Preparation and Thermal Rearrangement of a Benzofuran–Nitrene Adduct

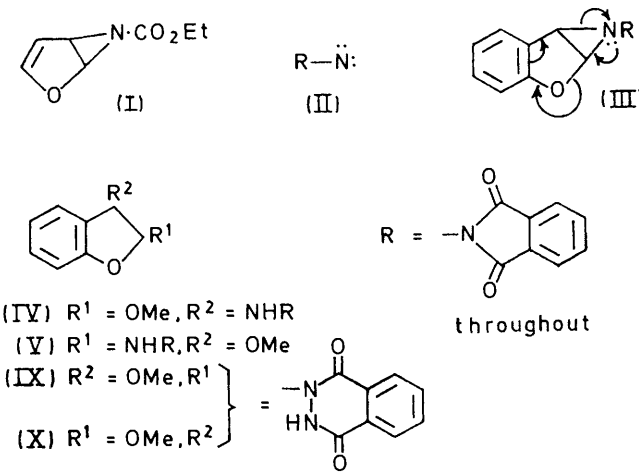
By **D. W. Jones**, Department of Organic Chemistry, The University, Leeds LS2 9JT

Phthalimidonitrene adds to benzo[*b*]furan to give 1a,6b-dihydro-1-phthalimidobenzofuro[2,3-*b*]azirine (III). With methanol compound (III) gives the expected products of aziridine ring opening and 19,20-dioxa-9,10-diazapentacyclo[10.7,1,$0^{1,9}$,$0^{2,7}$$0^{13,18}$]eicosa-2,4,6,10,13,15,17-heptaen-8-one (VI). The reactions of compound (VI) and its 10,11-dihydro-derivative with sodium methoxide are described.

In contrast to the reactions of heterocyclic compounds with carbenes,[1] the corresponding reactions with nitrenes have been little explored. In principle such reactions could provide fused heterocyclic systems such as the furan adduct (I). However bicyclic compounds were not obtained by the addition of ethoxycarbonylnitrene to furan, pyrrole, or thiophen. At the temperature (*ca.* 130°) required for generation of the nitrene from ethoxycarbonyl azide the initial adducts presumably rearranged.[2]

Isolation of such systems was expected to be easier at the lower temperatures used to generate certain amino-nitrenes.[3] Accordingly phthalimidonitrene (II) was generated at 0—5° by lead tetra-acetate oxidation of *N*-aminophthalimide in the presence of benzofuran. Rapid aqueous work-up of the reaction mixture and crystallisation of the product from warm benzene gave the unstable adduct (III), whose structure is supported fully by spectroscopic data. In particular the n.m.r. spectrum indicates the expected slow inversion about the nitrogen atom.[3,4] The protons of the dihydrofuran ring give rise to four doublets; the pair at τ 3·94 and 5·45 (J 4·5 Hz) correspond to one invertomer, and the pair at τ 4·1 and 5·34 (J 2·5 Hz) to the other. The intensities of the four signals indicate an invertomer ratio of *ca.* 1 : 1.

Chemical evidence for structure (III) is provided by treatment with methanol, which gives mainly the methyl ether (IV), a trace of the methyl ether (V), and an isomer of (III), the structure of which is discussed later. The constitution of the ether (IV) follows from its spectroscopic properties. Most notably the n.m.r. spectrum shows that the high-field (benzylic) proton is coupled to the amino-proton.† Both compounds (IV) and (V) have



$\lambda_{max.}$ 282 nm. They are distinguished by the fact that only the spectrum of (V) shows an immediate shift ($\lambda_{max.}$ 306 nm) on addition of sodium hydroxide. Only structure (V) can form an open-chain phenolic tautomer.

† In most of the compounds described the benzylic proton resonance is broadened, presumably by long-range coupling to an aromatic proton.

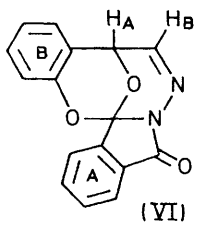
[1] C. W. Rees and C. E. Smithen, *Adv. Heterocyclic Chem.*, 1964, **3**, 57.

[2] K. Hafner and W. Kaiser, *Tetrahedron Letters*, 1964, 2185.

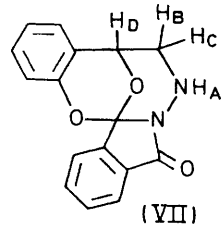
[3] D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *J. Chem. Soc.* (*C*), 1970, 576.

