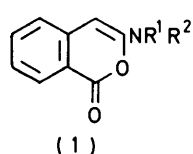


## The Chemistry of *N*-Substituted 3-Amino-1*H*-2-benzopyran-1-ones and 5-Amino-2,3-dihydrofuran-2-ones. Ene-type Reactions Involving Transfer of Acyl Groups.<sup>1</sup> X-Ray Crystal Structure of *cis*-3,4-Dihydro-4-morpholinocarbonyl-3-*p*-nitrophenyl-1*H*-2-benzopyran-1-one

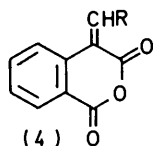
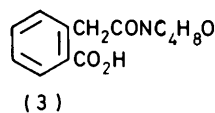
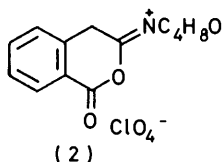
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The (secondary amino)-1*H*-2-benzopyran-1-ones (1) add numerous aromatic aldehydes to yield geometrically isomeric lactones (7) in a manner that constitutes an ene reaction in which an acyl group is transferred. Analogous dihydrobenzopyranones (14) and (15) were obtained from cyclohexanone and diphenylketen. Addition to imines gave dihydroisoquinolones (16) and (17), phenyl isocyanate yielded the tetrahydroisoquinolinedione (18), and nitrosobenzene and carbon disulphide afforded the adducts (19) and (25), respectively. The morpholinobenzopyran-1-one (1a) added to the azo-group of 4-phenyl-1,2,4-triazoline-3,5-dione to yield compound (20); a similar reaction with arenediazonium salts resulted in the phthalazinone derivatives (23). Addition to dimethyl acetylenedicarboxylate produced the naphthol (26); *trans*- $\beta$ -nitrostyrene afforded a mixture of two geometrically isomeric tetralones (27) and (28) with retained configuration. The unisolable morpholinobutenolide (30a) was intercepted by reaction with aromatic aldehydes and with dimethyl acetylenedicarboxylate to yield the adducts *cis*- and *trans*-(31), and (32), respectively. *N*-*t*-Butylsuccinisoimide reacts as the enamine tautomer (30b) with *p*-nitrobenzaldehyde, forming the  $\gamma$ -lactones (31d). X-Ray diffraction of the *cis*-isomer of 3,4-dihydro-4-morpholinocarbonyl-3-*p*-nitrophenyl-1*H*-2-benzopyran-1-one (7a) shows that the *p*-nitrophenyl group is equatorial and the morpholinocarbonyl substituent axial.

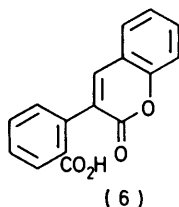
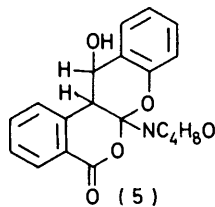
THE preparation of the *N*-substituted 3-(secondary amino)-1*H*-2-benzopyran-1-ones (isocoumarins) (1a—c) was described in the preceding paper. These compounds



- (1)  
a: NR<sup>1</sup>R<sup>2</sup> = morpholino  
b: NR<sup>1</sup>R<sup>2</sup> = piperidino  
c: NR<sup>1</sup>R<sup>2</sup> = pyrrolidino



- (4)  
a: R = *p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>  
b: R = PhCH=CH



were expected to behave as enamines<sup>2</sup> and one such reaction, namely protonation of the morpholino-derivative (1a) by perchloric acid to form the isoimidium salt (2), was noted. However, other reactions typical of

<sup>1</sup> Preliminary report, A. E. Baydar, G. V. Boyd, R. L. Monteil, P. F. Lindley, and M. M. Mahmoud, *J.C.S. Chem. Comm.*, 1976, 650.

<sup>2</sup> 'Enamines: Synthesis, Structure and Reactions,' ed. A. G. Cook, Marcel Dekker, New York, 1969.

<sup>3</sup> Ref. 2, p. 135.

enamines, in particular *C*-acylation<sup>3</sup> and *C*- or *N*-alkylation,<sup>4</sup> were not observed. Thus, treatment of the morpholinobenzopyranone with acetyl chloride gave homophthalic anhydride, there was no reaction with benzoyl chloride, and attempted methylation with methyl iodide resulted in recovery of the starting material, together with the corresponding amic acid (3). Enamines of cyclic ketones condense with aromatic aldehydes to form  $\alpha$ -arylmethylene ketones after elimination of the amine function.<sup>5</sup> The morpholinoisocoumarin reacted accordingly with *p*-dimethylaminobenzaldehyde and cinnamaldehyde to yield the known<sup>6</sup> *p*-dimethylaminobenzylidene- and cinnamylidene-homophthalic anhydrides (4a and b). Another reaction, in which the morpholino-derivative functioned as an enamine, was that with salicylaldehyde, which led to the coumarin (6). Salicylaldehyde and other *o*-hydroxyarenealdehydes are known<sup>7</sup> to add to enamines to yield 2-dialkylamino-4-hydroxychromans; in the present instance the primary adduct (5) is so constituted that it can undergo hydrolytic opening of the lactone ring, followed by elimination of water and morpholine, to form the observed product. The reactions of the isocoumarin (1a) just described are, however, not typical and a different kind of product was obtained when other aldehydes were used.

