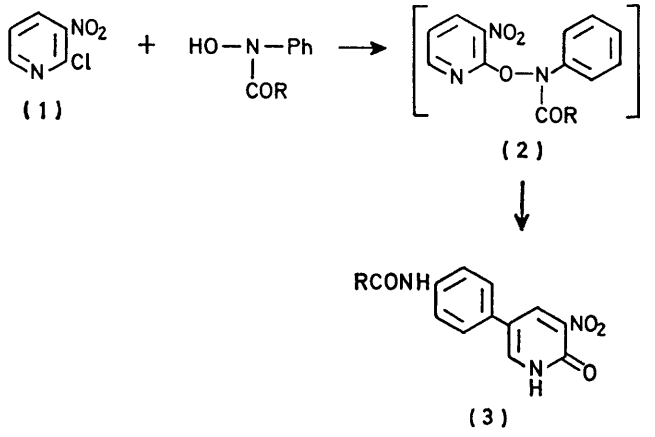
2-Aminoarylation of Heterocycles *via* a Benzidine-like Rearrangement

By **Tuvia Sheradsky,* Eliahu Nov,** and **Schely Avramovici-Grisaru,** Department of Organic Chemistry, The Hebrew University of Jerusalem, Israel

The reactions of 4-chloro-3-nitropyridine (4), 2-chloro-5-nitropyridine (5), and 2,4-dichloropyrimidine (11) with benzyl *N*-hydroxy-*N*-phenylcarbamate (6a) resulted in the introduction of the 2-aminophenyl group into the heterocycle. Mechanistic aspects of the reaction and its relationship with the benzidine rearrangement are discussed.

We have recently [1] described a method for arylation of heterocycles, which consists of the reaction of active halogeno-heterocycles with *N*-phenylhydroxamic acids or with *N*-hydroxy-*N*-phenylcarbamates, and proceeds *via* an oxygen analogue of the benzidine rearrangement. An example is the conversion of 2-chloro-3-nitropyridine (1) into 5(4-acylaminophenyl)-3-nitro-2-pyridone (3) *via* the intermediate hydroxylamine (2).

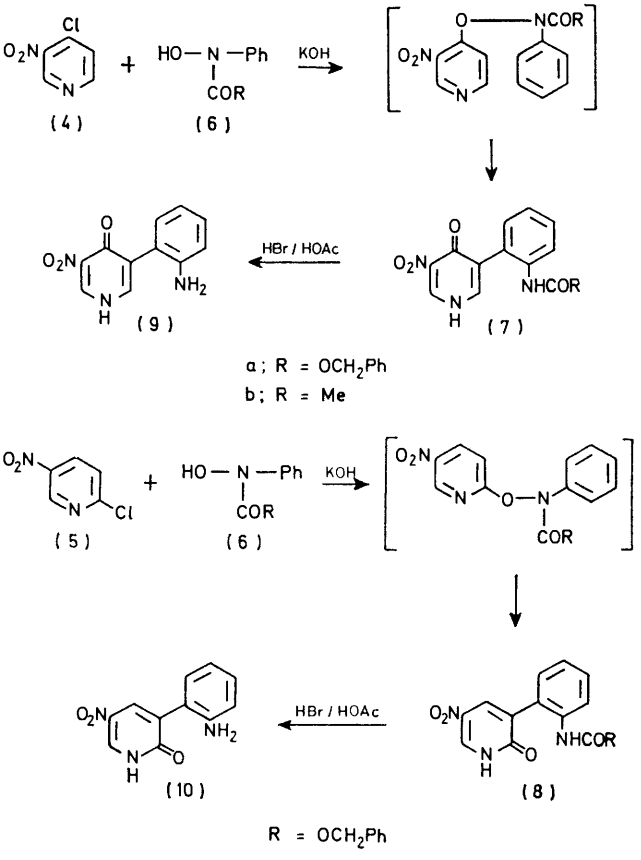


In all the previously studied cases, the heterocyclic ring involved had an unsubstituted carbon *para* to the reactive halogen, making this position available for smooth arylation. We have now extended our studies of the reaction, to include systems in which the reactive halogen is *para* to a nitrogen or to a substituted carbon.

