456. *Syntheses of Heterocyclic Compounds. Part II.*[1] *Cyclisation of o-Nitrophenyl Oxygen Ethers.*

By R. Higginbottom and H. Suschitzky.

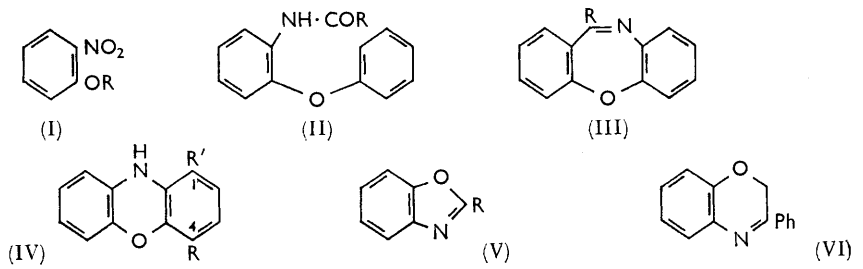
Heating ethers o-$NO_2 \cdot C_6H_4 \cdot OR$, where R = Ph, cyclohexyl, benzyl, or phenethyl, with or without a reductant, produced a number of oxygen-heterocycles (IV—VI). Treatment of *o*-formamido-, *o*-acetamido-, or *o*-benzamido-diphenyl ether with tetraphosphoric acid gave the dibenzoxazepines (III).

Recently we described the cyclisation of *N*-substituted *o*-nitroanilines directly through the nitro-group and suggested a mechanism for this reaction. As an extension of this work we have now prepared the nitrophenyl ethers (I; R = Ph or *o*-tolyl) from *o*-chloronitrobenzene and the potassium salt of the required phenol by an Ullmann-type reaction, and the ethers (I; R = benzyl or phenethyl) from *o*-nitrophenol and the corresponding halide. The cyclohexyl ether (I; R = cyclohexyl) was best made by adding *o*-chloronitrobenzene to a hot solution of metallic sodium in cyclohexanol. When, however, an analogous method was used for benzyl *o*-nitrophenyl ether 2,2′-dichloroazobenzene was the main product.

It was expected that pyrolysis of these ethers in presence of a reducing agent [2] might be a practicable route to oxazines and oxazoles, particularly in view of Waterman and Vivian's claim [3] to have obtained phenoxazine (IV; R = R′ = H) by heating the aryl ether (I; R = Ph) with sodium amalgam. Gilman and Moore,[4] however, could not definitely confirm this claim when using iron powder or ferrous oxalate, and our experiments employing various metal oxalates yielded only starting material and *o*-aminodiphenyl ether.

In contrast, pyrolysis of the *o*-tolyl ether with ferrous oxalate gave 4-methylphenoxazine (IV; R = Me, R′ = H). This was proved by showing the product to be different from the isomeric oxazepine (III; R = H) and comparing it with an authentic specimen of the phenoxazine obtained as follows: the nitrophenoxazine (IV; R = Me, R′ = NO_2) made by Turpin's method (cf. ref. 5) was reduced catalytically and the resulting amine diazotised and de-aminated without interference from the imino-group.

With the benzyl and the phenethyl ethers (I) ring closure involved all the available methylene groups and thus produced 2-phenylbenzoxazole (V; R = Ph) and a mixture



of 2-benzylbenzoxazole (V; R = CH_2Ph) and the 3-phenylbenzoxazine [6] (VI), respectively. Amines derived from the parent nitro-compounds were also formed in all these reactions, a result which has not been referred to previously.[3,7]

[1] Part I, Smith and Suschitzky, *Tetrahedron*, 1961, **16**, 80.
[2] Waterman and Vivian, *J. Org. Chem.*, 1949, **14**, 289.
[3] Waterman and Vivian, U.S.P. 2,292,808/1943.
[4] Gilman and Moore, *J. Amer. Chem. Soc.*, 1957, **79**, 3485.
[5] Brady and Waller, *J.*, 1930, 1218.
[6] Lellmann and Donner, *Ber.*, 1890, **23**, 172.
[7] Slack and Slack, *Nature*, 1947, **160**, 437.

Our recent observations on the pyrolysis of nitrogen analogues [1] were largely confirmed by the behaviour of the present series. Thus the reaction proceeded also when the nitro-ethers were heated either alone or diluted with sand. The presence of at least one hydrogen atom in the " bridge " connecting the rings seemed again essential for successful cyclisation of the nitro-groups, as instanced by failure to produce phenoxazine from *o*-nitrodiphenyl ether (I; R = Ph). Inconsistent with this statement is, however, the preparation of 4-methylphenoxazine (IV; R = Me, R′ = H) from the ether (I; R = *o*-tolyl). The reaction is, however, dependent on the presence of a reducing agent and for this reason probably proceeds through the amino- rather than the nitro-group, a situation experienced with 2-nitrobiphenyl.[1]

A number of dibenzo[*b*,*f*]-1,4-oxazepines (III; R = H, Me, or Ph) were prepared in good yield by a Bischler–Napieralski type of ring closure of *o*-acylaminodiphenyl ethers (II; R = H, Me, or Ph) with polyphosphoric acid. The phenyloxazepine (III; R = Ph) has previously been made by decomposition of 9-azido-9-phenylxanthen [8] and by the above route with phosphorus pentachloride or phosphoryl chloride.[9] A low melting point (m. p. 81°) and a poor carbon analysis were reported in the latter preparation for this substance which proved, however, to be identical with our product (m. p. 107°). Our crude oxazepines had intense lachrymatory and skin-irritant properties which have not been reported for the materials made in other ways.

