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1-Phenyl-, and 1-nitrophenylindoles when subjected to Mannich reaction conditions gave the corresponding 3-dialkylaminomethyl derivatives (IIc-IIk) in good yields.

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Various 3-dialkylaminoalkyl-1-phenylindoles (I; $n = 1-4$, $R' = R'' = \text{alkyl}$) have been found to have depressant action on the central nervous system of experimental animals (2), while certain others (I; $n = 3,4$, $R' = H$, $R'' = H$ or methyl) act as antidepressants (3). Although biological testing results have been reported for some of these compounds, information regarding their synthesis or other chemical data is lacking (2). In view of these findings and due to our continued interest in the chemistry of arylindoles, especially *N*-arylindoles, we decided to synthesize derivatives of I ($n = 1$, $R' = R'' = \text{alkyl}$). Compounds IIa and IIb are known compounds (2).

Since our earlier attempts to prepare II by *N*-arylation of gramine by the method of Ullmann did not produce the desired results, extensive decomposition taking place during the reaction (4), we decided to investigate the scope of the Mannich reaction for such syntheses. To our knowledge this reaction has not been carried out on *N*-arylindoles. Indoles are known to react under mild conditions

room temperature for a period of up to twenty-four hours, the initial reaction being carried out in acetic acid at 5° followed by heating at 50° for ten hours or using 99% dimethylamine, also proved unsuccessful. Finally, when the reaction was carried out in acetic acid at water bath temperature for a period of 24 hours (8), 3-dimethylamino-methyl-1-*p*-nitrophenylindole (IIj) was obtained in 89% yield from 1-*p*-nitrophenylindole, formalin and 40% dimethylamine. Under similar conditions the reaction with other arylindoles gave good yields (54-96%) of the expected products. The identity of these products were established by the elemental analyses and proton magnetic resonance spectra. Some of the products were also converted into their ethyl iodide salts.

EXPERIMENTAL

The pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer model R-20B using tetramethylsilane as an internal reference. Infrared absorption spectra were measured on a Perkin-Elmer model 180. Samples were examined as potassium bromide pellets or as thin films in the case of liquids. The melting points were observed on a Fisher-Johns apparatus and are uncorrected.

General Procedure.

A 40% aqueous solution of formalin was added to a cooled (5°) solution of a secondary amine in glacial acetic acid followed by dropwise addition of a saturated solution of 1-arylindole in acetic acid. The reaction mixture was then heated on a waterbath for 24 hours. At the end of the reaction period the reaction mixture was allowed to cool and basified with 2*N* sodium hydroxide solution. The precipitate was filtered, washed with water and purified. Using this general procedure, the following compounds were prepared.

3-(*N,N*-Diethylaminomethyl)-1-phenylindole (IIc).

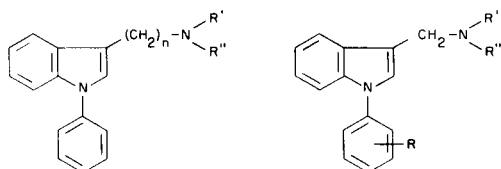
From the reaction of 1 g. of 1-phenylindole with 1 ml. of diethylamine and 0.5 ml. of formalin, a viscous oil was obtained which was purified by column chromatography on alumina. Using benzene as the eluent 1.1 g. (76%) of IIc was obtained as an oil; pmr (deuteriochloroform): δ 1.09 (t, J = 7 Hz, CH₃), 2.60 (q, J = 7 Hz, *N*-CH₂-CH₃), 3.82 (s, Ar-CH₂-N-), 7.02-7.88 (m, arom.); ir: 3050, 2865, 2800, 1592, 1498, 1450, 1312, 745, 690 cm⁻¹.

Anal. Calcd. for C₁₅H₂₂N₂: C, 82.08; H, 7.97; N, 10.07. Found: C, 82.00; H, 7.90; N, 9.95.

Compound IIc gave an ethyl iodide salt, m.p. 120-121° (ethanol).

3-(*N,N*-Dimethylaminomethyl)-1-*o*-nitrophenylindole (II d).