As examples which represent these two possibilities we have selected two isomers of compound (1), 4-chloro-3-nitropyridine (4) and 2-chloro-5-nitropyridine (5). The arylation reagent used was benzyl *N*-hydroxy-*N*-phenylcarbamate (6a), from which the benzyloxycarbonyl group can be easily removed. The reactions of compounds (4) and (5) with (6a) were carried out at room temperature with two equivalents of potassium hydroxide, and yielded isomeric products, (7) and (8) respectively, of the composition $C_{19}H_{15}N_3O_5$. Treatment of (7) and of (8) with hydrogen bromide in acetic acid removed the benzyloxycarbonyl groups quantitatively to give the free amines $C_{11}H_9N_3O_3$, (9) and (10) respectively.

Structural assignments for the products were based mainly on their ^1H n.m.r. spectra (at 270 MHz, expanded, see Table). The benzene rings in (9) and (10) exhibited the typical AA'BB' patterns of a 1,2-disubstituted ring and consisted of two doublets and two triplets (J 7 Hz) with further splitting (1.5 Hz). In compound (9) the pyridine ring exhibited two low-field singlets and in compound (10) two doublets with some (3.2 Hz) coupling. The only structures that could accommodate these data are of 3-(2-aminophenyl)-5-nitro-4-pyridone (9) and 3-(2-aminophenyl)-5-nitro-2-pyridone (10). The proposed structures are also supported by the i.r. and u.v. spectra (see Experimental section). Both compounds (9) and (10) could have been formed by an *ortho,ortho* benzidine-like rearrangement of the intermediate *O*-pyridyl-*N*-phenylhydroxylamines. In order to show that the rearrangement occurred after the two components had reacted and not during the acidolysis, we carried out the reaction of (4) with *N*-phenylacetohydroxamic acid (6b). The product obtained was identified by its n.m.r. spectrum, (in which the aromatic region was not obscured by the acyl protons as in compounds (7a) and (8) as 3-(2-acetylaminophenyl)-5-nitro-4-pyridone (7b).

A further example was the reaction of 2,4-dichloro-



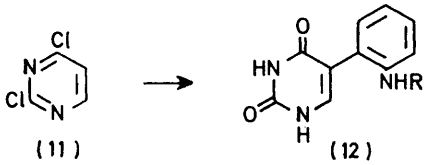
TABLE

^{1}H N.m.r. data for 2-aminophenyl heterocycles (δ values)

Compound	Heterocycle	Aryl: Doublets [a]	Aryl: Triplets [a]	Others
(9)	7.78 (s, 2-H)	6.76	6.64	
	8.79 (s, 6-H)	6.97	7.09	
(7b)	7.81 (s, 2-H)	7.18	7.33	1.91 (3 H, s)
	8.83 (s, 6-H)	7.68	7.38	
(10)	8.05 (d, 2-H) (*J* 3.25 Hz)	6.83	6.73	
	8.72 (d, 4-H)	7.11	7.15	
(12)	7.29 (d,[b] 6-H)	6.60	6.52	
	(*J* 6 Hz)	6.89	7.01	

[a] The coupling constants were 7.5 ± 0.2 Hz. All the lines were further split (*J* 1.5 Hz). [b] Coupling to the neighbouring NH.

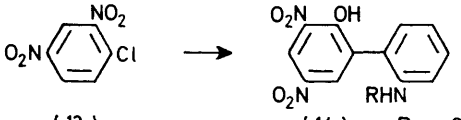
pyrimidine (11) with (6a). As expected the initial nucleophilic substitution occurred at the more reactive 4-position,[2] however partial hydrolysis of the chlorine at the 2-position also occurred under the reaction conditions. In order to avoid mixtures, an additional equivalent of potassium hydroxide was introduced to ensure a complete hydrolysis and the final product was identified as 5-(2-aminophenyl)uracil (12) (58% overall yield).



