Ring Transformations of 2-Morpholinofurans and *N*-(2,3-Dihydro-2-furylidene)morpholinium Salts

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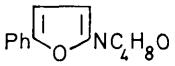
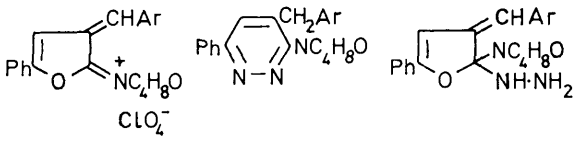
N-(3-Arylmethylene-2,3-dihydro-5-phenyl-2-furylidene)morpholinium perchlorates (2) reacted with hydrazine to yield 4-arylmethyl-3-morpholino-6-phenylpyridazines (3). 3-arylazo-2-morpholino-5-phenylfurans (9) similarly gave 4-(2-arylhydrazino)-3-morpholino-6-phenylpyridazines, and 2-morpholino-5-phenylfuran formed hydrazonotetrahydropyridazines (13) and (14). The alkoxydihydrofurans (6a and b) were obtained by the action of alcohols in the presence of bases on *N*-(2,3-dihydro-5-phenyl-3-diphenylcyclopropenylidene-2-furylidene)morpholinium perchlorate (5). The hydrofluoroborate of 2-morpholino-5-phenyl-3-phenylazofuran rearranged to the morpholide of 1,5-diphenylpyrazole-3-carboxylic acid on treatment with hydrochloric acid.

2-Dialkylaminofurans and their salts are described in the preceding paper [1] and it is shown that the hydroperchlorate of 2-morpholino-5-phenylfuran (1) condenses with aromatic aldehydes to form coloured arylmethylene derivatives (2). Since the products are readily hydrolysed by water it appeared of interest to investigate the action of other nucleophiles on these salts



(1)



(2) (3) (4)

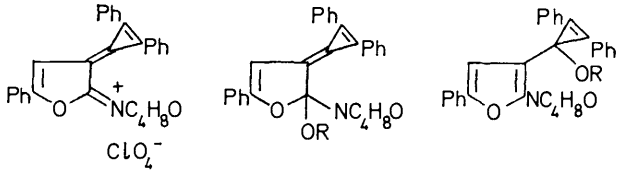
a; Ar = Ph
b; Ar = *p*-ClC_6H_4
c; Ar = *p*-MeC_6H_4
d; Ar = *p*-$MeO{\cdot}C_6H_4$
e; Ar = 3,4-$CH_2O_2{\cdot}C_6H_3$

and we chose the benzylidene compound (2a) for our initial studies. The perchlorate reacted with ammonia, ammonium acetate, aniline, phenylhydrazine, and 2,4-dinitrophenylhydrazine but no well-defined products could be isolated, apart from morpholinium perchlorate in two cases. Treatment with a mixture of ethanolic hydrazine and triethylamine gave a good yield of a colourless base, which proved to be the pyridazine (3a). The i.r. spectrum of this compound contained no band above 1587 cm^{-1}, apart from C–H stretching vibrations, and its n.m.r. spectrum showed the presence of the morpholine substituent and the benzylic methylene group. The signal of the pyridazine proton was submerged in the aromatic envelope. The product was characterised by the preparation of its hydrochloride. Analogous 4-arylmethylpyridazines (3b—e) were readily formed by the action of hydrazine on the iminium salts (2b—e), respectively. The bases and their hydrochlorides are listed in Table 1. The reaction presumably proceeds by initial attack of hydrazine at C-2 of the dihydrofuran ring to give, after proton abstraction, the aminals (4).

[1] G. V. Boyd and K. Heatherington, preceding paper.
[2] G. V. Boyd, *J.C.S. Perkin I*, 1973, 1731.

These intermediates then undergo ring-opening, recyclisation, and, finally, prototropy to form the pyridazines. A close analogy is the conversion [2] of 3-benzylidenephthalan-1-ylideneammonium salts into 1-dialkylamino-4-benzylphthalazines.

