% of the sample consisted of acid chloride and/or chloro ketone. (ii) Acid chloride was estimated by dissolving 200 mg. of the oily diazo ketone in 15 ml. of boiling methanol and adding immediately 5 ml. of 6 *N* nitric acid. The mixture was allowed to cool to room temperature and chloride ion was determined by the Volhard method. The results indicated a maximum anisoyl chloride content of 6 to 7%. This procedure gave good agreement with theory using *p*-anisoyl chloride. (iii) Diazo nitrogen evolution indicated that the diazo ketone content of the crude oil was 41 to 43%. (iv) The γ-collidine-benzyl alcohol rearrangement procedure[3] when applied to this sample of crude diazo ketone gave a 25% yield of *p*-anisic acid, the only product isolated. (v) An indole run on this crude diazo ketone was carried out using boron trifluoride at 150–160°. Vigorous evolution of nitrogen occurred but no indole and only a trace of *p*-anisanilide could be isolated from the reaction mixture at this lower temperature.

3-Ethyl-2-(p-methoxyphenyl)indole. The crude oily diazo ketone obtained by addition of 2.1 g. of *p*-anisoyl chloride to 1-diazopropane in ether by the method of Wilds and Meader[3] was used without purification, following removal of the solvent, in an attempt to prepare 3-ethyl-2-(*p*-methoxyphenyl)indole. A solution in 15 ml. of aniline and 2.0 g. of boron trifluoride etherate was heated at 185° for one hour. *p*-Anisanilide (1.35 g., 47% from the acid chloride) was the only product isolated.

For comparison, a Fischer synthesis was carried out from *p*-methoxybutyrophenone phenylhydrazone using hydrogen chloride in glacial acetic acid. This gave 3-ethyl-2-(*p*-anisyl)indole, m.p. 101–105°, as colorless elongated prisms, in a 69% yield from the ketone. The melting point

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(39) In addition 15–20% of crude 4-acetylbiphenyl was obtained, m.p. 115–118.5°, and identified by analysis and mixture m.ps. of the ketone and its 2,4-dinitrophenylhydrazone with known samples, and by comparison of ultraviolet and infrared spectra. This ketone apparently was formed from the diazoethyl ketone rather than being an accompanying impurity in the acid chloride, since the latter was prepared from acid which had been purified through its salt and recrystallized both as the acid and acid chloride. The ketone was not obtained from runs using the corresponding diazomethyl ketone.

of a sample recrystallized from 95% ethanol was 106–107° when taken in an evacuated tube (reported m.p. 90°).[40]

Anal. Calc'd for $C_{17}H_{17}NO$: C, 81.2; H, 6.83. Found: C, 81.4; H, 6.98 (sample mixed with V_2O_5).

The *s-trinitrobenzene derivative of 3-ethyl-2-(p-methoxyphenyl)indole* was obtained as dark red needles, from 95% ethanol, m.p. 99–100°.

Anal. Calc'd for $C_{17}H_{17}NO \cdot C_6H_3N_3O_6$: C, 59.5; H, 4.24. Found: C, 59.4; H, 4.49.

Reaction of diazo ketones with heterocyclic amine salts. 1-Phenacyl-4-picolinium bromide. A solution of 0.98 g. of α-diazoacetophenone and 1.16 g. of 4-picolinium bromide in 15 ml. of absolute ethanol was refluxed for 15 minutes (nitrogen evolution 94%). On cooling, 1.24 g. (65%) of 1-phenacyl-4-picolinium bromide separated, micro m.p. 265–267° (dec.). Removal of the solvent and recrystallization of the residue from a mixture of ethanol and ethyl acetate gave an additional 0.52 g. (27%), micro m. p. 265–268° (dec.), for a total yield of 92% (reported m.p. 261.2–261.8).[24]

2-Phenylindole from 1-phenacyl-4-picolinium bromide. A solution of 1.21 g. of 1-phenacyl-4-picolinium bromide in 10 ml. of freshly distilled aniline in a 50-ml. flask was immersed in a pre-heated oil-bath at 185° for one hour under a nitrogen atmosphere. Work-up of the reaction mixture gave 0.55 g. (68%) of 2-phenylindole, m.p. 185–190°, in three crops. The over-all yield from the diazo ketone was 62%. Recrystallization from petroleum ether raised the melting point to 189–190° alone and when mixed with an authentic sample of 2-phenylindole. Ultraviolet spectrum: maxima at 241 mμ (22,100), 309 mμ (29,500); minima at 235 mμ (21,400), 267 mμ (4900); inflection at 224 mμ (24,500).

1-(p-Chlorophenacyl)-4-picolinium bromide. A solution of 1.0 g. of p-chloro-α-diazoacetophenone and 1.0 g. of 4-picolinium bromide in 15 ml. of absolute ethanol on refluxing for 20 minutes evolved 86% of the theoretical volume of nitrogen. A total yield of 1.40 g. (78%) of 1-(p-chlorophenacyl)-4-picolinium bromide was isolated, micro m.p. 248–250° (dec.). Recrystallization from absolute ethanol raised the melting point to 249–250° (dec.).

