Syntheses of Heterocyclic Compounds. Part XVII.[1] 4-Nitroindoles and Nitrophenylpyrazolones with Tertiary Amine Substituents in the Benzene Ring

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4-Nitro-2-R-indoles (R = H, CO_2Et, CO_2H, or CO·t-amine) having a tertiary amine substituent in the 7-position have been prepared by nucleophilic displacement of halogen in the corresponding 7-chloro-4-nitroindole with the required base. Substitution of the activated halogen in chloronitrophenyl pyrazolones is also described.

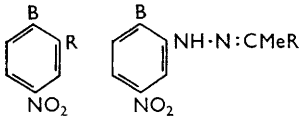
As a continuation of the study of routes to tertiary-amine substituted indoles,[1] we attempted unsuccessfully to cyclise the ethyl pyruvate phenylhydrazones (II; B = $C_5H_{10}N$ or $\overline{CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}N}$, R = CO_2Et) obtained by a Japp–Klingemann reaction[2] from ethylmethylacetoacetate and the corresponding diazotised anilines (I; B = $C_5H_{10}N$ or $\overline{C_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}N}$, R = N_2^+), or from the condensation of ethyl pyruvate with the required hydrazine (I; B as before, R = $NH{\cdot}NH_2$). Failure of these hydrazones to form indoles on treatment with acetic, sulphuric, or polyphosphoric acid is undoubtedly due to protonation of the basic substituent in these compounds (II; B as before), which deactivates the benzene ring towards cyclisation. This was demonstrated by the fact that the chloronitrophenylhydrazone (II; B = Cl, R = CO_2Et), prepared in an analogous manner to the t-amine substituted hydrazone, cyclised almost quantitatively in polyphosphoric acid at 80°. Success with this reagent in making nitroindoles appears to depend on the nature of the substituent in the pyrrole ring.[3] The chlorine in the resulting indole (III; B = Cl, R = CO_2Et) was replaced readily on treatment with secondary amines such as piperidine, morpholine, and others (see Table 2) on a water-bath, to give a mixture

[1] Part XVI, D. P. Ainsworth and H. Suschitzky, *J. Chem. Soc.* (*C*), 1967, 315.

[2] F. L. Allen, J. C. Brunton, and H. Suschitzky, *J. Chem. Soc.*, 1955, 1283.

[3] H. Singer and W. Shive, *J. Org. Chem.*, 1957, **22**, 84; S. M. Parmerter, A. G. Cook, and W. B. Dixon, *J. Amer. Chem. Soc.*, 1958, **80**, 4621; S. P. Hiremath and S. Siddappa, *J. Indian Chem. Soc.*, 1964, **41**, 357; A. R. Frasca, *Anales Asoc. quim. argentina*, 1962, [2], **50**, 1.

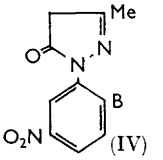
of the required indole (III; R = CO_2Et, B = base) and the corresponding amide (III; R = CO·B), with the latter in excess. When, however, the carboxyl function was removed, the chlorine in the indole (III; B = Cl, R = H) became inert to nucleophilic substitution under similar conditions. Only heating in a sealed tube for



(I)

(II)

(III)

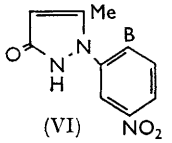


(IV)

RNH·NH·CO·CH_2·CMe:N·NHR

(R = 2-Cl-5-NO_2-C_6H_3-)

(V)



(VI)

15 hours at 140° with these amines produced the 7-substituted indoles (III; B = secondary amine, R = H). We previously [1] reported a similar example of unexpected "damping" in the reactivity of a chlorine atom in 2,3-polymethyleneindoles and tetrahydrocarbazoles, and ascribed it to the electron release of the π-excessive pyrrole nucleus,[4b] thereby opposing the nucleophilic activation of the nitro substituent. This explanation is in accord with the fact that introduction of an electron-withdrawing group (such as CO_2R) into the pyrrole ring "restores" the lability of the chlorine atom, presumably by diverting to some extent the deactivating flow of electrons. It appears that little work has been done on nucleophilic substitution in indoles.[4a]

When the indole ester (III; R = CO_2Et, B = Cl), dissolved in an excess of ethanol, was treated with 2 equiv. of a secondary amine, *e.g.*, piperidine, a nearly quantitative yield of the t-amine substituted indolecarboxylic ester (III; R = CO_2Et, B = $C_5H_{10}N$) with only trace amounts of the amide (III; B as before, R = CO·NC_5H_{10}) was obtained. Since aminolysis of esters is a reversible process [5] the above result is feasibly accounted for by the presence of ethanol. By contrast, the chlorine atom in the chloro-ester (III; R = CO_2Et, B = Cl) was not affected by ethanolic potassium hydroxide, and the reaction yielded only the potassium salt of the chloro-acid (III; R = CO_2H, B = Cl). The failure of the chlorine atom to react with potassium hydroxide under these conditions is probably due to rapid formation of the carboxylate ion, which, unlike the ester group, does not interfere with the π-excessive nature of the pyrrole ring. The pyrrolidino-ester (III; R = CO_2Er, B = C_4H_8N) was also readily hydrolysed, and the acid (III; R = CO_2H) was easily converted into the parent indole (III; R = H, B = C_4H_8N) by boiling in quinoline with copper oxide. The chloronitro-acid (III; B = Cl, R = CO_2H) was similarly decarboxylated.