The reaction of the cyclopropenylideneiminium perchlorate (5) [1] with ethanolic hydrazine and triethylamine took a different course, yielding an ethoxy-compound which regenerated the salt when treated with perchloric acid. The ether was also obtained when either hydrazine or triethylamine was omitted and when the salt was boiled with aqueous ethanolic sodium hydroxide. The n.m.r. spectrum of the product exhibited signals corresponding to an olefinic proton, morpholine protons, phenyl protons, and an *O*-ethyl group; its i.r. spectrum contained a characteristic cyclopropene absorption band at 1786 cm^{-1}. While the spectra are consistent with either structure (6a) or (7a), we prefer the former because the ether absorbed at a considerably longer wavelength (372 nm) than does 2-morpholino-5-phenylfuran (318 nm), a good model for the alternative. The methoxy-analogue (6b) was formed when methanol was used in place of ethanol in the hydrazine–triethylamine reaction. These ethers correspond to the postulated intermediates (4).



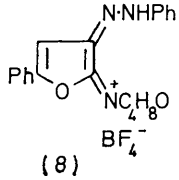
(5) (6) (7)

a; R = Et
b; R = Me

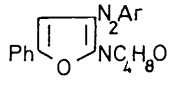
Derivatives of pyridazine were also obtained from 3-arylazo-2-morpholino-5-phenylfurans and their salts. The fluoroborate (8) was smoothly converted into the phenylhydrazinopyridazine (10a) on treatment with ethanolic hydrazine at room temperature. The reaction probably occurs by preliminary deprotonation of the salt to the azofuran (9a), because the latter reacted equally readily with hydrazine to give the same product. The hydrofluoroborates of the azo-compounds (9b—f) were similarly transformed into the pyridazines (10b—f), respectively (Table 2); the *p*-acetylphenylazofuran (9g)

yielded the hydrazone (10 h). The hydrazinopyridazines absorb maximally at 250—290 nm; * hence the tautomeric azo-forms (11) are ruled out. We consider that the spectra also exclude the cross-conjugated arylhydrazonodihydropyridazine structures (12), as these would require that the compounds absorb at much longer wavelengths; the phenylhydrazone (8), for example, which has a similar chromophore, is red ($\lambda_{max.}$ 480 nm).[1]

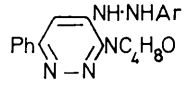
The ease with which the arylazomorpholinofurans are attacked by hydrazine is remarkable in view of the resistance of the furan nucleus to the action of bases [3] and we at first thought that it was due to the electron-withdrawing effect of the azo-group. It was found, however, that 2-morpholino-5-phenylfuran itself reacted with ethanolic hydrazine under mild conditions to yield a mixture of two products. The major component, obtained in 73% yield, was the hydrazonotetrahydropyridazine (13). Its i.r. spectrum indicated the presence of primary amino and azomethine groups, and the n.m.r. spectrum that of three protons attached to nitrogen



(8)



(9)



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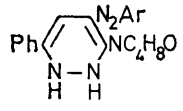

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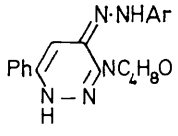
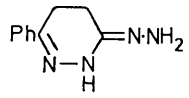


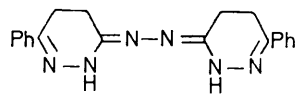
(12)

a; Ar = Ph
b; Ar = *p*-MeC_6H_4
c; Ar = *p*-$MeO{\cdot}C_6H_4$
d; Ar = *p*-ClC_6H_4
e; Ar = *p*-$EtO_2C{\cdot}C_6H_4$
f; Ar = *p*-$O_2N{\cdot}C_6H_4$
g; Ar = *p*-AcC_6H_4
h; Ar = *p*-$MeC(=N{\cdot}NH_2){\cdot}C_6H_4$

atoms and two adjacent methylene groups. The minor product (5% yield) is considered to be the azine (14) on the basis of its analytical figures and i.r. (secondary amine, azomethine) and n.m.r. spectra (two *N*-protons and four methylene groups). Compound (13) was also rapidly formed when the hydroperchlorate of the furan was added to an ethanolic solution of hydrazine. The reaction leading to the tetrahydropyridazines must be initiated by addition of hydrazine to the enamine system of compound (1) to yield the intermediate (15), the reverse of the formation of enamines from aminals.[4] The adduct then undergoes ring-opening, recyclisation, and replacement of the morpholine residue by a second molecule of hydrazine; but the precise sequence of these steps is not known.