The reaction of 1 g. of 1-*o*-nitrophenylindole with 1 ml. of a 40% aqueous solution of dimethylamine and 0.5 ml. of formalin gave a solid which was extracted with chloroform. After removal of the solvent the residue was purified by chromatography on alumina (benzene as eluent) giving II d, m.p. 77-78° (benzene), yield 1.17 g. (95%); pmr (deuterio-



I

- IIa $R = H$; $R' = R'' = \text{Me}$
 IIb $R = H$; $R' = R'' = -(\text{CH}_2)_5-$
 IIc $R = H$; $R' = R'' = \text{Et}$
 II d $R = 2-\text{NO}_2$; $R' = R'' = \text{Me}$
 IIe $R = 2-\text{NO}_2$; $R' = R'' = \text{Et}$
 II f $R = 2-\text{NO}_2$; $R' = R'' = -(\text{CH}_2)_5-$
 II g $R = 3-\text{NO}_2$; $R' = R'' = \text{Et}$
 II h $R = 3-\text{NO}_2$; $R' = R'' = -(\text{CH}_2)_5-$
 II i $R = 4-\text{NO}_2$; $R' = R'' = \text{Me}$
 II j $R = 4-\text{NO}_2$; $R' = R'' = \text{Et}$
 II k $R = 4-\text{NO}_2$; $R' = R'' = -(\text{CH}_2)_5-$

in the Mannich reaction to give good yields of 3-dialkylaminomethylindoles (5,6) and as such we tried to carry out this reaction on 1-phenylindole, 1-*ortho*-, 1-*meta*-, and 1-*para*-nitrophenylindoles.

The usual reaction conditions (using paraformaldehyde and dialkylamine hydrochloride in methanol) which are very successful in the Mannich reactions of indoles (6,7) failed to "aminoalkylate" 1-arylindoles. Other reaction conditions such as the use of dioxane and acetic acid at

chloroform): δ 2.31 (s, CH_3), 3.67 (s, Ar- CH_2-N), 7.00-8.10 (m, arom.); ir: 3100-3050, 2810, 2760, 1600, 1525 (NO_2), 1490, 1455, 1350 (NO_2), 1305, 850, 780, 740, 700 cm^{-1} .

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 69.21; H, 5.80; N, 14.24. Found: C, 69.12; H, 5.70; N, 14.12.

Compound II d gave an ethyl iodide salt, m.p. 210-211° (ethanol).

3-(*N,N*-Diethylaminomethyl)-1-*o*-nitrophenylindole (IIe).

The solid obtained from the reaction of 1 g. of 1-*o*-nitrophenylindole with 1 ml. of diethylamine and 0.5 ml. of formalin was purified by chromatography on alumina using benzene as eluent giving 1.3 g. (96%) of IIe, m.p. 59-60° (benzene); pmr (deuteriochloroform): δ 1.06 (t, J = 7 Hz, CH_3), 2.56 (q, J = 7 Hz, *N*- CH_2-CH_3), 3.78 (s, Ar- CH_2-N), 6.95-7.98 (m, arom.); ir: 3080-3050, 2865, 2800, 1605, 1530 (NO_2), 1495, 1455, 1350 (NO_2), 1305, 850, 780, 742, 700 cm^{-1} .

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 70.65; H, 6.55; N, 13.01. Found: C, 70.55; H, 6.40; N, 12.90.

1-*o*-Nitrophenyl-3-(1-piperidinomethyl)indole (II f).

From 1 g. of 1-*o*-nitrophenylindole, 1 ml. of piperidine, and 0.5 ml. of formalin, 1.13 g. (80%) of II f, m.p. 121-123° (aqueous ethanol) was obtained; pmr (deuteriochloroform): δ 1.48 (br.) and 2.38-2.46 (m, $-CH_2-$ piperidine), 3.70 (s, Ar- CH_2-N), 7.00-8.05 (m, arom.); ir: 3080-3050, 2850, 2800, 2770, 1605, 1530 (NO_2), 1494, 1455, 1345 (NO_2), 1310, 850, 780, 742, 700 cm^{-1} .

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.70; H, 6.31; N, 12.54. Found: C, 71.60; H, 6.20; N, 12.36.

3-(*N,N*-Diethylaminomethyl)-1-*m*-nitrophenylindole (II g).