The dibenzoxazepines were stable to refluxing concentrated hydrochloric acid and 20% aqueous sodium hydroxide for several hours. Fission of the ether linkage has been observed on reduction with sodium and ethanol and of the C=N bond on methylation with dimethyl sulphate.[9] Inspection of a model (Courtaulds) of dibenzoxazepine shows that coplanarity of the three rings is prevented by the nature of the bridging groups, the angle of deviation amounting to about 50°. Resonance stabilisation is thus unlikely to be responsible for the observed chemical stability of the system.

Experimental

Ultraviolet measurements (for ethanol solutions) were made with a Uvispek instrument (log ε are recorded in parentheses).

Preparation of o-*Nitrophenyl Ethers.*—(*a*) A mixture of *o*-chloronitrobenzene, a two-fold excess of the required potassium aryloxide, and a little copper bronze was heated with stirring to 150—160°, whereupon reaction occurred. This temperature was maintained for about 0·5 hr. and the mixture then poured into water. Ether-extraction followed by fractional distillation of the extract gave the product. *o*-Nitrodiphenyl [10] (80%), b. p. 150—152°/1·9 mm., and 2-methyl-2′-nitrodiphenyl ether [11] (65%), b. p. 160—162°/2·1 mm., were thus prepared. (*b*) A mixture of potassium *o*-nitrophenoxide (0·1 mol.) and benzyl or phenethyl chloride (0·1 mol.) in acetone (200 ml.) was heated with stirring over potassium carbonate (0·2 mol.) for 17 hr. Filtration followed by steam-distillation left an oil which was distilled *in vacuo*. This procedure gave benzyl *o*-nitrophenyl ether [12] (74%), m. p. 25°, and *o*-nitrophenyl phenethyl ether [13] (21%), b. p. 198°/1·8 mm.

Cyclohexyl o-*nitrophenyl ether* was made by dissolving metallic sodium (0·5 mol.) in nearly boiling cyclohexanol (5 mol.), adding *o*-chloronitrobenzene (0·5 mol.) during 2 hr., and working up as above. The ether (24%) had b. p. 140—142°/0·8 mm. (Found: C, 65·6; H, 6·8. $C_{12}H_{15}NO_3$ requires C, 65·15; H, 6·8%).

The ethers were characterised by reduction in ethanol with hydrogen over Raney nickel, followed by formylation, to give the *formyl* derivatives of the amino-ethers as follows: o-*amino-diphenyl*, m. p. 92·5° (Found: N, 6·6. $C_{13}H_{11}NO_2$ requires N, 6·6%); o-*aminophenyl* o-*tolyl*, m. p. 123° (Found: N, 6·2. $C_{14}H_{13}NO_2$ requires N, 6·2%); o-*aminophenyl benzyl*, m. p. 76°

[8] Galt, Loudon, and Sloan, *J.*, 1958, 1588.
[9] Brodrick, Donaldson, Nicholson, Short, and Wibberley, *J.*, 1953, 1079.
[10] Brewster and Groening, *Org. Synth.*, Coll. Vol. II, p. 445.
[11] Cook, *J. Amer. Chem. Soc.*, 1901, **23**, 806.
[12] Clerc-Bory, *Bull. Soc. chim. France*, 1954, **21**, 337.
[13] Sieglitz and Koch, *Ber.*, 1925, **58**, 78.

(Found: N, 6·2. $C_{14}H_{13}NO_2$ requires 6·2%); and o-*aminophenyl phenethyl ether* m. p. 103° (Found: N, 5·9. $C_{15}H_{15}NO_2$ requires 5·8%). Reduction of cyclohexyl *o*-nitrophenyl ether was accompanied by hydrolysis, yielding *o*-aminophenol (80%).

Pyrolyses of Nitro-ethers.—(a) *With a reductant.* A mixture of the nitro-ether (~5 g.) with an equal weight of ferrous oxalate dihydrate and lead shot (50 g.) was heated in a Pyrex tube in a silicone-oil bath at 250—280°. An exothermic reaction occurred, causing the temperature of the mixture to rise about 20° above that of the bath. At this point the bath-temperature was maintained for 0·5 hr. After cooling, the mixture was extracted in a Soxhlet apparatus with light petroleum (b. p. 40—60°), from which basic compounds were fractionally removed with hydrochloric acid (0·2N for primary amines, 5N for benzoxazole, and 10N for benzoxazine). The bases were obtained by addition of solid potassium carbonate to the acid extract and were purified by crystallisation.