[4] A. Albert, "Heterocyclic Chemistry," The Athlone Press, 1959, (*a*) p. 169; (*b*) p. 31.
[5] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 782.

We also carried out nucleophilic displacement reactions on the chloronitrophenylpyrazolinone (IV; B = Cl) which we obtained from 2-chloro-5-nitrophenylhydrazine and ethyl acetoacetate. The chlorine atom was readily replaced with piperidine or other amines, on a water-bath, to give the pyrazolinone (IV; B = $C_5H_{10}N$). Reaction of 2-chloro-5-nitrophenylhydrazine with diketen failed to give the expected pyrazolinone (IV) but yielded the hydrazone-hydrazide (V) instead, even when made to react with an excess of diketen on a water-bath. A similar result with diketen has been reported.[6] Treatment of this hydrazone (V) with hot hydrochloric acid gave the methylpyrazolinone (VI) whose chlorine atom was nucleophilically active under mild conditions.

EXPERIMENTAL

Tertiary Amine Substituted Nitrophenylhydrazines.—These compounds (I; B = Cl, $C_5H_{10}N$, or morpholino) were made as previously described.[1]

Ethyl Pyruvate 2-Substituted 5-Nitrophenylhydrazones.—(*a*) In a typical preparation 2-chloro-5-nitrophenylhydrazine (18·8 g.) and ethyl pyruvate (12·8 g.) were made to react in boiling ethanol (250 ml.) for 15 min. The hydrazone (II; B = Cl, R = CO_2Et) crystallised as yellow needles and was purified from benzene.

(*b*) In an alternative method, a cold aqueous solution of potassium hydroxide (51 ml.; 50%) was added to a stirred mixture of ethyl methylacetoacetate (20·5 g.) and absolute ethanol (150 ml.) kept at 0°. Ice–water (300 ml.) was added followed by an aqueous solution of the diazonium salt obtained from 2-chloro-5-nitroaniline (22·6 g.), hydrochloric acid (60 ml.), and sodium nitrite (10·5 g.) in water (30 ml.). Stirring was continued for 1 hr., and the mixture was then kept in the refrigerator overnight. The hydrazone which had separated was filtered off and purified from benzene. The corresponding piperidino- and morpholino-hydrazones were similarly prepared (Table 1).

TABLE 1

Ethyl pyruvate phenylhydrazones (II) prepared from phenyl hydrazine (method *a*) and by a Japp–Klingemann reaction (method *b*)

		Yield (%)		Found (%)		Reqd. (%)	
B	M. p.	(*a*)	(*b*)	C	H	C	H
Cl	159°	95	57	46·0	4·1	46·3	4·2
$C_5H_{10}N$	142	95	45	57·5	6·6	57·5	6·6
Morpholino ...	164	95	43	53·5	6·3	53·6	6·0

4-Nitroindole Esters (III; R = CO_2Et).—(*a*) The 2-chloro-5-nitrophenylhydrazone of ethyl pyruvate (10 g.) was heated in polyphosphoric acid (150 g.) at 80° with stirring for 15 min. The reaction was exothermic, and when the required temperature was reached no further heating was necessary. The mixture was poured on to crushed ice (500 g.), and *ethyl 7-chloro-4-nitroindole-2-carboxylate* filtered off and purified from benzene.

(*b*) The corresponding piperidino- and morpholino-indoles could not be prepared by this method. At 80° the hydrazone was recovered, and at higher temperature tars

[6] F. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, 1908, **93**, 948; H. Z. Lecher, R. P. Parker, and R. C. Conn, *J. Amer. Chem. Soc.*, 1944, **66**, 1969.

were obtained. On boiling each of these two hydrazones (1 g.) in a mixture of acetic (8 ml.) and sulphuric acid (2 ml.) for 6 hr. hydrolysis occurred. *4-Nitro-7-piperidinoindole-2-carboxylic acid* had m. p. 174° (Found: C, 54·8; H, 5·9. $C_{14}H_{17}N_4O_4$ requires C, 55·2; H, 5·9%), and *7-morpholino-4-nitroindole-2-carboxylic acid* had m. p. 215° (Found: C, 50·4; H, 5·4; N, 18·1. $C_{13}H_{16}N_4O_5$ requires C, 50·6; H, 5·2; N, 18·2%).