[4] R. S. Atkinson and C. W. Rees, *J. Chem. Soc.* (*C*), 1969, 772; D. J. Anderson, R. S. Atkinson, and D. C. Horwell, *ibid.*, 1971, 624.

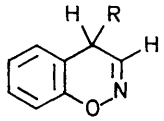
The isomer of (III) produced in boiling methanol is more conveniently obtained by rearrangement of (III) in boiling toluene. This isomer is assigned structure (VI) on the basis of the following evidence. Carbonyl absorption at 1725 cm^{-1} is consistent with a phthalimidine structure.[5] A band at 1760—1780 cm^{-1},



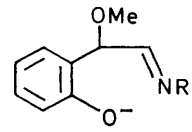
(VI)



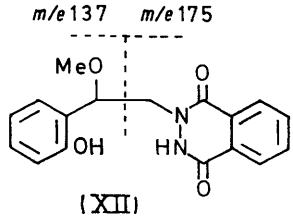
(VII)



(VIII)



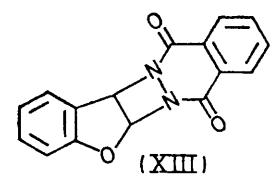
(XI)



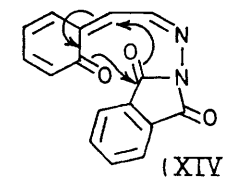
(XII)

characteristic of *N*-substituted phthalimides like (III), is absent. Similarly the n.m.r. spectrum ($CDCl_3$) shows the benzenoid ring A protons as an unsymmetrical signal at τ 2·2 rather than the symmetrical AA'BB' pattern characteristic of simple phthalimides. This resonance obscures the resonance of H_B which, as expected [6] occurs at higher field than in related compounds of presumed *anti*-configuration (τ 1—1·7) [3,7] and at a similar chemical shift to that of a cyclic imine.[8] The H_A signal appears as a doublet (J 3·5 Hz) at τ 4·5 and the ring B proton signal as a multiplet at τ 2·6—3·2.

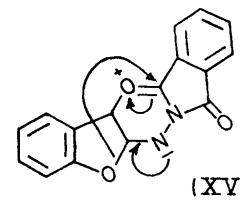
Reduction of compound (VI) over platinum proceeded without hydrogenolysis, which is slow for α-aryl-β-amino-compounds,[9] and gave the dihydro-derivative (VII), $\nu_{max.}$ 3280 and 1720 cm^{-1}, τ ($CDCl_3$–D_2O) 7·08 (1H, dd, J 13 and 1·5 Hz, H_B), 6·38 (1H, dd, J 13 and 3 Hz, H_C), and 4·8 (1H, dd, J 3 and 1·5 Hz, H_D). In the absence of D_2O the coupling of H_B and H_C with H_A (τ 5·8) is also apparent (J_{AB} 2·5, J_{AC} 13 Hz). The presence of a CH·CH_2·NH system in structure (VII) and consequently of a CH·CH=N system in (VI) is thus confirmed. This structural feature is also present in the mechanistically feasible alternative structure (VIII) for the rearrangement product. However both the the i.r. and n.m.r. data indicate the absence of an intact phthalimide residue. Further evidence favouring structure (VI) over (VIII) was provided by treatment of compound (VI) with sodium methoxide. The product (IX) retained an N–N bond. Formation of compound (IX) by treatment of (VI) with sodium methoxide (but not with methanol) presumably involves nucleophilic attack at the carbon atom benzylic to ring B, with concomitant formation of a phthalimide carbonyl system and departure of a phenolate anion to give the ion (XI) which will be in equilibrium with its ring tautomer [anion of (V)]. Gabriel–Colman [10] type ring expansion then gives the phthalohydrazide (IX). On similar treatment the dihydro-derivative (VII) gives the phenol (XII), as expected on the basis of this mechanism. The mass spectrum of this compound includes strong peaks at *m/e* 137 and 175 derived by the alternative α-cleavages indicated. This observation locates the methoxy-group in the benzylic position, an assignment further supported by the strong M — MeOH peak shown in the spectrum (*ortho*-effect). Chemical evidence relating to the structures of the methyl ethers includes the conversions (IV) ⟶ (X) and (V) ⟶ (IX) with sodium methoxide, and synthesis of compounds (IX) and (X) by treatment of the diazetidine (XIII) with boiling methanol; (XIII) was readily prepared by addition of benzo[*b*]furan to phthalazine-1,4-quinone.[11]



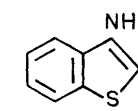
(XIII)



(XIV)



(XV)



(XVI)

Possible mechanisms for the conversion (III) ⟶ (VI) include a ring opening [(III) arrows] involving initial C–O fission assisted by the nitrogen lone pair and subsequent or concerted C–N cleavage * to the stabilised

* *Cf.* the rearrangement of chloroaziridines (ref. 3) and the solvolysis of chlorocyclopropanes (ref. 12).

