sideration in the screening of anti-inflammatory drugs using these kinds of experimental system, especially in evaluating the toxicity or anti-inflammatory activity of drugs that might be converted to an active metabolite like phenylbutazone.

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Arylindoles. I. Synthesis of Some N-Arylindoles[1]

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Indole, 2-phenylindole, indole-2-carboxylic acid, indole-3-carboxaldehyde, 3-acetylindole and gramine were condensed with bromobenzene and halonitrobenzenes under the Ullmann conditions (copper(II) oxide catalyst and N,N-dimethylformamide as the solvent). The corresponding N-arylindoles were isolated in good yields with the exception of the gramine due to its possible decomposition under these reaction conditions. Spectral data (infrared and proton magnetic resonance) for the new compounds is presented.

Keywords——N-arylation; Ullmann reaction; N-arylindoles synthesis; N-nitrophenylindole-3-carboxaldehydes; N-nitrophenylindole-2-carboxylic acids; N-arylindoles; 3-acetyl-N-arylindoles; copper-catalyzed condensations

Although C-, and N-alkylindoles as well as C-arylindoles may readily be obtained by means of a variety of methods, N-arylindoles are not easily accessible by these synthetic routes.[3] Indoles containing aryl substituents at the nitrogen have, however, been obtained in the Ninetzescu synthesis[4] but this method is also limited in its applications as it invariably leads to the 5-hydroxy derivatives containing other substituents in the 2 or 3 position of the indole ring. Another method used in the preparation of N-phenylindole–dehydrogenation of N-phenylindoline[5]–may also have its set back when applied as a general method for the dehydrogenations of arylindolines containing sensitive groups.

Recently Ullmann's reaction (copper-catalyzed condensation using aryl halides) has proved to be an efficient method for the syntheses of N-arylazoles[6] and was used with success for the N-arylation of indole.[7] Since the N-aryl analogs of the indoles that are biologically active may also present interesting pharmacological properties, in the present work we have tried to apply the Ullmann reaction for the arylation of indoles containing different substituents in the 2 and 3 position.

1) Taken in part from the Masters thesis of Emely Kazan Rocha, Instituto Militar de Engenharia, 1976.
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Results and Discussion

In the present work we chose bromobenzene and halonitrobenzenes as the arylaing agents for the synthesis of N-phenyl-, and N-nitrophenylindoles. The nitrophenylation, thus, could furnish the indoles which may not easily be obtainable from the simple *N*-phenylindole. Furthermore the nitro group could undergo various modifications *via* reduction of the nitro group giving other N-arylindoles.

The indoles chosen for the arylations were: indole, 2-phenylindole, indole-2-carboxylic acid, indole-3-carboxaldehyde, 3-acetylindole and gramine. These differently substituted indoles were chosen so as to have some notion about the scope of this reaction.

Various types of solvents have been used for the Ullmann arylation of azoles,[6] however in a previous phenylation of indole nitrobenzene was employed[8] while in the other arylations of indole pyridine was used.[7] During our previous study we had found that in some arylations good yield were obtained with N,N-dimethylformamide as the reaction solvent[7] and in the present work we decided to use this solvent as this has the advantage of giving better yields as well as better work-up conditions.

The catalyst used for the arylations was the copper (II) oxide the same catalyst we had used in our earlier work.[7]

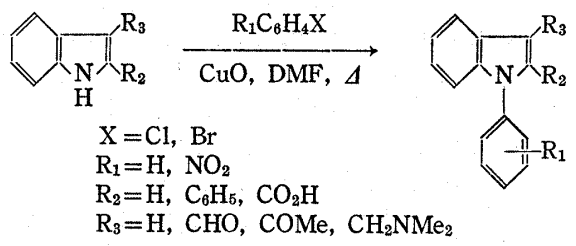

Chart 1. N-Arylation of Indoles

Arylations

The arylation reaction is presented in the Chart 1 followed by the discussion of the arylation of various indoles.

Arylation of Indole

The arylations of indole were repeated using N,N-dimethylformamide as the reaction solvent and nitrophenylindoles were obtained in higher yields than reported by us.[7] In the phenylation of indole N-phenylindole was isolated in comparative yields in replacing the solvent nitrobenzene by N,N-dimethylformamide and the catalyst copper(I) bromide by copper(II) oxide.

