Reaction of 1,3-Dipoles with 3-Pyrrolidino-2-benzopyran-1-one

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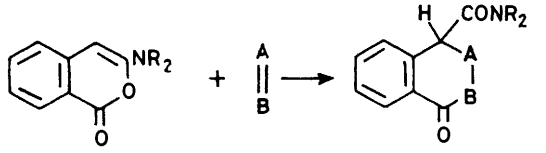
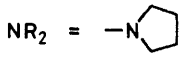
3-Pyrrolidino-2-benzopyran-1-one behaves differently towards various 1,3-dipoles: diphenyl-nitrile imine gives the pyrazolobenzopyranone (3), benzonitrile oxide and *N*-benzylideneaniline *N*-oxide yield derivatives (6) and (7), respectively, of 2,3-benzoxazepin-1-one, and *p*-nitrophenyl azide forms a mixture of 2-*p*-nitrophenyl-3-(*N*-pyrrolidinecarbonyl)phthalimidine (10) and *N*-(*p*-nitrophenylcarbamoyl)pyrrolidine (13).

WE have observed [1] that 3-dialkylamino-2-benzopyran-1-ones, such as compound (1), react with electrophilic compounds containing multiple bonds to yield products (2) of an ' acyl-ene reaction ' rather than the simple adducts expected from their enamine structure. Since enamines react with 1,3-dipolar compounds to yield five-membered heterocycles,[2] we were interested to examine the behaviour of a compound of type (1) towards various 1,3-dipoles, and we now report on the reactions of the pyrrolidino-derivative with such species.



(1) (2)

(3) (4)

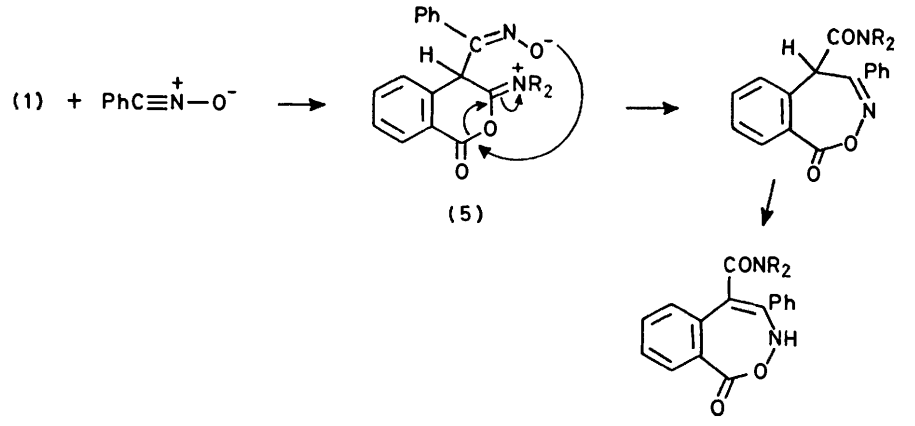


RESULTS AND DISCUSSION

Nitrile imines, produced by the action of bases on halogenated hydrazones, undergo 1,3-cycloaddition to enamines to form pyrazolines, which are readily converted into pyrazoles by loss of the dialkylamino-moiety.[3-5] The benzopyranone (1) reacted with diphenyl-nitrile imine to give a yellow adduct, whose i.r. spectrum showed the presence of an NH group and a single carbonyl band at 1 730 cm^{-1} due to the benzopyranone structure. The product is accordingly formulated as the pyrazolobenzopyranone (4), formed by a prototropic change from the initial cycloadduct (3). The direction of addition is assumed to be as shown by analogy to that of diphenyl-nitrile imine to pyrrolidino-cyclopentene.[4] The benzopyranone thus behaved as an enamine in the reaction with the nitrile imine.