[5] Z.-T. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, 1961, **26**, 2273.

[6] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 226.

[7] R. E. Harmon, J. L. Parsons, and S. K. Gupta, *J. Org. Chem.*, 1969, **9**, 2760.

[8] Q. Khuong-Huu and A. Pancrazi, *Tetrahedron Letters*, 1971, 37.

[9] R. L. Augustine, 'Catalytic Hydrogenation,' Arnold, London, 1965, p. 135.

[10] S. Gabriel and J. Colman, *Ber.*, 1900, **33**, 980, 2630; L. R. Caswell and R. D. Campbell, *J. Org. Chem.*, 1961, 4175.

[11] *Cf.* O. L. Chapman and S. J. Dominiani, *J. Org. Chem.*, 1966, **31**, 3862.

[12] R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, 1965, **87**, 395.

quinone methide (XIV). Ring closure [(XIV) arrows] then gives (VI). This mechanism is supported by the reaction of phthalimidonitrene with simple furans, which affords stable ring-opened products related to (XIV).[13] An alternative mechanism involves initial cleavage of the benzylic C–N bond, participation by the neighbouring phthalimido-group leading to (XV), and rearrangement [(XV) arrows] to (VI). Investigation of substituent effects should allow a decision between these alternatives.

In addition to *cis*-diphthaloyltetrazene [14] the reaction of compound (II) with benzo[*b*]thiophen affords the insertion product (XVI) but no isolable aziridine. The constitution (XVI) was confirmed by synthesis from benzo[*b*]thiophen-3(2*H*)-one and *N*-aminophthalimide.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Unless otherwise specified, i.r. spectra refer to Nujol mulls, u.v. spectra to ethanolic solutions, and n.m.r. spectra to solutions in deuteriochloroform, measured with a Varian A60A spectrometer. Mass spectra were obtained with an A.E.I. MS902 instrument. Petroleum refers to light petroleum, b.p. 60—80°, and chromatography on silica to short column chromatography over Kieselgel G (Merck).[15]

Addition of Phthalimidonitrene to Benzofuran.—Finely ground *N*-aminophthalimide (1·25 g), dichloromethane (20 ml), and benzofuran (1·5 g) were cooled to 0—5° in an ice-bath, and lead tetra-acetate (3·65 g; dried by pressing between filter papers) was added in small portions during 10—15 min with stirring. The orange-yellow product was diluted with dichloromethane and washed with water, and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure at room temperature. The crystalline product, after being stirred with a little cold benzene, was sufficiently pure for most purposes (yield 1·47 g). A sample crystallised from *warm* benzene formed prisms of 1a,6b-*dihydro*-1-*phthalimidobenzofuro*[2,3-b]*azirine* (III), m.p. 139—142° (decomp.) (Found: C, 69·4; H, 3·6; N, 10·0. $C_{16}H_{10}N_2O_3$ requires C, 69·1; H, 3·6; N, 10·1%), $\nu_{max.}$ 1705, 1760 cm^{-1}.

