689. *Indoles. Part IV.* Synthetical Applications of the Oxidative Fission of the $C_{(2)}$–$C_{(3)}$ Bond in Indoles.*

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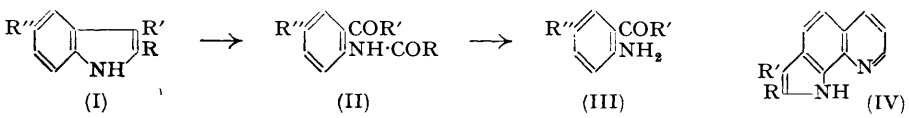
Suitably substituted indoles were converted into 2-*o*-benzamidobenzoylpyridine and into 2-acetamidophenyl benzyl ketone and its 5-methyl- and 5-nitro-analogues. These derivatives were hydrolysed to the corresponding amines.

4′ : 5′-Dimethylpyrrolo(3′ : 2′-7 : 8)quinoline gave by the same method 8-acetamido-7-acetylquinoline, from which were obtained 7-acetyl-8-amino- and 8-amino-7-ethyl-quinoline.

Earlier work has been concerned with aspects of oxidative fission of the indole $C_{(2)}$–$C_{(3)}$ bond (I ⟶ II). We now describe applications of this type of reaction to the synthesis of 2-aminoaryl ketones (III).

(*a*) Hitherto 2-*o*-aminobenzoylpyridine (III; R′ = 2-C_5H_4N, R″ = H) has been prepared by a tedious many-staged process (Nunn and Schofield, *J.*, 1952, 583). Oxidation of a suitable 3-2′-pyridylindole promised to make the compound more readily available. No 3-2′-pyridylindole has been described. Accordingly, the readily available 2-phenacyl-



pyridine (Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301) was converted into its phenyl- (*idem, ibid.*), *p*-tolyl-, and *p*-nitrophenyl-hydrazone. The first two were readily cyclised in high yield by hydrochloric acid to 2-phenyl- (I; R = Ph, R′ = 2-C_5H_4N, R″ = H) and 5-methyl-2-phenyl-3-2′-pyridylindole (I; R = Ph, R′ = 2-C_5H_4N, R″ = Me), but all attempts to cyclise the nitro-compound failed. The yield of 2-phenyl-3-2′-pyridylindole produced by boron trifluoride in acetic acid was lower, probably because of co-ordination of the reagent with the pyridyl group, and similar complications in the other cases are mentioned in the Experimental section.

Treatment of 2-phenyl-3-2′-pyridylindole in ethyl acetate with a large excess of ozone gave a good yield of 2-*o*-benzamidobenzoylpyridine, which was readily hydrolysed to 2-*o*-aminobenzoylpyridine. The method makes this amine easily available on the 10-g. scale, and is potentially of wider application than the earlier process.

(*b*) *o*-Aminophenyl benzyl ketone (III; R′ = CH_2Ph, R″ = H) has not been obtained before. The nitration of benzyl phenyl ketone (List, *Ber.*, 1893, **26**, 2452) is not useful in this connection, and earlier attempts at synthesis (Ruggli, Caspar, and Hegedus, *Helv. Chim. Acta*, 1937, **20**, 250; Lothrop and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363) failed.

3-Benzyl-2-methylindole was obtained in unstated yield from a Fischer reaction by Kuroda (*J. Pharm. Soc. Japan*, 1923, **493**, 131), and by use of cuprous chloride as catalyst Janetsky and Verkade (*Rec. Trav. chim.*, 1945, **64**, 129) isolated the compound in 40% yield. We found zinc chloride to be a better catalyst, and boron trifluoride improved the yield further. By the Fischer reaction we also prepared 3-benzyl-2 : 5-dimethyl-, 3-benzyl-2-methyl-5-nitro-, and 3-benzyl-2-methyl-7-nitro-indole, and 2-methyl-3-(1′-naphthylmethyl)indole.

No crystalline product was isolated from the chromic acid oxidation of 3-benzyl-2-methylindole, a result expected in view of the absence of an electronegative substituent. Small yields of unidentified products were isolated from the 5- and the 7-nitro-compound. However, ozonisation and subsequent hydrolysis gave moderate yields of *o*-aminophenyl benzyl, 2-amino-5-methylphenyl benzyl, 2-amino-5-nitrophenyl benzyl, and *o*-amino-

* Part III, *J.*, 1953, 612.

phenyl 1-naphthylmethyl ketone, from the appropriate indoles. The diazotisation of these amines has been described by Ockenden and Schofield (*J.*, 1953, in the press).