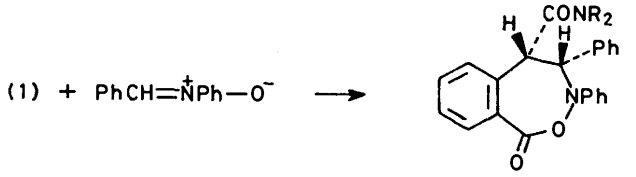
Nitrile oxides [4,6] and nitrones [7] readily add to enamines to form isoxazoles and isoxazolines, respectively. However, this type of reaction was not observed when the benzopyranone (1) was treated with benzonitrile oxide and *N*-benzylideneaniline *N*-oxide. The action of the former yielded an adduct, which showed lactone and amide absorptions at 1 705 and 1 625 cm^{-1}, respectively; the presence of a pyrrolidinecarbonyl group was confirmed by the appearance of a fragment of mass 98 in the mass spectrum. The ^1H n.m.r. spectrum showed the absence of a methine proton but the presence of a labile proton, which is assigned to that of an NH group. These data suggest that the adduct is the benzazepinone (6), formed from the 1,5-dipolar intermediate (5) as shown. A similar reaction occurred on prolonged heating of compound (1) with the diphenylnitrone in acetonitrile; the complex mixture contained, besides unchanged nitrone and decomposed starting materials, the adduct (7). I.r. carbonyl absorptions at 1 735 and 1 635 cm^{-1} are attributed, respectively, to those of the lactone and the amide group. The mass spectrum showed the pyrrolidinecarbonyl fragment, and the ^1H n.m.r. spectrum exhibited signals due to two adjacent methine protons, whose coupling constant of 3.5 Hz suggests [8] that the compound has the *cis*-configuration. 2,3-Benzoxazepin-1-ones appear to be new. Gottlieb [9] and others [10] claimed to have prepared the 4-methyl-5*H*-derivative by fusion of phenylacetone-*o*-carboxylic acid oxime, but the red colour of the product indicates that it has a different structure.

Yet another kind of reaction occurred when the



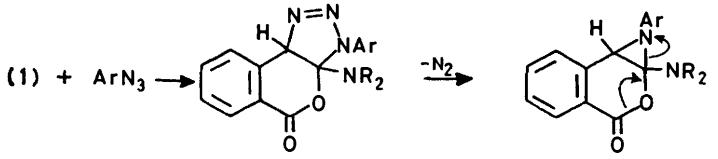
(5)

(6)

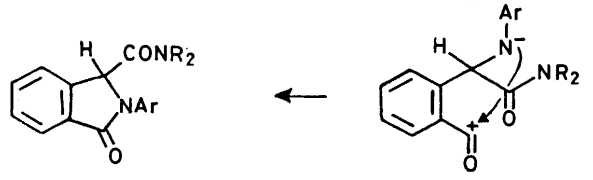


(7)

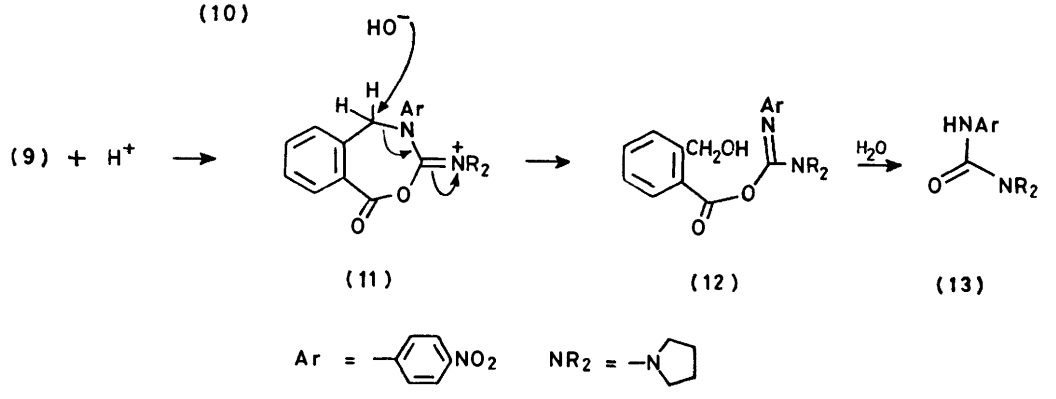
$NR_2 = -N\square$



(8) (9)