Arylation of 2-Phenylindole

The arylation of 2-phenylindole proceeded without difficulty and reasonable yields (34—58%) of N-(*o*-, *m*-, and *p*-nitrophenyl)-2-phenylindoles were obtained.

Arylation of Indole-2-carboxylic Acid

In this arylation good yields of N-arylindole-2-carboxylic acids were obtained. The arylation with *o*-bromonitrobenzene, however, did not succeed under these conditions. During these arylations corresponding *N*-arylindoles were also isolated and these possibly arise from the copper-catalyzed decarboxylations during the arylation reaction.[9] This type of decarboxylation has also been observed earlier.[7] The N-arylindole-2-carboxylic acids also undergo thermal decarboxylation and a small amount of N-*p*-nitrophenylindole-2-carboxylic acid was decarboxylated at its melting point to give N-*p*-nitrophenylindole.

Arylation of Indole-3-carboxaldehyde

Our initial attempts to N-arylate indole-3-carboxaldehyde using *o*-chloronitrobenzene failed but later on employing more reactive aryl halides N-arylindole-3-carboxaldehydes were isolated in good yields. The yields of these aldehydes were very good keeping in view the

8) A.F. Pozharskii, B.K. Martsokha, and A.M. Simonov, *Zh. Obshch. Khim.*, **33**, 1005 (1963).
9) H.G. Rule and F.R. Smith, *J. Chem. Soc.*, **1937**, 1096; M. Nillson, *Acta Chem. Scand.*, **20**, 423 (1966).

observations of SitRina and Simonov who, in the Ullmann arylation of imidazole by *p*-bromobenzaldehyde, found that longer reaction times had deterimental effect on the yields of the *p*-(imidazol-N-yl)benzaldehyde.[10]

Arylation of 3-Acetylindole

The arylation of 3-acetylindole under present conditions gave good yields of the corresponding N-aryl compounds. Although it has been reported that the 3-acetylindole exchanges the acetyl group for alkyl when heated with alcohols and alkoxides,[11] there was no evidence of the removal of the acetyl group during arylations. The literature search revealed that the only N-aryl-3-acetylindole known is N-phenyl-3-acetylindole and this was obtained from the corresponding 2-acetylindole by way of rearrangement.[12]

Arylation of Gramine

The attempts to arylate gramine did not meet success. *o*-Chloronitrobenzene and *m*-bromonitrobenzene either in pyridine or N,N-dimethylformamide were without affect. Using *p*-bromonitrobenzene, the only identifiable product isolated (and in small yield) was *p*-N,N-dimethylnitroaniline. As it is well known that gramine is thermally unstable decomposing with the formation of dimethylamine,[13] a similar decomposition might be responsible for these unsuccessful reactions. The formation of *p*-N,N-dimethylnitroaniline may be explained by way of a nucleophilic attack displacing dimethylamino group from the gramine.[14] Alternately, as it has been observed earlier, under the present reaction conditions the solvent (N,N-dimethylformamide) may take part in the reaction giving such products.[15]

All the N-arylindoles obtained in this work are presented in the Table I. The structute of all the new compounds was established by means of their elemental analyses (Table II) and their infrared and proton magnetic resonance spectra (Table III).

The results of the present work indicate that the indole as well as suitably substituted indoles having a free NH can successfully undergo N-arylation under Ullmann reaction conditions.

Experimental

The proton magnetic resonance (PMR) spectra were obtained on a Hitachi Perkin-Elmer model R-20B spectrometer operating at 60 Mc/s (tetramethylsilane as internal standard). The infrared (IR) absorption spectra were determined by the Perkin-Elmer model 727 spectrophotometer and were measured in potassium bromide disks. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected.

Arylations of Indoles——A mixture of indole (0.05 mol), aryl halide (0.05 mol), anhydrous potassium carbonate (7 g) and copper(II) oxide (0.25 g) in N,N-dimethylformamide (10 ml) was heated under reflux for a period of 20 to 24 hr. At the end of this period the reaction mixture was worked-up according to the one of the three procedures:

Procedure A: The reaction mixture was filtered, washed with chloroform and the solvents removed from the combined extract under reduced pressure. The residue was purified by chromatography over a column of alumina. The isolated N-arylindole was crystallized from a suitable solvent.