The reaction of 0.5 g. of 1-*m*-nitrophenylindole with 0.5 ml. of diethylamine and 0.3 ml. of formalin gave an oily product which was extracted with chloroform. The extract was freed of the solvent and subjected to chromatography on alumina. Elution with benzene gave 0.37 g. (54%) of II g as an oil; pmr (deuteriochloroform): δ 1.11 (t, J = 7 Hz, CH_3), 2.62 (q, J = 7 Hz, *N*- CH_2-CH_3), 3.82 (s, Ar- CH_2-N), 7.10-8.40 (m, arom.); ir: 3090-3050, 2870, 2845, 2800, 1610, 1530 (NO_2), 1490, 1452, 1348 (NO_2), 1310, 860, 800, 748, 730 cm^{-1} .

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 70.65; H, 6.50; N, 13.01. Found: C, 70.35; H, 6.40; N, 12.96.

Compound II g gave an ethyl iodide salt, m.p. 75-76° (ethanol).

1-*m*-Nitrophenyl-3-(1-piperidinomethyl)indole (II h).

From 1 g. of 1-*m*-nitrophenylindole, 1 ml. of piperidine, and 0.5 ml. of formalin, 0.85 g. (60%) of II h was obtained, m.p. 90.5-91° (aqueous ethanol); pmr (deuteriochloroform): δ 1.49 (br.) and 2.40-2.49 (m, $-CH_2-$ piperidine), 3.70 (s, Ar- CH_2-N), 7.10-8.40 (m, arom.); ir: 3090-3050, 2800, 2770, 1610, 1530 (NO_2), 1488, 1452, 1346 (NO_2), 1310, 860, 800, 748 730 cm^{-1} .

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.70; H, 6.31; N, 12.54. Found: C, 71.75; H, 6.40; N, 12.60.

3-(*N,N*-Dimethylaminomethyl)-1-*p*-nitrophenylindole (II i).

The reaction of 1 g. of 1-*p*-nitrophenylindole, 1 ml. of dimethylamine, and 0.5 ml. of formalin gave 1.1 g. (89%) of II i, m.p. 103° (aqueous

ethanol); pmr (deuteriochloroform): δ 2.30 (s, CH_3), 3.64 (s, Ar- CH_2-N), 7.11-8.42 (m, arom.); ir: 3120-3040, 2810, 2760, 1593, 1515 (NO_2), 1500, 1450, 1340 (NO_2), 1320, 855, 750, 744, 695 cm^{-1} .

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.21; H, 5.80; N, 14.24. Found: C, 69.22; H, 5.70; N, 14.20.

Compound II i gave an ethyl iodide salt, m.p. 207-208° (ethanol).

3-(*N,N*-Diethylaminomethyl)-1-*p*-nitrophenylindole (II j).

The reaction of 1.2 g. of 1-*p*-nitrophenylindole with 1 ml. of diethylamine and 0.5 ml. of formalin resulted in the formation of 1.35 g. (83%) of II j, m.p. 210° (aqueous ethanol); pmr (deuteriochloroform): δ 1.08 (t, J = 7 Hz, CH_3), 2.60 (q, J = 7 Hz, *N*- CH_2-CH_3), 3.78 (s, Ar- CH_2-N), 7.11-8.42 (m, arom.); ir: 3120-3050, 2860, 2800, 1593, 1515 (NO_2), 1500, 1452, 1340 (NO_2), 1320, 852, 750, 740, 692 cm^{-1} .

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 70.65; H, 6.55; N, 13.01. Found: C, 70.55; H, 6.60; N, 12.98.

1-*p*-Nitrophenyl-3-(1-piperidinomethyl)indole (II k).

From 1 g. of 1-*p*-nitrophenylindole, 1 ml. of piperidine, and 0.5 ml. of formalin, an oily product was obtained which was purified by chromatography on alumina (benzene as eluent) giving 1.2 g. (85%) of II k as a viscous oil; pmr (deuteriochloroform): δ 1.48 (br.) and 2.42-2.51 (m, $-CH_2-$ piperidine), 3.73 (s, Ar- CH_2-N), 7.11-8.50 (m, arom.); ir: 3120-3050, 2850, 2800, 2770, 1590, 1513 (NO_2), 1500, 1450, 1340 (NO_2), 1320, 851, 750, 740, 694 cm^{-1} .

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.70; H, 6.31; N, 12.54. Found: C, 71.65; H, 6.36; N, 12.40.

Compound II k gave an ethyl iodide salt, m.p. 183-184° (ethanol).

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