(10)



(11) (12) (13)

Ar = $-C_6H_4NO_2$ $NR_2 = -N\square$

benzopyranone was heated with *p*-nitrophenyl azide. Two products were isolated. The first had the composition $C_{19}H_{17}N_3O_4$, *i.e.* that of an adduct that had lost nitrogen; its i.r. spectrum showed amide absorption at 1 660 and a band at 1 710 cm^{-1}, which is near the carbonyl vibration of phthalimidine.[11] Mass spectrometry confirmed the molecular weight and the presence of the pyrrolidinecarbonyl substituent. These data, together with the ^1H n.m.r. spectrum, which showed a signal due to a methine proton, indicate that the compound is 2-*p*-nitrophenyl-3-(*N*-pyrrolidinecarbonyl)-phthalimidine (10). The second product was readily identified as the known[12] *N*-(*p*-nitrophenylcarbamoyl)-pyrrolidine (13). A reaction path which accounts for the formation of both compounds involves the triazoline (8) and the aziridine (9) as intermediates. 1,3-Dipolar cycloadditions of aryl azides to enamines to yield triazolines are well documented[13] and triazolines are known[14] to lose nitrogen to form aziridines. In the present instance the strained aziridinobenzopyranone (9) can undergo ring-opening and recyclisation to yield the phthalimidine, as shown. To account for the formation of the urea derivative (13), we suggest that the aziridinobenzopyranone is hydrolysed as follows: the carbon–carbon bond of the three-membered ring is broken by protonation at the benzylic carbon atom; the resulting iminium cation (11) yields the imino-ester (12) by attack of hydroxide ion at the same carbon atom. Further hydrolysis gives the product and *o*-hydroxymethylbenzoic acid, which, however, was not isolated.

EXPERIMENTAL

I.r. spectra refer to Nujol mulls unless stated otherwise.

3,3a-*Dihydro*-1,3-*diphenyl*-3a-*pyrrolidinopyrazolo*[3,4-c]-[2]*benzopyran*-5(2H)-*one* (4).—A solution of N^1-α-chlorobenzylidene-N^2-phenylhydrazine[15] (2.2 g, 1.9 mol equiv.) in acetone (40 ml) was added during 15 min to a solution of 3-pyrrolidino-2-benzopyran-1-one (1.07 g, 0.005M) and triethylamine (3.03 g, 6 mol equiv.) in acetonitrile (50 ml), stirred under nitrogen. The mixture was stirred for a further 8 h, during which time the *product* (0.9 g, 44%) crystallised. It formed yellow needles, m.p. 194—196 °C (decomp.); $\nu_{max.}$ 3 295, 1 730, and 1 600 cm^{-1}; δ(CF_3CO_2D) 8.37br (NH), 7.90—7.10 (m, 14 H, Ar), and 3.20—2.90 (m, 4 H) and 2.00—1.60 (m, 4 H) (pyrrolidino); *m/e* 409 (M^+) (Found: C, 76.05; H, 5.6; N, 10.0. $C_{26}H_{23}N_3O_2$ requires C, 76.25; H, 5.65; N, 10.25%).