(11) (12)

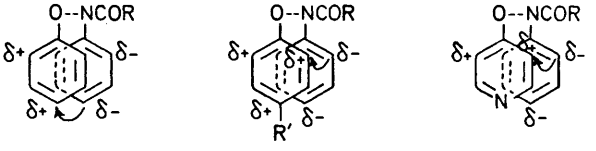
a; R = CO_2CH_2Ph
b; R = H

In the nitroaryl series we have checked the reaction course by carrying out the reaction of (6a) with 2,4-dinitrochlorobenzene (13). An *ortho,ortho* rearrangement was observed also in this case, and the final product (14b) was identified as 2-amino-2′-hydroxy-3′,5′-dinitrobiphenyl. Its n.m.r. spectrum showed for one ring two doublets (δ 7.85 and 8.50) with *meta* splitting (3 Hz) while the second ring exhibited a typical pattern for a 1,2-disubstituted benzene ring as above. Both compounds (14a) and (14b) were amorphous materials and were best purified and characterized as their potassium salts.



(13) (14) a; R = CO_2OCH_2Ph
b; R = H

Careful examination of the reaction mixtures revealed no other isomers. It can thus be concluded that the presence of a substituent or a nitrogen atom at a position *para* to the oxygen in the intermediate *N*,*O*-diarylhydroxylamines causes an *ortho,ortho* rearrangement. In this respect the rearrangement differs from the benzidine rearrangement of hydrazobenzenes,[3] where *ortho,ortho* bond formation is very rare. This difference confirms the theory that the positions of bond formations in the benzidine rearrangement are controlled by charge distributions in the polar transition state.[4] In the present case the reaction does not require acid catalysis, and the first step is, therefore, a simple heterolysis of the nitrogen–oxygen bond. The fragments would then be an aryloxenium ion and acylaniline anion. Charge delocalizations in both would involve mainly the *ortho* and *para* positions of the rings. In a transition state in which the two rings are parallel, linking between the *para* positions would be the most favourable, because of spatial proximity and least hindrance. Thus the *para,para* rearrangement is the normal reaction course (15).



(15) (16) (17)

If, however, one *para* position is blocked by a substituent and bond-making there is impossible, charge distribution and special proximity would now lead to *ortho,ortho* linking (16). Presence of nitrogen in the ring would alter the charge distribution, since an electron deficient nitrogen atom would not easily accommodate a positive charge. The main contributors to the transition state would then be structures with negative charges localized on the *ortho* ring carbons, leading again to an *ortho,ortho* bond (17).

On the other hand, in the well known rearrangement of hydroazobenzenes, protonated species are involved and a bond in the *para*-position is formed as shown in (18). If however such bond formation is prevented by the presence of a substituent, a bond is made through the amino-group, to give semidines (19).

(18) (19)

The introduction of an *o*-aminophenyl group onto heterocycles can be of high synthetic utility, since the *ortho*-amino-group can serve as the reactive centre for the preparation of polycyclic systems containing pyridine and pyrimidine.

EXPERIMENTAL

M.p.s were taken with a Thomas–Hoover apparatus. N.m.r. spectra at 60 MHz were recorded with a Varian T-60 or E.M.-360 spectrometer and at 270 MHz with a Brucker WH-270 spectrometer with scale expansion to *ca.* 0.2 p.p.m./

cm [solvent $(CD_3)_2SO$]. I.r. spectra were taken with a Perkin-Elmer 157 spectrometer (Nujol mulls) and u.v. spectra with a Unicam SP 800 spectrometer (ethanolic solutions).