(13)



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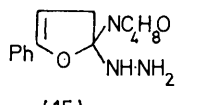

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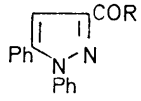

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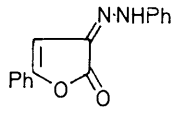

(17)

a; R = morpholino
b; R = OH

A different type of ring transformation occurred when the phenylhydrazonodihydrofurylidenemorpholinium salt (8) was heated with dilute hydrochloric acid: the pyrazole derivative (16a) was produced, accompanied by the butenolide (17). The rearrangement is closely related to the formation [5] of the corresponding acid (16b) by acid or alkaline treatment of this butenolide and to the conversion [6] of the coupling product of 2,5-dimethylfuran with *p*-nitrobenzenediazonium chloride into 3-acetyl-5-methyl-1-*p*-nitrophenylpyrazole. Treatment of the iminium salt (8) with concentrated hydrochloric acid gave the pyrazolecarboxylic acid (16b),[7] which might have arisen from the morpholide (16a) and/or the butenolide (17).

EXPERIMENTAL

For general remarks, see the preceding paper.

Formation of 4-Arylmethyl-3-morpholino-6-phenylpyridazines (3) *from* N-(3-*Arylmethylene-2,3-dihydro-5-phenyl-2-furylidene)morpholinium Perchlorates* (2) (*Table* 1).—The arylmethylene compound (0·5 g) was stirred with ethanol (25 ml), and triethylamine (2 ml) and hydrazine hydrate (2 ml) were added consecutively. Stirring was continued until the salt had disappeared and then for a further 30 min. The solution was poured into water (250 ml) and the mixture was extracted with ether (3 × 100 ml). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residual oil crystallised in the case of compound (3a); in other reactions, the oil was treated with a saturated ethanolic solution of hydrogen chloride and the solid pyridazine hydrochloride was collected. The salt was treated with aqueous sodium carbonate and the resulting base was extracted with ether. Evaporation of the dried extract left the crystalline pyridazine.

3-Diphenylcyclopropenylidene-2,3-dihydro-2-ethoxy-2-morpholino-5-phenylfuran (6a).—A stirred suspension of the perchlorate (5) (0·5 g) in ethanol (25 ml) was successively treated with triethylamine (2 ml) and hydrazine hydrate (2 ml), as described above. After the usual work-up, the *product* (0·28 g, 63%) crystallised; m.p. 142—143° (from ethanol), $\nu_{max.}$ 1786, 1608, 1560, 1113, and 1070 cm^{-1}, $\lambda_{max.}$ 229 nm (ε 21,000), 263 (16,700), 336 (24,800), and 372infl nm (18,600), τ 2·3—2·8 (m, 3 × Ph), 3·12 (s, 4-H), 6·4 (m) and 6·6 (m)

* A further band at 368 nm in the spectrum of compound (10f) is attributed to the presence of the nitro-group.

[3] A. P. Dunlop and F. N. Peters, 'The Furans,' Reinhold, New York, 1953, p. 663.

[4] L. W. Haynes, in 'Enamines: Synthesis, Structure and Reactions,' ed. A. G. Cook, Marcel Dekker, New York, 1969, p. 59.

[5] W. Dieckmann, *Ber.*, 1914, **47**, 1435.

[6] R. H. Eastman and F. L. Detert, *J. Amer. Chem. Soc.*, 1948, **70**, 962.

[7] C. Beyer and L. Claisen, *Ber.*, 1887, **20**, 2178.