4-*Phenyl*-5-N-(*pyrrolidinecarbonyl*)-2,3-*benzoxazepin*-1(3H)-*one* (6).—A solution of the benzopyranone (1) (0.54 g, 0.0025M) and triethylamine (0.5 g, 2 mol equiv.) in acetonitrile (40 ml) was stirred under nitrogen and a solution of *N*-α-chlorobenzylidenehydroxylamine[16] (0.43 g, 1.1 mol equiv.) in acetonitrile (10 ml) was added during 20 min. After 2 h the solvent was removed; the residue was dissolved in chloroform (50 ml) and the solution was washed successively with water (100 ml), 2N hydrochloric acid (100 ml), and water (100 ml) and then dried ($MgSO_4$). The solution was evaporated and the oily residue chromatographed on 2-mm thick Merck Kieselgel GF 254 plates, using ethyl acetate–light petroleum as eluant, to give the *benzoxazepinone* (0.07 g, 8.4%), m.p. 155—156 °C (from chloroform–light petroleum); $\nu_{max.}$ ($CHCl_3$) 1 705 and 1 625 cm^{-1}; δ($CDCl_3$) 9.23 (s, disappears with D_2O, NH), 7.99—7.00 (m, 9 H, Ar), and 3.30—3.05 (m, 4 H), and 1.90—1.65 (m, 4 H) (pyrrolidino); *m/e* 334 (M^+), 98 (pyrrolidinecarbonyl$^+$), and 77 (Ph^+) (Found: C, 71.65; H, 5.35; N, 8.2. $C_{20}H_{18}N_2O_3$ requires C, 71.85; H, 5.45; N, 8.4%).

cis-4,5-*Dihydro*-3,4-*diphenyl*-5-(N-*pyrrolidinecarbonyl*)-2,3-*benzoxazepin*-1(3H)-*one* (7).—A solution of the benzopyranone (0.215 g, 0.001M) and *N*-benzylideneaniline *N*-oxide[17] (0.197 g, 1 mol equiv.) in acetonitrile (20 ml) was refluxed for 72 h, when t.l.c. indicated that no further change was taking place. After removal of the solvent the residue was chromatographed as described above to give the *product* (0.067 g, 16%), m.p. 266—267 °C (from chloroform–ether), $\nu_{max.}$ 1 736, 1 635, and 1 600 cm^{-1}; δ($CDCl_3$) 8.35—6.90 (m, 14 H, Ar), 4.62 (d, CH), 4.12 (d, CH) (*J* 3.5 Hz), and 3.75—3.25 (m, 4 H) and 2.20—1.65 (m, 4 H) (pyrrolidino); *m/e* 412 (M^+) and 98 (pyrrolidinecarbonyl$^+$) (Found: C, 76.0; H, 5.95; N, 6.55. $C_{26}H_{24}N_2O_3$ requires C, 75.7; H, 5.9; N, 6.8%).

Reaction of the Benzopyranone (1) *with* p-*Nitrophenyl Azide*.—A solution of the benzopyranone (1.08 g, 0.005M) and the azide (0.82 g, 1 mol equiv.) in acetonitrile (50 ml) was refluxed for 1 week. The solvent was removed and the residual oil was chromatographed as above to yield a solid, which was crystallised from acetone–ether to give 2-*p*-*nitrophenyl*-3-(N-*pyrrolidinecarbonyl*)*phthalimidine* (10) (0.6 g, 34%), m.p. 246—247 °C; $\nu_{max.}$ 1 710, 1 660, and 1 600 cm^{-1}; δ(CF_3CO_2D) 8.50—7.50 (m, 8 H, Ar), 6.47 (s, CH), and 4.20—3.50 (m, 4 H) and 2.40—1.90 (m, 4 H) (pyrrolidino); *m/e* 351 (M^+) and 98 (pyrrolidinecarbonyl$^+$) (Found: C, 64.95; H, 4.85; N, 11.9. $C_{19}H_{17}N_3O_4$ requires C, 64.95; H, 4.9; N, 11.95%). The mother-liquors yielded *N*-(*p*-nitrophenylcarbamoyl)pyrrolidine (13) (0.1 g, 8.5%), m.p. 184—186 °C (lit.,[12] m.p. 185—186 °C); $\nu_{max.}$ 3 400 and 1 660 cm^{-1}; δ($CDCl_3$) 8.23 (d, 2 H) and 7.61 (d, 2 H) (*J* 9 Hz, Ar), 3.85—3.60 (m, 4 H) and 2.40—2.15 (m, 4 H) (pyrrolidino), and 1.55 (s, NH); *m/e* 235 (M^+), 98 (pyrrolidinecarbonyl$^+$), and 70 (pyrrolidino$^+$).

[9/760 *Received*, 16*th May*, 1979]

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