Reaction of 4-*Chloro*-3-*nitropyridine* (4) *with Benzyl* N-*Hydroxy*-N-*phenylcarbamate* (6a).—To a solution of the carbamate (6a) [5] (1.22 g, 5 mmol) in ethanolic potassium hydroxide (1M; 20 ml), a solution of 4-chloro-3-nitropyridine (4) [6] (0.8 g, 5 mmol) in ethanol was added. The mixture was left at room temperature for 24 h. The precipitated potassium chloride was filtered off and the filtrate evaporated. The dark red residue was triturated with dilute acetic acid, with which treatment it was transformed to a yellow precipitate. This was collected by filtration, triturated with a sodium hydrogen carbonate solution, filtered off, and crystallized from ethyl acetate to give 3-(2-*benzyloxycarbonylamino*)-5-*nitro*-4-*pyridone* (7a) as yellow crystals (1.1 g, 61%), m.p. 181—183 °C, $\lambda_{max.}$ 233 (log ε 4.13) and 337 nm (3.59); $\nu_{max.}$ 3 370, 3 140 (NH), 1 740, and 1 645 cm^{-1} (C=O); δ 5.13 (s, 2 H), 7.37 (s, 5 H), 7.3—7.7 (m, 4 H), 7.90 (s, 1 H), 8.75 (s, 1 H, exchangeable with D_2O), and 8.92 (s, 1 H) (Found: C, 62.4; H, 4.4; N, 11.6. $C_{19}H_{15}N_3O_5$ requires C, 62.5; H, 4.1; N, 11.5%).

Compound (7a) (0.36 g) was dissolved in 2M-hydrogen bromide in acetic acid (10 ml) and heated under reflux for 20 min. A precipitate was formed, collected, and suspended first in sodium hydrogen carbonate solution and then in dilute acetic acid. Crystallization from n-butanol afforded 3-(2-*aminophenyl*)-5-*nitro*-4-*pyridone* (9) as an orange solid (0.2 g, 87%), m.p. 215—216 (decomp.), $\lambda_{max.}$ 234 (log ε 4.10) and 334 nm (3.47); $\nu_{max.}$ 3 450, 3 380, 3 360 (NH), and 1 640 cm^{-1} (C=O); n.m.r.: see Table (Found: C, 57.0; H, 3.7; N, 18.45. $C_{11}H_9N_3O_3$ requires C, 57.1; H, 3.9; N, 18.2%).

3(2-*Acetylaminophenyl*)-5-*nitro*-4-*pyridone* (7b). This compound was prepared from (4) (1.22 g) and *N*-phenylacetohydroxamic acid (6b) [7] (0.7 g) as described above for (7a). The product (7b) (1.1 g, 78%) was obtained as pale yellow crystals, m.p. 231—232 °C; $\lambda_{max.}$ 233 (log ε 4.15) and 338 nm (3.68); $\delta_{max.}$ 3 180 (NH) and 1 670 and 1 645 cm^{-1} (C=O); n.m.r. see Table (Found: C, 56.9; H, 4.05; N, 15.2. $C_{13}H_{11}N_3O_4$ requires C, 57.1; H, 4.1; N, 15.4%).

Reaction of 2-*Chloro*-5-*nitropyridine* (5) *with* (6a).—This reaction was carried out under the same conditions as those described for the reaction of (4) with (6a). The product, however, did not solidify on trituration with dilute acetic acetic acid and was extracted with ethyl acetate. Evaporation gave a yellow oil which could not be induced to crystallize and was chromatographed on silica gel (30 g). Elution with benzene–ethyl acetate (3 : 1) and crystallization from ethanol gave 3-(2-*benzyloxycarbonylamino*)-5-*nitro*-2-*pyridone* (8) (0.7 g, 36%) as bright yellow plates, m.p. 148—149 °C, $\lambda_{max.}$ 230 (log ε 4.17) and 315 nm (4.09); $\nu_{max.}$ 3 470 (NH) and 1 750 and 1 640 cm^{-1} (C=O); δ 5.13 (s, 2 H), 7.35 (s, 5 H), 7.35—7.8 (m, 4 H), 8.07 (d, 1 H), 8.80 (d, 1 H, J = 3 Hz), and 8.95 (s, 1 H, exchangeable with D_2O) (Found: C, 62.2; H, 4.2; N, 11.75. $C_{19}H_{15}N_3O_5$ requires C, 62.5; H, 4.1; N, 11.5%).

Removal of the benzyloxycarbonyl group from compound (8), as described for (7a) yielded 3-(2-*aminophenyl*)-5-*nitro*-2-*pyridone* (10), m.p. 250 °C (decomp.) (85% yield) $\lambda_{max.}$ 312 nm (log ε 4.02); $\nu_{max.}$ 3 440, 3 360 (NH_2), and 1 625 cm^{-1} (C=O); n.m.r. see Table (Found: C, 51.0; H, 5.0; N, 16.3. $C_{11}H_9N_3O_3 \cdot 1.5H_2O$ requires C, 51.2; H, 4.7; N, 16.3%).