(8H, morpholine), and 6·4 (2H, q) and 8·78 (3H, t) (*J* 7 Hz, Et) (Found: C, 80·1; H, 6·3; N, 2·9. $C_{31}H_{29}NO_3$ requires C, 80·3; H, 6·3; N, 3·0%).

The ether was also obtained when the reaction was carried out (*a*) without the addition of triethylamine (69% yield), (*b*) without the addition of hydrazine hydrate (59% yield), and (*c*) by using a mixture of ethanol (15 ml) and 5N-sodium hydroxide (10 ml) and boiling for 1 h under reflux (65% yield).

The *methoxy-analogue* (6b) (0·30 g, 69%) was prepared by substituting methanol for ethanol in the first-mentioned procedure; it had m.p. 99—100° (from methanol), $\nu_{max.}$ 1786, 1609, 1562, 1115, and 1086 cm^{-1}, $\lambda_{max.}$ 228 (ε 21,900), 268 (15,600), 331 (21,700), and 366infl nm (16,800), τ 2·3—2·9 (m, 3 × Ph), 3·12 (s, 4-H), 6·4 (m) and 6·6 (m) (8H, morpholine), and 6·74 (s, Me) (Found: C, 79·9; H, 6·1; N, 3·1. $C_{30}H_{27}NO_3$ requires C, 80·1; H, 6·1; N, 3·1%).

A solution of the ethoxy-compound (6a) (50 mg) in ether (20 ml) was treated with a few drops of perchloric acid. The ether was decanted from the resulting oil and acetone was added, giving the perchlorate (5) (47 mg, 84%), identified by its i.r. spectrum. A similar result was obtained when the methyl ether (6b) was used.

4-(2-Arylhydrazino)-3-morpholino-6-phenylpyridazines (10) (*Table* 2).—Hydrazine hydrate (2 ml) was added to a stirred suspension of the hydrofluoroborate (0·2 g) of an azofuran (9) or the free base (0·2 g) in ethanol (25 ml). Stirring was continued, with brief gentle heating if necessary, until a clear solution had formed. After refrigeration overnight, the product usually crystallised, but in some cases it was necessary to evaporate some of the solvent.

Reaction of 2-Morpholino-5-phenylfuran (1) *with Hydrazine*.—A mixture of the furan (1·0 g), hydrazine hydrate (3 ml), and ethanol (15 ml) was heated under reflux for 1·5 h, then cooled, and the precipitated *NN'-bis-(2,3,4,5-tetrahydro-6-phenylpyridazin-3-ylidene)hydrazine* (14) (0·033 g, 5%) was collected; it had m.p. 208—209°, $\nu_{max.}$ 3410, 1643, and 1338 cm^{-1}, $\lambda_{max.}$ 230 (ε 13,400) and 348 nm (39,000), τ 0·4 (s, 2 × NH), 2·0—2·2 (m) and 2·5—2·6 (m) (2 × Ph), and 7·1—7·4 (m, 4 × CH_2) (Found: C, 69·4; H, 6·0; N, 24·4. $C_{20}H_{20}N_6$ requires C, 69·7; H, 5·9; N, 24·4%). The filtrate was concentrated to 10 ml; on cooling, *3-hydrazono-2,3,4,5-tetrahydro-6-phenylpyridazine* (13) (0·22 g, 27%) crystallised as plates, m.p. 197—200°, $\nu_{max.}$ 3300, 3180, 3050, 1650, 1588, and 1342 cm^{-1}, $\lambda_{max.}$ 228 (ε 8900) and 310 nm (17,900), τ 2·3—2·4 (m) and 2·6—2·8 (m) (Ph), 6·0—7·0br (s, 3 × NH), and

