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SYNTHESES OF HETEROCYCLIC COMPOUNDS—I

CYCLIZATION OF N-SUBSTITUTED *O*-NITROANILINES

R. H. SMITH and H. SUSCHITZKY
Department of Chemistry and Applied Chemistry, Royal College of Advanced Technology, Salford, and Salford Technical College, Salford, Lancs.

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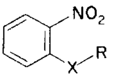
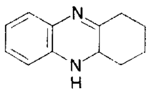
Abstract—Internal cyclization of a nitrogroup was carried out by heating the N-substituted *o*-nitroanilines (I; R = C_6H_{11}—, $C_6H_5.CH_2$, $C_6H_5.CH_2.CH_2$—, X = NH) in the presence of ferrous oxalate[1] (Waterman and Vivian's method) as a potential route to partly hydrogenated nitrogen heterocycles. A mechanism for this type of ring-closure is proposed.

APPROPRIATE nitrocompounds have been successfully cyclized to nitrogen hetero-aromatic structures by heating them with reducing agents such as metallic iron or ferrous oxalate.[1] We have now sought to extend this method to the preparation of partly reduced hetero-aromatic systems by using *o*-nitroanilines with at least one methylene or methine group attached to the basic nitrogen: cyclization of cyclohexyl *o*-nitroaniline (I; R = C_6H_{11}—, X = NH) yields the benzimidazole (VI) and not the anticipated hexahydrophenazine (II). When the nitrocompound is heated in admixture with sand, ferrous oxalate, and lead shot, a white, crystalline substance of m.p. 123°, analysing correctly for the expected phenazine (II) is obtained. It could, however, neither be dehydrogenated by heating with palladium-charcoal, nor made to condense with benzaldehyde, results which are at variance with the usual behaviour of hydrogenated phenazines.[2]



I



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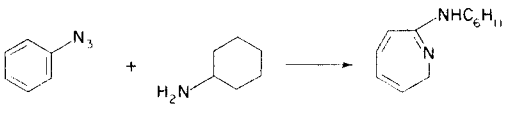

III
IV

A superficial resemblance of the starting materials used for the preparation of 2-cyclohexylamino-7-hydro-azepine[3] (III → IV) and (VI) as well as melting point of the former (124°) prompted a comparison of the two compounds, but a mixed melting point was found to be depressed. The ultra-violet spectrum of the product (VI) resembles 2-alkyl substituted benzimidazoles,[4] and since this compound (VI) appeared to be saturated (no reduction with sodium and ethanol or Adam's catalyst and hydrogen occurred) 2-cyclopentyl benzimidazole (V; R = C_5H_9, R′ = H) was prepared by an unambiguous route. Identity was again ruled out because of the difference in the melting points. The saturation of the side-chain and nature of the

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[1] H. C. Waterman and D. L. Vivian, *J. Org. Chem.* **14**, 289 (1949).

[2] G. R. Clemo and H. McIlwain, *J. Chem. Soc.* 1991 (1934); 258 (1936); H. McIlwain, *J. Chem. Soc.* 1701 (1937).

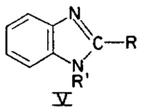
[3] R. Huisgen, *Chem. Ber.* **91**, 1 (1958); R. Huisgen and M. Appl, *Chem. Ber.* **91**, 12 (1958).

[4] H. A. Staab, *Chem. Ber.* **90**, 1322 (1957); A. Hunger, J. Kebrle, A. Rossi and K. Hoffmann, *Helv. Chim. Acta* **43**, 802 (1960).

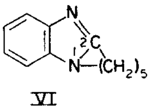
ultra-violet spectrum could equally well be accounted for by a pentamethylene bridge between the 1 and 2 positions of a benzimidazole (VI), a structure which is supported by the absence of an NH-band in the infra-red spectrum. This benzimidazole which had been unambiguously prepared by Saunders[5] proved identical with our compound.

Pyrolysis of N-benzyl 2-nitroaniline (I; R = $C_6H_5CH_2$—, X = NH) with ferrous oxalate gave 2-phenylbenzimidazole (V; R = Ph, R′ = H) in good yield with very little tar. Thermal decomposition of 2-nitro-N-phenethylaniline (I; R = $C_6H_5.CH_2CH_2$, X = NH) was expected to yield two products since cyclization might involve either methylene group in the side chain. When an acid extract of the tarry reaction mixture was chromatographed on alumina a little benzimidazole together with an unknown substance in fair yield was separated. The latter's ultra-violet spectrum was similar in contour to that of 2-phenylbenzimidazole and its infra-red spectrum suggested absence of an NH-group. The spectral and analytical characteristics of this substance would be those anticipated from 1-phenethyl-2-phenylbenzimidazole (V; R = Ph, R′ = $C_6H_5.CH_2.CH_2$), and this was confirmed by an unambiguous synthesis in which 2-amino-N-phenethyl aniline and benzoic acid were condensed in hot tetraphosphoric acid. In contrast to the usual behaviour of benzimidazoles this compound could not be degraded with benzoyl chloride under Schotten-Baumann conditions.[6]