Reaction of 2,4-*Dichloropyrimidine* (11) *with* (6a).—Ethanolic potassium hydroxide (1M; 30 ml) containing 2,4-dichloropyrimidine (11) (1.35 g, 10 mmol) and (6a) (2.44 g, 10 mmol) was left at room temperature for 48 h. The precipitate formed was filtered off and the filtrate concentrated to 10 ml; additional precipitate was collected. The combined solids were suspended in dilute acetic acid, filtered, and crystallized from dimethylformamide–water to give 2.6 g (76%) of 5-(2-*benzyloxycarbonylaminophenyl*)-*uracil* (12a) as colourless crystals, m.p. 238—240 °C; $\lambda_{max.}$ 238 (log ε 4.18) and 277 nm (3.95); $\nu_{max.}$ 3 400, 3 220 (NH), and 1 710 and 1 645 cm^{-1} (C=O); δ 5.01 (s, 2 H), 7.35 (s, 5 H), 7.2—7.5 (m, 4 H), and 7.63 (s, 1 H) (Found: C, 64.0; H, 4.6; N, 12.3. $C_{18}H_{15}N_3O_4$ requires C, 64.1; H, 4.5; N, 12.5%).

Removal of the benzyloxycarbonyl group from (12a) with hydrogen bromide in acetic acid gave a 90% yield of 5-(2-*aminophenyl*)*uracil* (13b), m.p. 294—295 °C (decomp.); $\lambda_{max.}$ 238 (log ε 4.05) and 264 nm (3.96); $\nu_{max.}$ 3 410, 3 335, 3 230 (NH, NH_2), and 1 660 cm^{-1} (C=O); n.m.r.: see Table (Found: C, 58.8; H, 4.6; N, 20.7. $C_{10}N_9N_3O_2$ requires C, 59.1; H, 4.5; N, 20.7%).

Reaction of 2,4-*Dinitrochlorobenzene* (13) *with* (6a).—To a solution of (6a) (1.22 g, 5 mmol) in ethanolic potassium hydroxide (0.5 M; 20 ml), a solution of 2,4-dinitrochlorobenzene (13) (1 g, 5 mmol) in ethanol (10 ml) was added and the mixture was left at room temperature for 24 h. The precipitated solid was suspended in dilute acetic acid and filtered. Crystallization from ethyl acetate gave the potassium salt of 2-*benzyloxycarbonylamino*-2′-*hydroxybiphenyl* (1.25 g, 56%) as a brick-red solid, m.p. 241—242 °C (decomp.); $\lambda_{max.}$ 363 nm (log ε 4.16); $\delta_{max.}$ 3 180 (NH) and 1 705 cm^{-1} (C=O); δ 5.03 (s, 2 H), 7.20 (s, 5 H), 7.10—7.52 (m, 4 H), 7.88 (d, 1 H), 8.52 (d, 2 H, J 3 Hz), and 9.13 (s, 1 H, exchangeable with D_2O) (Found: c, 53.5; H, 3.3; N, 9.3. $C_{20}H_{19}KN_3O_7$ requires C, 53.6; H, 3.1; N, 9.4%).

A sample of this salt (0.45 g) was refluxed in hydrogen bromide in acetic acid solution (2M; 12 ml) for 20 min. The yellow precipitate formed was filtered off, washed with ethanol, and treated with ethanolic potassium hydroxide (0.1 M; 40 ml); evaporation and crystallization from ethyl acetate gave the potassium salt of 2-*amino*-3′,5′-*dinitro*-2′-*hydroxybiphenyl* (0.18 g, 55%), m.p. 257 °C (decomp.), $\lambda_{max.}$ 364 nm (log ε 4.10); $\nu_{max.}$ 3 420 and 3 200 cm^{-1}; n.m.r.: see text (Found: C, 44.3; H, 2.8; N, 13.0. $C_{12}H_8KN_3O_5$ requires C, 44.7; H, 2.8; N, 13.0%).

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