TABLE 1

4-Arylmethyl-3-morpholino-6-phenylpyridazines (3) and their hydrochlorides

Compound	Yield (%)	M.p. (°C) [a]	Found (%) C	H	N	Formula	Required (%) C	H	N	$\nu_{max.}$/cm^{-1}	$\lambda_{max.}$/nm (ε)
(3a)	86	121	76·2	6·5	12·7	$C_{21}H_{21}N_3O$	76·1	6·4	12·7	1587, 1117 [b]	262 (16,200) [c]
(3a), HCl	79	146—149	68·3	6·3	11·3	$C_{21}H_{22}ClN_3O$	68·6	6·0	11·4	3000—2200, 1611, 1586, 1114	262 (16,200)
(3b)	90	145	69·3	5·6	11·6	$C_{21}H_{20}ClN_3O$	69·0	5·5	11·5	1588, 1115	264 (17,100)
(3b), HCl	73	164—166	61·4	5·5	10·0	$C_{21}H_{21}Cl_2N_3O,0·5H_2O$	61·3	5·4	10·2	3600—3200, 3000—2200, 1611, 1586, 1115	264 (16,000)
(3c)	80	124—126	76·7	6 9	12·2	$C_{22}H_{23}N_3O$	76·5	6·7	12·2	1584, 1112	262 (16,300)
(3c), HCl	77	154—156	68·2	6·7	10·3	$C_{22}H_{24}ClN_3O,0·5EtOH$	68·3	6·7	10·4	3460, 3000—2200, 1609, 1585, 1113	262 (16,000)
(3d)	80	92	72·9	6·2	11·4	$C_{22}H_{23}N_3O_2$	73·1	6·4	11·6	1605, 1112, 1030	263infl (16,000), 275 (16,700)
(3d), HCl	83	149—151	65·5	6·0	10·2	$C_{22}H_{24}ClN_3O_2,0·25H_2O$	65·6	6·1	10·4	3600—3200, 3000—2100, 1610, 1586, 1110, 1040	263infl (17,800), 275 (18,600)
(3e)	78	148—149	70·3	5·8	11·0	$C_{22}H_{21}N_3O_3$	70·4	5·6	11·2	1589, 1114, 1042	261infl (17,300), 280 (18,200)
(3e), HCl	75	139—140	64·2	5·6	10·0	$C_{22}H_{22}ClN_3O_3$	64·2	5·4	10·2	3000—2100, 1610, 1585, 1113, 1036	262infl (12,200), 280 (12,800)

[a] From ethanol. [b] Morpholine ether. [c] τ 2·05—3·0 (m, 2 × Ph and 5-H), 6·03 (s, CH_2), and 6·20 (4H, t) and 6·70 (4H, t) (*J* 4·5 Hz, morpholine).

TABLE 2

4-(2-Arylhydrazino)-3-morpholino-6-phenylpyridazines (10)

Compound	Yield (%)	M.p. (°C) [a]	Found (%) C	H	N	Formula	Required (%) C	H	N	$\nu_{max.}$/cm^{-1}	$\lambda_{max.}$/nm (ε)
(10a)	78, [b] 67 [c]	205—206	69·1	6·1	20·1	$C_{20}H_{21}N_5O$	69·1	6·1	20·2	3280, 3200infl, 1604, 1112	251 (30,000) [e]
(10b)	76 [b]	209—211	69·7	6·5	19·6	$C_{21}H_{23}N_5O$	69·8	6·4	19·4	3275, 3215, 1600, 1106	254 (30,000)
(10c)	48 [b]	192—193	66·4	6·2	18·5	$C_{21}H_{23}N_5O_2$	66·8	6·1	18·6	3275, 3200infl, 1603, 1239, 1105, 1033	250 (31,100), 290infl (12,300)
(10d)	81 [b]	221	63·0	5·3	18·0	$C_{20}H_{20}ClN_5O$	62·9	5·3	18·3	3270, 3220, 1598, 1108	251 (36,100)
(10e)	62 [b]	181—183	65·3	6·0	16·8	$C_{23}H_{25}N_5O_3$	65·6	6·0	16·7	3260, 3200infl, 1700, 1605, 1270, 1105	250 (29,500), 289 (29,300)
(10f)	44 [b]	238—240 [d]	61·5	5·5	20·9	$C_{20}H_{20}N_6O_3$	61·2	5·1	21·4	3355, 3280, 1590, 1535, 1328, 1110	255 (35,100), 290infl (17,600) 368 (23,400)
(10h)	24 [b]	210—212 [d]	64·7	6·4	23·2	$C_{22}H_{25}N_7O,0·5EtOH$	64·8	6·6	23·0	3360, 3300—3100, 3270, 1611, 1108	253 (33,500), 282 (31,600)