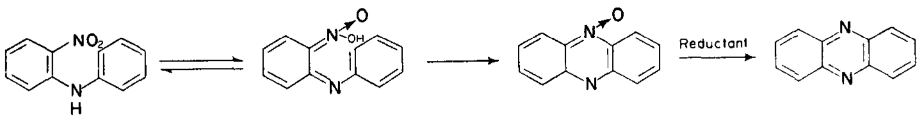
No experimental evidence has so far been put forward to account for direct, thermal cyclization through a nitro-group. A suggestion has been made that two or more molecules of *o*-nitrobiphenylamine and reducing agent might participate to form phenazine.[7] A plausible mechanism which satisfies most observations can be formulated by envisaging loss of one molecule of water from the nitro-compound, probably reacting in its *aci*-form to give an intermediate N-oxide. The Wohl-Aue reaction[8] in which for instance phenazine-N-oxides are made by heating anilines with corresponding nitrobenzenes has a compelling analogy. On this basis the function of the reductant, such as ferrous oxalate, is to act as an oxygen acceptor converting the N-oxide into the final product. To illustrate the steps involved the following scheme can be written for the preparation of phenazine from *o*-nitrobiphenylamine (VII → X).



V



VI



VII VIII IX X

Two significant consequences, verifiable by experiment, follow from such a reaction scheme. First, product formation should result from pyrolysis of the nitrocompound alone, because N-oxides are known to deoxygenate on heating[9] albeit in small yield.

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[5] K. H. Saunders, *J. Chem. Soc.* 3275 (1955).

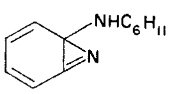
[6] J. B. Wright, *Chem. Revs.* **48**, 486 (1951).

[7] D. L. Vivian, G. Y. Greenberg and J. L. Hartwell, *J. Org. Chem.* **16**, 1 (1951).

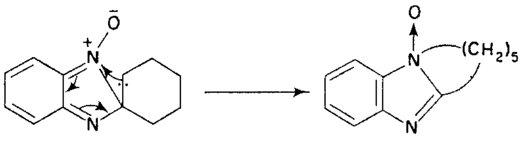
[8] S. Maffei, S. Pietra and A. Cattaneo, *Gazz. Chim. Ital.* **83**, 327 (1953).

[9] C. C. J. Culvenor, *Rev. Pure Appl. Chem. Austral.* **3**, 83 (1953).

Secondly, cyclization by removal of water according to the above sequence (VII → X) could only take place if the "bridge" group connecting the two rings of the nitrocompound contained at least one hydrogen atom to enable formation of the *aci*-form (VIII). The first prediction was confirmed when on heating the previously discussed nitrocompounds (I; R = C_6H_{11}—, $C_6H_5.CH_2$—, $C_6H_5.CH_2CH_2$—, X = NH) as well as *o*-nitrobiphenylamine (I; R = Ph-, X = NH) alone or in sand, we obtained the same nitrogen heterocycles as are produced in presence of a reductant. The second suggestion is borne out by the failure of the nitrocompounds (I; R = Ph, X = S, SO_2 or O) to give cyclized products.[10] A claim that phenoxazine was formed from *o*-nitrobiphenylether (I; R = Ph, X = O)[11] must be viewed with reserve since other workers were unable to repeat this reaction.[12] The successful preparation of carbazole from 2-nitrobiphenyl[1] and ferrous oxalate, however, appeared to be inconsistent with the postulated reaction scheme until we found that 2-aminobiphenyl is produced as by-product which is known to give carbazole on heating[13] and that the nitrocompound cannot be made to ring-close in absence of a reductant. 2-Hydroxylaminobiphenyl was excluded as a possible precursor since it failed to give carbazole under the conditions of the reaction. Other workers[14] have recently confirmed that this hydroxylamine cannot be made to cyclize.



XI



XII XIII

The ring enlargement (VI) observed with cyclohexyl *o*-nitroaniline (I; R = C_6H_{11}, X = NH) cannot be similar in mechanism to that yielding the 2*H*-azepine (IV). Intermediate azirine formation (XI) operative in the latter reaction[3] is hardly feasible with a cyclohexyl ring since the resulting structure would lack the necessary resonance stabilization associated with such intermediates.[15] It seems, however, reasonable to assume that, in accordance with our mechanism (cf. VII → X) the spirane N-oxide (XII) is the intermediate in the cyclization of the nitroaniline (I; R = C_6H_{11}, X = NH) since this reaction course involves the most reactive carbon atom of the cyclohexane ring. The driving force for the subsequent changes (XII → XIII → VI; indicated by arrows) is provided by the strongly polarizable N-oxide function and the attainment of a stable benzimidazole structure.

It is not suggested that cyclization of a nitrogroup in presence of a reductant invariably proceeds by the mechanism outlined above. Ring-closure in some cases occurs indirectly, i.e. after reduction of the nitrocompound. Nitrocompounds are

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[10] H. C. Waterman and D. L. Vivian, *J. Org. Chem.* **21**, 914 (1956); H. Suschitzky and R. Higginbottom, unpublished.