Reaction of the Aziridine (III) *with Methanol.*—Compound (III) (900 mg) was heated in boiling methanol (50 ml) for 2 h. Evaporation left an oil that was chromatographed on silica; elution with benzene–ether (4 : 1) gave 2,3-*dihydro*-2-*methoxy*-3-(N′N′-*phthaloylhydrazino*)*benzofuran* (IV) (610 mg), m.p. 121—122° (from methanol or benzene–petroleum) (Found: C, 65·6; H, 4·8; N, 8·8. $C_{17}H_{14}N_2O_4$ requires C, 65·8; H, 4·6; N, 9·0%), $\nu_{max.}$ 1720, 1718, 1750, 1768, and 3300 cm^{-1}, τ 2·1—2·35 (AA′BB′ pattern, phthaloyl), 2·4—3·3 (4H, m, aromatic), 4·3 (1H, d, *J* 1 Hz), 5·24 (1H, d, *J* 3·5 Hz, NH), and 5·5 (1H, d, *J* 3·5 Hz, benzylic).* On addition of D_2O the resonance at τ 5·24 disappeared and the doublet at 5·5 collapsed to a broad singlet ($W_{\frac{1}{2}}$ 3·0 Hz). Continued elution with the same solvent gave 2,3-*dihydro*-3-*methoxy*-2-(N′N′-*phthaloylhydrazino*)*benzofuran* (V) (50 mg) which t.l.c. [benzene–ether (4 : 1)] on silica revealed was contaminated with a trace of ether (IV) which prevented proper crystallisation. This product, $\nu_{max.}$ 3240, 3280, 1705, 1720, 1755, and 1775 cm^{-1}, *M* 310, was characterised by conversion into the highly crystalline ether (IX) as described later. Continued elution with the same solvent gave 19,20-*dioxa*-9,10-*diazapentacyclo*[10,7,1,$0^{1,9}$,$0^{2,7}$,$0^{13,18}$]-*eicosa*-2,4,6,10,13,15,17-*heptaen*-8-*one* (VI) (150 mg), prisms (from benzene), m.p. 186—188° [Found: C, 69·3; H, 3·3; N, 9·9%; *M* (osmometer), 276. $C_{16}H_{10}N_2O_3$ requires C, 69·1; H, 3·6; N, 10·1%; *M*, 278], $\nu_{max.}$ 1725 cm^{-1}.

Gabriel–Colman Reactions of Compounds (IV) *and* (V).—Compound (IV) (200 mg) was boiled with a solution of sodium methoxide [from sodium (35 mg) and methanol (3·5 ml)] for 3·5 h. The product was diluted with water, made acid by addition of acetic acid, and extracted into dichloromethane. Evaporation of the dried ($MgSO_4$) extract gave a product only part (150 mg) of which dissolved in benzene–ether (4 : 1). Silica chromatography of the soluble product in benzene–ether (4 : 1) gave 2,3-*dihydro*-2-*methoxy*-3-(1,2,3,4-*tetrahydro*-1,4-*dioxophthalazin*-2-*yl*)*benzofuran* (X) (50 mg), m.p. 230—232° (from chloroform–benzene) (Found: C, 65·90; H, 4·35; N, 8·80. $C_{17}H_{14}N_2O_4$ requires C, 65·8; H, 4·6; N, 9·0%), $\nu_{max.}$ 2300—3300, 1440—1510, and 1530—1670 cm^{-1} (all with several sub-maxima), τ [$(CD_3)_2SO$] 6·48 (3H, s, OMe), 4·1 (1H, d, *J* 2·3 Hz), 3·53 (1H, d, *J* 2·3 Hz), 3·3—2·5 (4H, m, aromatic), 2·3—1·9 (3H, m, aromatic), and 1·9—1·5 (1H, m, aromatic).

The impure ether (V) (50 mg) gave the isomeric *phthalazinylbenzofuran* (IX) (15 mg) after boiling with sodium methoxide solution [from sodium (33 mg) and methanol (3·3 ml)] for 2 h, work-up as just described, and crystallisation of the unchromatographed product from benzene; m.p. 203—210° (Found: C, 65·8; H, 4·55; N, 8·95%), $\nu_{max.}$ 1468, 1480, 1497, 1565, 1597, 1612, 1622, 1635, 1645, and 2300—3200 cm^{-1}, τ [$(CD_3)SO$] 6·55 (3H, s, OMe), 4·52 (1H, d, *J* 3 Hz, benzylic), 2·95 (1H, d, *J* 3 Hz), 3·2—2·3 (4H, m, aromatic), 2·1—1·9 (3H, m, aromatic), and 1·8—1·5 (1H, m, aromatic).

Addition of Benzofuran to Phthalazine-1,4-*dione.*—2,3-Dihydrophthalazine-1,4-dione [16] (1·25 g) in acetonitrile (20 ml) containing benzofuran (1·5 g) was oxidised at 0—5° by the addition of lead tetra-acetate over 30 min with vigorous stirring. The green colour that developed after each addition of lead tetra-acetate was allowed to fade before further addition of oxidant. After being stirred for a further 90 min, the mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$), carefully filtered under gravity, and evaporated under reduced pressure on a water-bath. Trituration of the product with benzene gave 5a,13a-*dihydrobenzofuro*[2′,3′:3,4][1,2]*diazeto*[1,2-b]*phthalazine*-7,12-*dione* (XIII) (1·47 g), m.p. 202—208° (decomp.) (from chloroform) (Found: C, 69·15; H, 3·8; N, 10·1. $C_{16}H_{10}N_2O_3$ requires C, 69·1; H, 3·6; N, 10·1%), $\nu_{max.}$ 1605 and 1650br cm^{-1}, τ 3·52 (1H, d, *J* 4·5 Hz, benzylic), 3·08 (1H, d, *J* 4·5 Hz), 2·5—2·0 (3H, m, aromatic), 2·0—1·6 (1H, m, aromatic), and 3·0—2·5 (4H, m, aromatic).