Anal. Calc'd for $C_{14}H_{13}BrClNO$: C, 51.5; H, 4.01. Found: C, 51.2; H, 4.07.

1-(p-Chloro-α-methylphenacyl)-4-picolinium bromide. A solution of 0.85 g. of p-chloro-α-diazopropiophenone and 0.76 g. of 4-picolinium bromide in 15 ml. of absolute ethanol on refluxing for 10 minutes evolved 79% of the theoretical volume of nitrogen. A total of 0.57 g. (39%) of 1-(p-chloro-α-methylphenacyl)-4-picolinium bromide, micro m.p. 187–191° (dec.), was isolated. Further recrystallization from absolute ethanol raised the melting point to 206–207° (dec.).

Anal. Calc'd for $C_{15}H_{15}BrClNO$: C, 52.9; H, 4.44. Found: C, 52.3; H, 4.61.

1-Phenacylpiperidinium bromide. When a solution of 1 g. of α-diazoacetophenone and 1.25 g. of piperidine hydrobromide in 15 ml. of absolute ethanol was heated at reflux for 20 minutes, little nitrogen was evolved. Replacement of the alcohol with 15 ml. of 2-methoxyethanol and heating at the higher reflux temperature (124°) for 15 minutes resulted in evolution of a total of 75–85% of the theoretical volume of nitrogen. Removal of the solvent and washing the residue with ethyl acetate gave 1.55 g. (78%) of crude 1-phenacylpiperidinium bromide, m.p. 190–210° (dec.). Recrystallization from a mixture of 95% ethanol and ethyl acetate raised the melting point to 229–231° (dec.); reported 220°.[41]

A similar run in 2-methoxyethanol containing 0.11 g. of piperidine, in addition to the salt, and heating for 1 hour gave 83% of crude product, m.p. 185–195° (dec.). In each case the ethyl acetate filtrate contained some unreacted diazoketone.

Attempts to isolate the intermediate phenacylaniline salt. Several attempts were made to isolate the phenacylaniline presumed to be the intermediate in the formation of 2-substituted indoles from diazo ketones. Runs were made using p-chloro-α-diazoacetophenone or α-diazoacetophenone and (a) aniline hydrobromide in absolute ethanol as the solvent, (b) aniline as the solvent with aniline hydrobromide or hydrochloride at 90–120°, (c) aniline and boron fluoride in ether at 30°, and (d) 2-naphthylamine hydrobromide in ethanol. In all cases the amine salt was the only crystalline product obtained, together with dark oils or tars, and no satisfactory method for isolation of an intermediate in the indole reaction was found.

Treatment of α-diazopropiophenone with aniline and alcoholic silver nitrate. The following was an attempt to duplicate the report of Baddeley, Holt, and Kenner,[17] which did not contain experimental details. A homogeneous solution of 25 ml. of 10% aqueous silver nitrate and 5 ml. of freshly distilled aniline in 95% ethanol was added with stirring to 3.2 g. of crude, oily α-diazopropiophenone. The mixture was heated at reflux for 30 minutes during which time nitrogen was evolved, a silver mirror formed, and a dark brown precipitate deposited. An excess of 10% hydrochloric acid was added to the reaction mixture and the precipitate was removed by filtration. The acidic filtrate was washed with benzene, made basic with 10% sodium hydroxide solution, and steam-distilled to remove aniline. The residue was sublimed at 0.05 mm. and 130° to give 1.28 g. of oily crystals, m.p. 92–110°. Chromatography of this material on activated alumina yielded 0.24 g. of β-anilinopropiophenone, m.p. 115.5–116.5° (reported m.p. 115–116°).[42]

Anal. Calc'd for $C_{15}H_{15}NO$: C, 80.0; H, 6.71. Found: C, 79.8; H, 6.63.

The benzoyl derivative was prepared by refluxing 82 mg. of β-anilinopropiophenone with 500 mg. of benzoyl chloride in 5 ml. of pyridine for 1.5 hours. The N-benzoyl-β-anilinopropiophenone crystallized from 95% ethanol as colorless prisms, m.p. 163–164°.

Anal. Calc'd for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.81. Found: C, 79.7; H, 5.82.

The *acetyl derivative* was prepared by refluxing a mixture of 50 mg. of β-anilinopropiophenone in 1 ml. of acetic anhydride for 20 minutes. The N-acetyl-β-anilinopropiophenone crystallized from petroleum ether (60–68°) as colorless prisms, m.p. 87.5–88.5°.

Anal. Calc'd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.41. Found: C, 76.1; H, 6.45.

No other significant products were isolated from the reaction mixture. Extensive decomposition on the alumina column precluded isolation of other basic products. The neutral fraction yielded 0.49 g. of a red-brown oil and 37 mg. of yellow crystalline material, m.p. 111–124°, neither of which was identified.

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