(b) *Without a reductant.* The above procedure was followed except that the nitro-compound was heated alone or in admixture with 10 times its weight of sand. The reactions were again exothermic. Pyrolyses results for both methods (*a* and *b*) are set out in a Table. Products were identified by mixed melting points with authentic materials.

Pyrolyses of nitro-ethers.

R in *o*-$NO_2{\cdot}C_6H_4{\cdot}OR$	Products. (Yields in %.) Heating with a reductant	Heating with sand or alone
Phenyl	*o*-Aminodiphenyl ether (20) *	Starting material (60); *o*-nitrophenol (15)
Cyclohexyl	*o*-Nitrophenol (20); *o*-aminophenol (45)	*o*-Nitrophenol (70)
o-Tolyl	*o*-$NH_2{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4Me$-*o* (10) *; 4-methylphenoxazine (15)	*o*-Nitrophenol (10)
Benzyl	*o*-Aminophenyl benzyl (5%) *; 2-phenylbenzoxazole (12%)	2-Phenylbenzoxazole (15)
Phenethyl	*o*-Aminophenyl phenethyl ether * (12); 2-benzylbenzoxazole (5); 3-phenyl-2*H*-1,4-benzoxazine (12)	2-Benzylbenzoxazole (8)

* Identified as formyl derivative.

4-*Methylphenoxazine.*—A benzene solution of 4-methyl-1-nitrophenoxazine (2·6 g.) obtained by Brady and Waller's method [5] was reduced with Raney nickel and hydrogen. Removal of the catalyst and the solvent left a dark solid which was dissolved in water (20 c.c.) and hydrochloric acid (10 c.c.) and diazotised with sodium nitrite at −5°. The diazonium solution was added to ice-cold 30% hypophosphorous acid (10 c.c.), and the mixture was kept at 5° for 2 days. Recrystallisation, from aqueous ethanol, of a precipitate then obtained by addition of sodium hydrogen carbonate gave 4-*methylphenoxazine* (0·4 g.), m. p. 167° (Found: N, 7·5. $C_{13}H_{11}NO$ requires N, 7·1%). Its *picrate* (from ethanol) had m. p. 206° (Found: N, 13·4. $C_{19}H_{14}N_4O_8$ requires N, 13·1%).

2-*Benzylbenzoxazole.*—Phenylacetic acid (2·7 g.) and *o*-aminophenol (2·2 g.) were heated for 1 hr. in polyphosphoric acid (33 g.) at 150°. A precipitate obtained by pouring the mixture into water was taken up in ether and washed with N-sodium hydroxide. Evaporating the fluorescent solution gave 2-benzylbenzoxazole (75%), m. p. 34° (Found: C, 80·6; H, 5·3. Calc. for $C_{14}H_{11}NO$: C, 80·4; H, 5·3%). This has been reported [14] as a liquid, b. p. 163—165°/3 mm.

Ring-closure with Polyphosphoric Acid.—The formyl, acetyl (m. p. 85°), and benzoyl (m. p. 77°) derivatives of *o*-aminodiphenyl ether (2·5 g. in each case) were heated with polyphosphoric acid (20 g.) at 150—160° for 3 hr. with stirring. The mixture was poured into water, yielding a precipitate. Its ethereal solution, when washed with potassium carbonate and treated with charcoal, yielded on evaporation the crude dibenzoxazepine. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave: *dibenz*[b,f]-1,4-*oxazepine* (1·7 g.), m. p. 72° (Found: N, 7·0. $C_{13}H_9NO$ requires N, 7·2), $\lambda_{max.}$ 208 (log ε 4·27), 232 (4·23), and 272 mμ (3·78) [*picrate*, m. p. 216° (Found: N, 13·5. $C_{19}H_{12}N_4O_8$ requires N, 13·2%)]; 11-*methyldibenz*[b,f]-1,4-*oxazepine* (1·7 g.), m. p. 81°, $\lambda_{max.}$ 208 (4·37) and 285 mμ (3·62) (Found: N, 6·9. $C_{14}H_{11}NO$ requires

[14] Bywater, Coleman, Kamm, and Merritt, *J. Amer. Chem. Soc.*, 1945, **67**, 905.

N, 6·7%) [*picrate*, m. p. 153° (Found: N, 12·5. $C_{20}H_{14}N_4O_8$ requires N, 12·8%)]; 11-phenyldibenz[*b*,*f*]-1,4-oxazepine (1·4 g.), m. p. 107°, $\lambda_{max.}$ 208 (4·56), 238 (4·31), and 340 mμ (3·85) (Found: N, 5·4. Calc. for $C_{19}H_{13}NO$: N, 5·2%) (Galt *et al.*[8] give m. p. 108°).

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ROYAL COLLEGE OF ADVANCED TECHNOLOGY,
SALFORD, LANCS.

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