Procedure B: At the end of the reaction the reaction mixture was diluted with water (500 ml) and the precipitated solid was collected by filtration, treated with activated carbon and crystallized from a suitable solvent.

Procedure C: The reaction mixture was diluted with water (500 ml) and extracted with chloroform (3×100 ml) and the solvent removed from the extract under reduced pressure giving the N-arylindole which was further purified. The aqueous layer was acidified with hydrochloric acid and let stand overnight. The precipitated N-arylindole-2-carboxylic acid was filtered off and purified by crystallization from a suitable solvent.

10) L.M. Sitkina and A.M. Simonov, *Khim. Geterotsikl. Soedin*, **1966**, 143.
11) C. Alberti, *Gazz. Chim. Ital.*, **67**, 238 (1937); *idem*, *ibid.*, **69**, 568 (1939).
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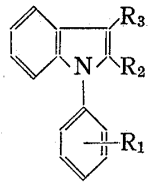
TABLE I. N-Arylindoles



Compd. No.	R_1	R_2	R_3	Aryl halide[a]	Procedure	Yield (%)	mp (°C)	Solvent
1	H	H	H	D	A	50	[b]	
2	*o*-NO_2	H	H	E	A	48	82—83[c]	EtOH
3	*m*-NO_2	H	H	G	A	38	67—68[d]	EtOH
4	*p*-NO_2	H	H	H	A	77	133—134[e]	EtOH
5	*o*-NO_2	C_6H_5	H	E	A	52	178—179	EtOH
6	*m*-NO_2	C_6H_5	H	G	A	34	140—141	EtOH
7	*p*-NO_2	C_6H_5	H	H	A	58	137	EtOH
8	H	CO_2H	H	D	C	67[f]	172—173[g] (dec.)	H_2O
9	*m*-NO_2	CO_2H	H	G	C	50[h]	230 (dec.)	MeOH
10	*p*-NO_2	CO_2H	H	H	C	45[i]	263—264 (dec.)	EtOH
11	H	H	CHO	D	B	60	77—78[j]	EtOH+H_2O
12	*o*-NO_2	H	CHO	F	B	56	128	EtOH+H_2O
13	*m*-NO_2	H	CHO	G	B	76	188—189	EtOH+H_2O
14	*p*-NO_2	H	CHO	H	B	88	268—269 (dec.)	MeCOMe+H_2O
15	H	H	COMe	D	B	62	136—138[k]	MeOH
16	*o*-NO_2	H	COMe	F	B	70	193	AcOH
17	*m*-NO_2	H	COMe	G	B	68	196	AcOH
18	*p*-NO_2	H	COMe	H	B	97	193	AcOH

a) D, bromobenzene; E, *o*-chloronitrobenzene; F, *o*-bromonitrobenzene; G, *m*-bromonitrobenzene; H, *p*-bromonitrobenzene.
b) bp 100° (0.025 mmHg), 110° (0.5 mmHg), (lit. bp 179—180° (11 mmHg) and 189—191° (20 mmHg) ref. 8).
c) lit. mp 82—83° ref. 7. *d*) lit. mp 67—68° ref. 7. *e*) lit. mp 133—134° ref. 7.
f) 1-Phenylindole was also isolated from the reaction in 23% yield.
g) lit. mp 176° (E. Fischer and O. Hess, *Ber.*, **17**, 559 (1884).
h) 1-*m*-Nitrophenylindole was also isolated from this reaction in 15% yield.
i) 1-*p*-Nitrophenylindole was also isolated from this reaction in 12% yield.
j) lit. mp 76.5—77.5° (C.A. Rodriguez and P.R. Leeming, Brit. Pat., 1220628 (1971) [*C.A.*, **75**, 5690 (1971)].
k) lit. mp 141—143° (ref. 12).