Reaction of Compound (XIII) *with Methanol.*—Compound (XIII) (100 mg) in methanol (4 ml) was boiled under reflux (2 h). The product was filtered to remove a trace of suspended material and the solution evaporated to give residue. The n.m.r. spectrum indicated the presence of a mixture (9 : 1) of the compounds (X) and (IX) which were not separable by chromatography on either silica or alumina in a variety of solvent systems. Crystallisation of the

* The *cis* or *trans* stereochemistry of 2,3-dihydrobenzofurans cannot be decided on the basis of $J_{vic.}$ (M. P. Mertes, L. J. Powers, and E. Shefter, *Chem. Comm.*, 1970, 620). The mode of formation of our dihydrobenzofurans favours a *trans* stereochemistry, but a *cis* stereochemistry is not excluded.

[13] D. W. Jones, unpublished observations.
[14] D. W. Jones, *Chem. Comm.*, 1970, 1084.
[15] B. J. Hunt and W. Rigby, *Chem. and Ind.*, 1967, 1868.
[16] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 1937, 16.

mixture from benzene gave compound (X), identical (mixed m.p. and i.r. spectrum) with that obtained before.

Thermal Rearrangement of Compound (III).—Compound (III) (1 g) was heated in boiling toluene (3 h). After removal of solvent under reduced pressure on the water-bath, the highly coloured product was chromatographed on neutral alumina (grade III) in benzene–ether (9 : 1). After elution had removed coloured impurities (orange band) compound (VI) (280 mg), m.p. 186—188° (from benzene), was obtained.

Catalytic Hydrogenation of Compound (VI).—Compound (VI) (108 mg) in ethyl acetate (5 ml) was hydrogenated over Adams catalyst (20 mg) at atmospheric pressure (2·5 h; uptake 1 mol. equiv.). The product was diluted with ethyl acetate to dissolve the solid which had separated; the solution was filtered and evaporated to give the *dihydro-derivative* (VII) (80 mg), m.p. 174—175° (from ethanol) [Found: C, 68·25; H, 4·3; N, 10·1%; *M* (osmometer), 276. $C_{16}H_{12}N_2O_3$ requires C, 68·6; H, 4·3; N, 10%; *M*, 280].

Reaction of Compound (VI) *with Sodium Methoxide.*—Compound (VI) (160 mg) was boiled with sodium methoxide solution [from sodium (30 mg) and methanol (7·5 ml)] for 4 h. The product was diluted with water, acidified with acetic acid, and extracted into ether. Evaporation of the dried ($MgSO_4$) extract and chromatography on silica in benzene–ether (4 : 1) gave the methyl ether (IX) (84 mg), identical (mixed m.p. and i.r. spectrum) with the samples previously prepared.

Reaction of Compound (VII) *with Sodium Methoxide.*—Compound (VII) (100 mg) in methanol (2 ml) was treated with sodium methoxide solution (3 ml) [from sodium (100 mg) and methanol (10 ml)], and the mixture was boiled under reflux. After 2 h more sodium methoxide solution (3 ml) was added and the mixture was boiled for a further 2 h. *2,3-Dihydro-2-(o-hydroxy-2-methoxyphenethyl)phthalazine-1,4-dione* (XII) (50 mg), obtained by work-up as in the preceding experiment, had m.p. 180—183° (from benzene) (Found: C, 65·6; H, 5·2; N, 8·6. $C_{17}H_{16}N_2O_4$ requires C, 65·4; H, 5·2; N, 9·0%), $\nu_{max.}$ 1460, 1505, 1590br, 1630, 2300—3200, and 3320 cm^{-1}, τ [$(CD_3)_2SO$] 6·9 (3H, s, OMe), 6·8—6·4 (OH), 6·12 (1H, dd, *J* 13 and 4·5 Hz, CH_2), 5·48 (1H, dd, *J* 13 and 8·5 Hz, CH_2), 4·79 (1H, dd, *J* 8·5 and 4·5 Hz, benzylic), 3·4—2·5 (4H, m, aromatic), 2·3—1·9 (3H, m, aromatic), and 1·9—1·6 (1H, m, aromatic).

[1/1548 *Received, August 25th,* 1971]