(*c*) An ethanolic solution (25 ml.) of the chloronitroindole (2·0 g.) made in (*a*) was heated with the required secondary amine (2·1 equiv.) for 3 hr. The solvent was removed *in vacuo* until the product began to precipitate. Purification was from benzene and results are in Table 2.

4-Nitroindole-carboxyamides.—(*a*) Ethyl 7-chloro-4-nitroindole-2-carboxylate (1·0 g.) was made to react with the required secondary amine (10 ml.) at 100° for 3 hr. The base was removed under reduced pressure and the product chromatographed, in benzene, on alumina. The first fractions contained a little of the 7-t-amine substituted ester (*ca.* 5%), and later fractions yielded 7-t-amine substituted indole-carboxyamides (80—90%) which were purified from benzene (Table 3).

(*b*) Alternatively, the 7-t-amine substituted indole esters (Table 2) were boiled in an excess of an amine different from the 7-substituent, and the products worked up as above.

4-Nitroindolecarboxylic Acids.—(*a*) Hydrolysis of ethyl 7-chloro-4-nitroindole-2-carboxylate (6 g.) in a mixture of ethanol (100 ml.), potassium hydroxide (5 g.), and water (10 ml.) at room temperature for 6 hr. produced a copious precipitate of the potassium salt. Addition of water produced a clear solution from which the indolecarboxylic acid separated when excess of hydrochloric acid was added. It was filtered off and purified from aqueous ethanol. Acids with a t-amine substituents were similarly prepared (Table 4), but isolation was carried out by acidification of the hydrolysate with acetic acid to pH 6.

TABLE 2

7-Substituted 4-nitroindole esters (III; R = CO_2Et)

B	M. p.	Yield (%)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Cl	190°	90	49·2	3·2	49·2	3·4
C_4H_8N	164	95	59·8	5·8	59·4	5·7
$C_5H_{10}N$	135	95	60·3	5·8	60·5	6·0
Morpholino ...	183	95	56·8	5·3	56·4	5·4
$C_6H_{12}N$	133	77	61·2	6·3	61·6	6·4
4-Methyl-1-piperazinyl	160	88	58·1	6·3	57·8	6·1

TABLE 3

7-Substituted 4-nitroindole-2-carboxyamides (III)

7-Subst.	R = COB	M. p.	Yield (%)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
C_4H_8N	—	223°	95	61·7	6·3	62·2	6·1
$C_5H_{10}N$	—	218	92	63·7	6·7	64·2	6·8
$C_6H_{12}N$	—	218	38	65·1	7·0	65·6	7·3
Morpholino	—	202	89	56·8	5·5	56·7	5·6
4-Methyl-1-piperazinyl	—	211	87	59·2	6·9	59·1	6·8
C_4H_8N	$C_5H_{10}N$	230	95	63·1	6·5	63·1	6·5
,, ...	Morpholino	214	90	59·4	6·0	59·3	5·9
$C_5H_{10}N$	C_4H_8N	166	95	63·0	6·3	63·1	6·5
,, ...	Morpholino	150	89	60·8	6·4	60·3	6·2
Morpholino	C_4H_8N	244	95	59·8	6·0	59·3	5·9
,,	$C_5H_{10}N$	236	93	60·7	6·5	60·3	6·2

(*b*) The t-amine substituted acids in Table 4 were also obtained by refluxing 7-chloro-4-nitroindole-2-carboxylic acid (1·0 g.) in an excess of the appropriate secondary amine (10 ml.) for 3 hr. The product was obtained by acidification of the reaction mixture with 6N-acetic acid to pH 6 and purified from aqueous acetic acid.

TABLE 4

7-Substituted 4-nitroindole-2-carboxylic acids (III; R = CO_2H)

7-Subst.	M. p.	Yield (%)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Cl	305°	91	44·5	2·4	44·9	2·1
C_4H_8N	314	89	53·6	5·2 *	53·3	5·2
$C_5H_{10}N$	228	86	57·8	5·3	58·1	5·2
$C_6H_{12}N$	224	61	59·1	5·6	59·4	5·7
Morpholino ...	273	88	53·1	4·5	53·6	4·5

* Analysed as monohydrate.

7-Substituted 4-Nitroindoles.—(*a*) A mixture of 7-chloro-4-nitroindole-2-carboxylic acid (4·0 g.), cupric oxide (0·5 g.), and freshly distilled quinoline (50 ml.) was heated under nitrogen at reflux for 2 hr., and then poured on to crushed ice (200 g.) containing hydrochloric acid (60 ml.). Filtration was followed by repeated extraction with ether, and the combined extracts were washed with a 10% aqueous solution of sodium hydrogen carbonate, and dried ($MgSO_4$); removal of the solvent gave *7-chloro-4-nitroindole*.