(*c*) To identify the compound obtained by nitrating 7-ethylquinoline and reducing the product (Long and Schofield, *J.*, 1953, 2350), we required to synthesise 8-amino-7-ethylquinoline unambiguously. For this purpose ethyl methyl ketone 8-quinolylhydrazone was converted unto 4′ : 5′-dimethylpyrrolo(3′ : 2′-7 : 8)quinoline (IV; R = R′ = Me). The latter was converted by ozone into 8-acetamido-7-acetylquinoline. Catalytic reduction of this compound in acetic acid, in the presence of palladium–barium sulphate and perchloric acid (Long and Schofield, *loc. cit.*) gave 8-acetamido-7-ethylquinoline. Hydrolysis completed the orientation. No homogeneous product could be obtained by ozonisation of 4′-ethyl-5′-methylpyrrolo(3′ : 2′-7 : 8)quinoline (IV; R = Me, R′ = Et).

Experimental

(*a*) *Preparation of* 2-o-*Aminobenzoylpyridine.—Arylhydrazones.* Usually the ketone and arylhydrazine were heated in equivalent amounts at 95° for 1 hr. With examples which are not described further the resulting oil was dried (Na_2SO_4) in ether and used directly. Methyl phenethyl ketone *p*- (65%), m. p. 111—112°, and *o*-nitrophenylhydrazone (74%), m. p. 85—86°, formed copper-coloured and reddish-brown needles, respectively, from alcohol; these decomposed after a while. 2-*Phenacylpyridine* p-*nitrophenylhydrazone* (obtained from the components at 135° for ¾ hr.) formed dark orange leaflets, m. p. 147—149° (Found: C, 68·4; H, 5·3. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·9%), from alcohol.

2-*Phenyl*-3-2′-*pyridylindole.* 2-Phenacylpyridine phenylhydrazone (11·5 g.) (Goldberg, Barkley, and Levine, *loc. cit.*) and concentrated hydrochloric acid (200 c.c.) were refluxed for 3 hr. Most of the solvent was removed and the solution was basified at 0° with ammonia solution. Crystallisation from aqueous alcohol gave 2-*phenyl*-3-2′-*pyridylindole* (7·9 g.), needles, m. p. 201—202° (Found: C, 84·6; H, 5·0; N, 10·3. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%). By this method 26·3 g. of 2-phenacylpyridine gave 24·0 g. of product.

The hydrazone (0·87 g.), acetic acid (10 c.c.), and boron trifluoride etherate (0·46 g.), when refluxed for 3 hr., gave the indole (0·42 g.; m. p. 196—199°).

5-*Methyl*-2-*phenyl*-3-2′-*pyridylindole.* Phenacylpyridine *p*-tolylhydrazone (1·0 g.) and concentrated hydrochloric acid (20 c.c.) were refluxed for 3 hr. Isolated as above, the product formed fawn needles (from aqueous alcohol) of 5-*methyl*-2-*phenyl*-3-2′-*pyridylindole* (0·61 g.), m. p. 194—196° (Found: C, 84·0; H, 5·6. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·7%).

When the hydrazone (1·57 g.), acetic acid (16 c.c.), and boron trifluoride etherate (0·79 g.) were refluxed for 3 hr., and the solution was filtered and concentrated, a dark oil resulted. Crystallisation from aqueous alcohol gave a mixture of fawn needles and yellow prisms. The former (0·34 g.) were removed with benzene and were identical with the above indole. The yellow prisms [0·55 g.; m. p. 160—170° (decomp.)] were identical with material obtained by refluxing the indole with boron trifluoride in acetic acid.

After phenacylpyridine *p*-nitrophenylhydrazone had been refluxed with boron trifluoride in acetic acid for 4 days, removal of the solvent and passage of the product in benzene through alumina gave small pale yellow needles, m. p. 150—151°. The same compound was obtained by similar treatment of phenacylpyridine. The nitro-hydrazone could not be converted into an indole.

2-o-*Aminobenzoylpyridine.* 2-Phenyl-3-2′-pyridylindole (8·0 g.) in ethyl acetate (400 c.c.) was treated at room temperature with 3 equivalents of approximately 5%-ozonised oxygen (8 hr.). Removal of the solvent and crystallisation from aqueous ethanol of the oily product from three such experiments gave material (18·6 g.; m. p. 111—113°) pure enough for the next step. 2-o-*Benzamidobenzoylpyridine* formed leaflets, m. p. 113—114° (Found: C, 75·7; H, 4·6. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·7%).