TABLE II. Elemental Analyses

Compd. No.	Formula	Calculated (%)			Found (%)		
		C	H	N	C	H	N
5	$C_{20}H_{14}N_2O_2$	76.42	4.49	8.91	76.43	4.53	9.18
6	$C_{20}H_{14}N_2O_2$	76.42	4.49	8.91	76.30	4.42	8.80
7	$C_{20}H_{14}N_2O_2$	76.42	4.49	8.91	76.38	4.50	8.91
9	$C_{15}H_{10}N_2O_4$	63.83	3.57	9.93	63.55	3.64	9.91
10	$C_{15}H_{10}N_2O_4$	63.83	3.57	9.93	64.00	3.56	10.20
12	$C_{15}H_{10}N_2O_3$	67.66	3.79	10.52	67.68	3.86	10.60
13	$C_{15}H_{10}N_2O_3$	67.66	3.79	10.52	67.50	3.70	10.36
14	$C_{15}H_{10}N_2O_3$	67.66	3.79	10.52	67.80	3.82	10.25
16	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.32	4.28	9.73
17	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.45	4.36	9.78
18	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.56	4.34	9.81

Table III. Spectral Properties of N-Arylindoles

Compd. No.	IR (cm^{-1})	PMR (δ, ppm)	Solvent
2	*a*)	6.68 (d; J=3Hz; H-3); 7.00—8.10 (m; aromatic).	$CDCl_3$
3	*a*)	6.62 (d; J=3 Hz; H-3); 7.00—8.30 (m; aromatic).	$CDCl_3$
4	*a*)	6.68 (d; J=3 Hz; H-3); 7.00—8.40 (m; aromatic).	$CDCl_3$
5	1521, 1340 (NO_2).	6.80 (s; H-3); 6.90—8.00 (m; aromatic).	$CDCl_3$
6	1512, 1340 (NO_2).	6.80 (s; H-3); 7.00—8.30 (m; aromatic).	$CDCl_3$
7	1530, 1340 (NO_2).	6.80 (s; H-3); 7.00—8.20 (m; aromatic).	$CDCl_3$
8	3500—3300 (br.; OH); 1670 (C=O).	6.83—7.75 (m; aromatic); 11.05 (s; $CO_2\underline{H}$).	$CDCl_3$
9	3500—3300 (br.; OH); 1670 (C=O); 1520, 1355 (NO_2).	6.90—8.30 (m; aromatic); 10.35 (s; $CO_2\underline{H}$).	$CDCl_3$+DMSO-d_6
10	3500—3300 (br.; OH); 1675 (C=O); 1520, 1355 (NO_2).	6.90—8.50 (m; aromatic); 10.00—11.00 (br.; $CO_2\underline{H}$).	$CDCl_3$+DMSO-d_6
11	1665 (C=O).	7.10—8.40 (m; aromatic); 10.05 (s; C$\underline{H}$O).	$CDCl_3$
12	1670 (C=O); 1530, 1348 (NO_2).	6.88—8.40 (m; aromatic); 10.00 (s; C$\underline{H}$O).	$CDCl_3$
13	1670 (C=O); 1540, 1348 (NO_2).	7.22—8.58 (m; aromatic); 10.06 (s; C$\underline{H}$O).	$CDCl_3$+DMSO-d_6
14	1655 (C=O); 1538, 1343 (NO_2).	*b*)	—
16	1640 (C=O); 1525, 1355 (NO_2).	2.52 (s; COC$\underline{H}_3$); 6.90—8.35 (m; aromatic).	CD_3CO_2D
17	1625 (C=O); 1525, 1355 (NO_2).	2.53 (s; COC$\underline{H}_3$); 7.10—8.40 (m; aromatic).	CD_3CO_2D
18	1640 (C=O); 1530, 1360 (NO_2).	2.50 (s; COC$\underline{H}_3$); 6.35—8.42 (m; aromatic).	CD_3CO_2D

a) see ref. 7. *b*) The compd. is not soluble enough in common solvents for spectral run at room temp.

The results of these arylations are presented in Table I. The elemental analyses of the N-arylindoles obtained are in Table II and their spectral properties are given in Table III.

Decarboxylation: A small amount of 1-*p*-nitrophenylindole-2-carboxylic acid was heated at 265—270° for a few minutes till no more evolution of the gas was observed. On cooling 1-*p*-nitrophenylindole, mp 133—134° was isolated and compared with the authentic sample (mp, mixed mp, IR and PMR spectra).

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