(*b*) 4-Nitro-7-pyrrolidinoindole was obtained by a method analogous to (*a*).

(*c*) A mixture of the required secondary amine (10 ml.) and 7-chloro-4-nitroindole (1·0 g.) was heated in a sealed tube at 140° for 15 hr. Solvent removal furnished the 7-t-amine substituted indole which was purified from benzene. The 7-perhydroazepinoindole required purification by chromatography over alumina with benzene as eluant. All products prepared under (*a*)—(*c*) are listed in Table 5.

TABLE 5

7-Substituted 4-nitroindoles (III; R = H)

7-Subst.	M. p.	Yield (%)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Cl	198°	90	49·3	2·1	48·9	4·6
C_4H_8N	243	92	62·4	6·0	62·3	5·7
$C_5H_{10}N$	175	90	63·9	6·1	63·7	6·2
$C_6H_{12}N$	133	66	65·0	6·7	64·8	6·6
Morpholino ...	186	87	58·3	5·2	58·3	5·3
4-Methyl-1-piperazinyl	167	85	60·0	6·2	60·0	6·2

3-Methyl-1-(5-nitro-2-piperidinophenyl)2-pyrazolin-5-one.—A mixture of 2-chloro-5-nitrophenylhydrazine (4·7 g.) and ethyl acetoacetate (3·3 g.) in ethanol (10 ml.) was heated for 0·5 hr. on a water-bath. The solvent was removed and the mixture heated for a further 0·5 hr. On cooling, the *2-chloro-5-nitrophenylhydrazone* of ethyl acetoacetate separated, m. p. 79—80° (from benzene) (96%) (Found: C, 48·5; H, 5·0; N, 13·8. $C_{12}H_{14}ClN_3O_4$ requires C, 48·1; H, 4·7; N, 14·0%). The hydrazone (3·0 g.) was heated on a steam-bath for 40 min. with polyphosphoric acid (30 g.), with stirring. The mixture was cooled and poured on to crushed ice (100 g.). The product which precipitated was filtered off and crystallised from benzene to give the *product*, m. p. 146° (81%) (Found: C, 47·8; H, 3·3; N, 16·4. $C_{10}H_8ClN_3O_3$ requires C, 47·4; H, 3·2; N, 16·6%).

The pyrazolinone (1·0 g.) was heated with piperidine (5·0 g.) on a steam-bath for 1 hr. The excess of base was then removed under reduced pressure, and the *piperidinophenylpyrazolinone* (IV; B = $C_5H_{10}N$), m. p. 86° (80%), was obtained (Found: C, 60·0; H, 6·4; N, 18·1. $C_{15}H_{18}N_4O_3$ requires C, 59·6; H, 6·0; N, 18·5%).

3-*Methyl*-2-(2-t-*amino*-5-*nitrophenyl*)-3-*pyrazolin*-5-*one*.—A mixture of 2-chloro-5-nitrophenylhydrazine (9·4 g.) and diketen (5·0 g.) in ethanol (50 ml.) was kept boiling for 15 min. during which the *hydrazone-hydrazide* (V) separated from the solution. It was filtered off and had m. p. 212—213° (from ethanol) (89%) (Found: C, 43·5; H, 3·1; N, 19·5. $C_{16}H_{14}Cl_2N_6O_5$ requires C, 43·6; H, 3·2; N, 19·0%). The hydrazone-hydrazide (10·5 g.) was heated with hydrochloric acid (100 ml.) for 2 hr. on a steam-bath, and then water (100 ml.) was added. After cooling, the product was extracted with chloroform, and the solvent removed, to leave pale yellow 3-*methyl*-2-(2-*chloro*-5-*nitrophenyl*)-3-*pyrazolin*-5-*one*, m. p. 221—222° (from ethyl methyl ketone). The pyrazolinone (1·0 g.) was heated in an excess of various amines (10 ml.) on a water-bath for 3 hr. The excess of the base was then removed under reduced pressure and the residual product was purified from ethyl methyl ketone or acetic acid (Table 6).

TABLE 6

2-Aryl-3-methyl-3-pyrazolin-5-ones (VI)

B	M. p.	Yield (%)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Cl	222°	78	47·5	3·2	47·4	3·2
C_4H_8N	294	95	58·7	5·8	58·3	5·6
$C_5H_{10}N$	284	92	59·4	6·1	59·6	6·0
$C_6H_{12}N$	252	90	60·7	6·1	60·7	6·4
Morpholino ...	269	85	55·1	5·3	55·3	5·3
4-Methyl-1-piperazinyl	275	88	57·1	6·3	56·8	6·0

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