[11] H. C. Waterman and D. L. Vivian, U.S.P. **2**, 292. 808 (1943).

[12] H. Gilman and L. O. Moore, *J. Amer. Chem. Soc.* **79**, 3485 (1957); H. Suschitzky and R. Higginbottom, unpublished.

[13] A. Blank, *Chem. Ber.* **24**, 306 (1891).

[14] E. Wenkert and B. F. Barnett, *J. Amer. Chem. Soc.* **82**, 4671 (1960).

[15] D. Cram and J. Hatch, *J. Amer. Chem. Soc.* **75**, 33 (1953).

unlikely intermediates since the reaction conditions are unfavourable for their formation.[16]

EXPERIMENTAL

The required nitrocompounds were made as previously described.[17]

Ultra-violet absorption spectra were measured in ethanol on a Unicam S.P. 500 spectrophotometer and are quoted as $\lambda_{max}(m\mu)$ with log ε in parentheses.

Pyrolyses with a reductant. The nitrocompound in admixture with an equal weight of ferrous oxalate and approx 8 times its weight of lead shot was placed into a pyrex tube and heated in a silicone oil bath to 220–240° and kept at that temp for 30 min. The reaction mixture was extracted with pet. ether (b.p. 40–60°) in a soxhlet and the extract treated with 2N HCl to remove basic products. The crude organic bases were precipitated by addition of ammonium hydroxide solution and usually purified by recrystallization (pet ether).

TABLE 1. PYROLYSES OF NITROCOMPOUNDS

Nitrocompound	Products yields in (%)	
	heating with ferrous oxalate	heating alone or with sand
2-Nitrobiphenylamine	phenazine (50)	phenazine (15)
2-Nitrobiphenyl	carbazole (35) 2-aminobiphenyl (18)	tar and starting material
N-Benzyl-*o*-nitroaniline	2-phenylbenzimidazole (40)	2-phenylbenzimidazole (20)
N-cyclohexyl-*o*-nitroaniline	hexahydroazepino-(1′,2′-1,2)benzimidazole (21)[a]	hexahydroazepino-(1′,2′-1,2)benzimidazole (15)
N-phenethyl-*o*-nitroaniline	1-phenethyl-2-phenylbenzimidazole (7)[b] benzimidazole (6)[c]	phenylbenzimidazole (10) benzimidazole (10)

[a] Its methiodide had m.p. 226° (Found: C, 47·6; H, 5·2; N, 8·7. Calc. for $C_{13}H_{17}IN_2$: C, 47·6; H, 5·2; N, 8·5%) and its yellow *picrate* m.p. 217–219° (Found: C, 52·0; H, 4·4. $C_{18}H_{17}N_5O_7$ requires: C, 52·0; H, 4·1%). Its ultra-violet spectrum was λ_{max} 252 (2·60), 275 (2·44), 283 (2·61).

[b] Separated by chromatography on alumina with benzene.

[c] Separated as for *b* with benzene and methanol (equal volumes).

Pyrolyses without a reductant. The nitrocompound was heated alone or in admixture with 10 times its weight of purified sand as previously described. Low yields in both methods are accounted for by tar formation, unchanged material, losses due to gaseous products (carbon monoxide, dioxide and ammonia were identified), and formation of carbonyl compounds. Results obtained by these methods are tabulated.

2-*Cyclopentylbenzimidazole.* Cyclopentyl carboxylic acid (10 g) and *o*-phenylene diamine (5·0 g) were heated at a gentle reflux for 1 hr. A hot ethanolic extract of the reaction mixture deposited 2-*cyclopentyl benzimidazole* as white crystals (1·9 g) m.p. 253–55° (ethylenedichloride), λ_{max} 243 (3·85), 274 (3·86), 281 (3·90) (Found: C, 77·4; H, 8·0; N, 14·8. $C_{12}H_{14}N_2$ requires: C, 77·4; H, 7·6; N, 15·0%).

1-*Phenethyl*-2-*phenyl benzimidazole.* A solution of 2-amino-N-phenethylaniline (3·4 g) obtained by reduction of an ethanolic solution of N-phenethyl-*o*-nitro-aniline with activated hydrogen (Raney nickel; 100 atm), benzoic acid (2·0 g) and tetraphosphoric acid (120 g) was kept at 120° for 1 hr with stirring. The reaction mixture was poured into water (500 ml), the tarry precipitate removed by

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[16] I. J. Rinkes, *Chem. Weekblad* **11**, 1062 (1914).

[17] B. Ashton and H. Suschitzky, *J. Chem. Soc.* 4559 (1957).

filtration, and the filtrate treated with excess of ammonium hydroxide solution. A red oil separated which, when chromatographed on alumina as a benzene solution, yielded *1-phenethyl-2-phenyl benzimidazole* m.p. 90–92° as white needles (n-hexane) λ_{max} 285 (3·15) (Found: C, 84·7; H, 6·05; N, 9·7. $C_{21}H_{18}N_2$ requires: C, 84·5; H, 6·1; N, 9·4%).

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