The benzamido-compound (18·6 g.) and concentrated hydrochloric acid (200 c.c.) were refluxed for 24 hr. Concentration, basification, and crystallisation of the product from methanol gave the desired amine (10·0 g.; m. p. 141—143°). The pure substance formed long, golden blades, m. p. 143—145° (Found: C, 72·5; H, 5·3. Calc. for $C_{12}H_{10}ON_2$: C, 72·7; H, 5·1%) alone and mixed with an authentic specimen (Nunn and Schofield, *loc. cit.*).

(*b*) *Preparation of* o-*Aminophenyl Ketones.—*3-*Benzyl*-2-*methylindole.* Methyl phenethyl ketone phenylhydrazone (8·0 g.; b. p. 180—184°/2 mm.), acetic acid (80 c.c.), and boron trifluoride etherate (5·0 g.) were refluxed for 6 hr. The hot solution was filtered and concen-

trated; crystallisation of the residue from methanol gave the indole (4·95 g., m. p. 118—119°). Alternatively, the hydrazone (9·6 g.) and powdered zinc chloride (6·6 g.) were heated gently until the mildly exothermic reaction began. The product was isolated by steam-distillation, extraction of the residue with ether, and crystallisation from methanol. 3-Benzyl-2-methylindole (4·9 g.) formed glistening needles, m. p. 119—120° (Found: C, 85·9; H, 6·6. Calc. for $C_{16}H_{15}N$: C, 86·8; H, 6·8%).

3-Benzyl-2 : 5-dimethylindole. The tolylhydrazone (8·5 g.), acetic acid (85 c.c.), and boron trifluoride etherate (5·1 g.) were refluxed for 6 hr. Filtration, concentration, and recrystallisation from methanol gave the *indole* (57%) as crisp flakes, m. p. 114—116° (Found: C, 87·0; H, 7·3. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3%).

3-Benzyl-2-methyl-5-nitroindole. Methyl phenethyl ketone *p*-nitrophenylhydrazone (6·5 g.) and concentrated hydrochloric acid (65 c.c.) were heated at 95° for 5 hr. The product was crystallised from methanol (yield, 3·55 g.). *3-Benzyl-2-methyl-5-nitroindole* formed yellow leaflets, m. p. 160—161° (Found: C, 71·7; H, 5·05. $C_{15}H_{14}O_2N_2$ requires C, 72·1; H, 5·3%). The hydrazone (6·5 g.), acetic acid (65 c.c.), and boron trifluoride etherate (3·4 g.) when refluxed for 6 hr. gave, after one crystallisation from methanol, 50% of the indole, m. p. 159—160°.

3-Benzyl-2-methyl-7-nitroindole. Methyl phenethyl ketone *o*-nitrophenylhydrazone (7·8 g.) gave *3-benzyl-2-methyl-7-nitroindole* (2·5 g.), which formed orange needles, m. p. 137—138° (Found: C, 71·8; H, 5·0%), from methanol.

2-Methyl-3-1′-naphthylmethylindole. The appropriate hydrazone (10·5 g.), acetic acid (100 c.c.), and boron trifluoride etherate (5·3 g.) were refluxed for 3 hr. After filtration and removal of the solvent the dark oily product was passed in benzene through alumina. Addition of light petroleum (b. p. 60—80°) to the concentrated eluate gave *2-methyl-3-1′-naphthylmethylindole* (4·95 g.), which separated from benzene–light petroleum as prisms, m. p. 147—149° (Found: C, 88·9; H, 6·2. $C_{20}H_{17}N$ requires C, 88·5; H, 6·3%).

o-Aminophenyl benzyl ketone and related compounds. The relevant indole (0·5 g.) was treated with the theoretical amount of 5%-ozonised oxygen. Experiments in ethyl acetate (25 c.c.) were at 0°, and the products were isolated by concentration at room temperature. With acetic acid (25 c.c.) as solvent the products were isolated by basification and extraction with ether. The acetamido-compounds were hydrolysed by refluxing aqueous alcoholic hydrochloric acid for 3 hr. Concentration, basification, and recrystallisation of the precipitate gave the amine.