[a] Analytically pure without recrystallisation. [b] Prepared from the hydrofluoroborate of the azofuran. [c] Prepared from the azofuran. [d] Decomp. [e] τ 2·0—3·3 (m, 2 × Ph and 5-H), 3·52 (s, NH), 4·16 (s, NH), and 6·13 (4H, t) and 6·65 (4H, t) (*J* 4·5 Hz, morpholine).

7·1—7·6 (m, 2 × CH_2) (Found: C, 64·1; H, 6·5; N, 29·5. $C_{10}H_{12}N_4$ requires C, 63·8; H, 6·4; N, 29·4%). Further concentration of the filtrate gave the *hydrate* of compound (13) (0·413 g, 46%), pale yellow needles, m.p. 197—198°, $\nu_{max.}$ 3500—2800, 1658, 1588, and 1315 cm^{-1}, $\lambda_{max.}$ 228 (ε 8700) and 310 nm (17,700) (Found: C, 58·3; H, 6·8; N, 27·2. $C_{10}H_{12}N_4,H_2O$ requires C, 58·2; H, 6·8; N, 27·2%).

The hydrate (0·205 g, 66%) was also obtained when the hydroperchlorate (0·5 g) of the furan (1) was added to a solution of hydrazine hydrate (2 ml) in ethanol (15 ml).

Reaction of N-(2,3-*Dihydro*-5-*phenyl*-3-*phenylhydrazono*-2-*furylidene*)*morpholinium Tetrafluoroborate* (8) *with Hydrochloric Acid*.—(*a*) A mixture of the salt (0·2 g), ethanol (2 ml), and N-hydrochloric acid (20 ml) was heated at *ca.* 80° for 10 min and then cooled; the resulting orange precipitate was recrystallised from acetonitrile to give 5-phenyl-3-phenylhydrazonofuran-2(3*H*)-one (17) (0·027 g, 22%), m.p. 225—226° (decomp.) (lit.,[5] 227°), $\nu_{max.}$ 3250, 1748, and 1600 cm^{-1}, $\lambda_{max.}$ 228 (ε 8700), 252 (13,900), 294 (4600), and 431 nm (32,300) (Found: C, 73·1; H, 4·7; N, 10·8. Calc. for $C_{16}H_{12}N_2O_2$: C, 72·7; H, 4·6; N, 10·6%). The filtrate slowly deposited N-(1,5-*diphenylpyrazole*-3-*carbonyl*)*morpholine* (16a) (0·066 g, 42%), plates, m.p. 119—120°, $\nu_{max.}$ 1623 and 1115 cm^{-1}, $\lambda_{max.}$ 248 nm (ε 14,000) (Found: C, 72·2; H, 5·7; N, 12·5. $C_{20}H_{19}N_3O_2$ requires C, 72·1; H, 5·7; N, 12·6%).

(*b*) A mixture of the salt (8) (0·2 g), concentrated hydrochloric acid (10 ml), and acetic acid (10 ml) was boiled under reflux for 2 h. The resulting solution was poured into water (150 ml), whereupon 1,5-diphenylpyrazole-3-carboxylic acid (16b) (0·104 g, 83%) was deposited; it had m.p. 185° (lit.,[7] 185°), $\nu_{max.}$ 3200—2400 and 1695 cm^{-1}, $\lambda_{max.}$ 253 nm (ε 11,100) (Found: C, 72·5; H, 4·8; N, 10·5. Calc. for $C_{16}H_{12}N_2O_2$: C, 72·7; H, 4·6; N, 10·6%).

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