1. R = Ph, R′ = H 2. R = Ph, R′ = Me
3. R = Ph, R′ = NO_2 4. R = α-$C_{10}H_7$, R′ = H

Acetamido-ketone	Yield, %, in EtOAc	Yield, %, in AcOH	Form	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
1	40	60 [1]	Yellow needles [2]	97—98°	$C_{16}H_{15}O_2N$	75·5	6·1	75·9	6·0
2	35	35	Needles [2]	81—83	$C_{17}H_{17}O_2N$	77·4	6·5	76·4	6·4
3	45	45	Yellow prisms [3]	174—175	$C_{16}H_{14}O_4N_2$	64·3	4·9	64·4	4·7
4	—	47 [1]	Fawn plates [2]	148—149	$C_{20}H_{17}O_2N$	78·0	5·8	79·2	5·7

[1] The same yields were obtained from 2 g. of the indole. [2] From ether–light petroleum (b. p. 60—80°). [3] From aqueous ethanol.

Amino-ketone, as	Acet-amide, g.	HCl, c.c.*	Yield of amine, %	Form	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
1	4·2	50	83	Leaflets [1]	103—104°	$C_{14}H_{13}ON$	79·6	6·2	79·6	6·2
2	0·43	5	80	Fawn plates [2]	104—106	$C_{15}H_{15}ON$	80·2	6·8	80·0	6·7
3	0·8	10	74	Golden needles [2]	163—165	$C_{14}H_{12}O_3N_2$	65·3	4·9	65·6	4·9
4	1·55	15	75	Blades [2]	133—135	$C_{18}H_{15}ON,\frac{1}{4}H_2O$	81·6	6·0	81·3	5·9

* Volume of concentrated acid taken, together with an equal volume of water and 2 volumes of alcohol, except for the hydrolysis of 4, when 3 volumes of alcohol were taken.
[1] From light petroleum (b. p. 60—80°). [2] From ethanol.

(*c*) *Synthesis of 8-Amino-7-ethylquinoline.*—*4′ : 5′-Dimethylpyrrolo(3′ : 2′-7 : 8)quinoline.* Ethyl methyl ketone 8-quinolylhydrazone (5·0 g.), concentrated hydrochloric acid (80 c.c.), and acetic acid (80 c.c.) were refluxed for 3 hr. Most of the solvent was removed and the solution was basified. The *pyrroloquinoline* (73%) formed lemon-coloured plates, m. p. 156—158°, from ethanol (Found: C, 79·1; H, 6·0. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2%).

4′-Ethyl-5′-methylpyrrolo(3′ : 2′-7 : 8)quinoline. Methyl *n*-propyl ketone 8-quinolylhydrazone (2·9 g.), concentrated hydrochloric acid, and acetic acid (50 c.c. of each) similarly gave the *4′-ethyl-5′-methyl* compound (70%), which formed yellow plates, m. p. 123—125° (Found: C, 79·8;

H, 6·9. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7%), from light petroleum (b. p. 60—80°) containing a trace of benzene.

7-*Acetyl*-8-*aminoquinoline*. The dimethylpyrroloquinoline (0·5 g.) in ethyl acetate (25 c.c.) was treated with the theoretical amount of ozonised oxygen. Removal of the solvent and crystallisation of the oily residue from benzene–light petroleum (b. p. 60—80°) gave the desired product (0·13 g.). Use of acetic acid gave a slightly better yield (0·2 g.). 8-*Acetamido*-7-*acetylquinoline* formed pale yellow needles, m. p. 157—158·5° (Found: C, 68·9; H, 5·4. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3%).

The acetamido-compound (0·6 g.), water (10 c.c.), and hydrochloric acid (10 c.c.) were refluxed for 2 hr. Basification of the solution and crystallisation of the product from light petroleum (b.p. 60—80°) containing a trace of benzene gave yellow crystals of 7-*acetyl*-8-*aminoquinoline*, m. p. 107—109° (Found: C, 70·8; H, 5·3. $C_{11}H_{10}ON_2$ requires C, 70·9; H, 5·4%).

8-*Amino*-7-*ethylquinoline picrate*. 8-Acetamido-7-acetylquinoline (0·4 g.), when shaken with acetic acid (25 c.c.), perchloric acid (2 c.c.), and palladium–barium sulphate (0·4 g.) at 90° absorbed the correct amount of hydrogen in 2 hr. Filtration, concentration, and basification provided an oil which was refluxed with 6N-hydrochloric acid (35 c.c.). Basification and ether extraction gave an oil (0·2 g.), which with picric acid (0·28 g.) in methanol (5 c.c.) provided pure 8-amino-7-ethylquinoline picrate, m. p. 203—204° (decomp.) alone and mixed with a specimen prepared according to Long and Schofield (*loc. cit.*).

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