The action of benzaldehyde on the morpholinobenzopyranone in boiling acetic acid gave two isomeric products, which were separated by fractional crystallisation. Analysis indicated that they were adducts; the i.r. spectrum of each exhibited lactone and amide carbonyl absorptions near 1730 and 1635 cm<sup>-1</sup>, respectively, and the n.m.r. spectra, which were similar, contained two

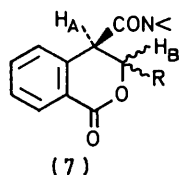
<sup>4</sup> Ref. 2, p. 119.

<sup>5</sup> L. Birkofer, S. M. Kim, and H. D. Engles, *Chem. Ber.*, 1962, **95**, 1495.

<sup>6</sup> Ng. Buu-Hoi, *Compt. rend.*, 1940, **211C**, 330.

<sup>7</sup> L. A. Paquette, *Tetrahedron Letters*, 1965, 1291.

doublets due to methine protons on adjacent carbon atoms. The adducts are therefore formulated as the geometrically isomeric dihydro-1*H*-2-benzopyran-1-ones, *cis*- and *trans*-(7a). The higher melting, less soluble



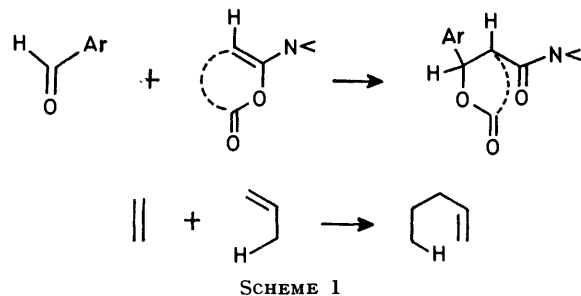
- a; N< = morpholino, R = Ph  
 b; N< = morpholino, R = *o*-NO<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>  
 c; N< = morpholino, R = *m*-NO<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>  
 d; N< = morpholino, R = *p*-NO<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>  
 e; N< = morpholino, R = *m*-HOC<sub>6</sub>H<sub>4</sub>  
 f; N< = morpholino, R = *p*-HOC<sub>6</sub>H<sub>4</sub>  
 g; N< = morpholino, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>  
 h; N< = morpholino, R = *p*-ClC<sub>6</sub>H<sub>4</sub>  
 i; N< = morpholino, R = 2-furyl  
 j; N< = morpholino, R = 2-thienyl  
 k; N< = piperidino, R = Ph  
 l; N< = piperidino, R = *p*-ClC<sub>6</sub>H<sub>4</sub>  
 m; N< = pyrrolidino, R = *p*-NO<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>  
 n; N< = morpholino, R = PhCH<sub>2</sub>

isomer showed  $J_{AB}$  3 Hz, suggesting<sup>8</sup> that it had the *cis*-configuration; the coupling constant of the methine protons in the *trans*-compound was 11 Hz.

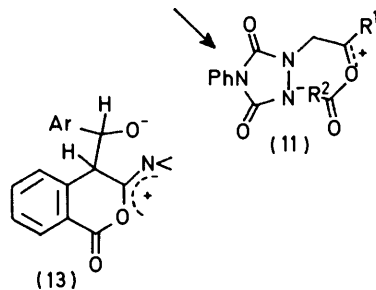
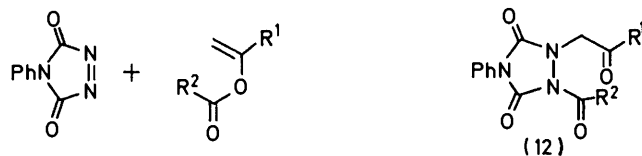
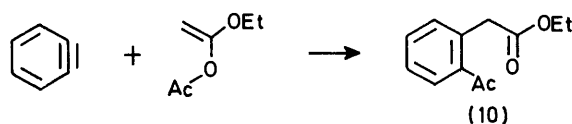
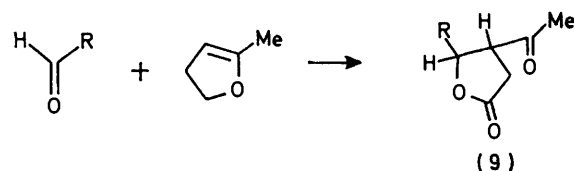
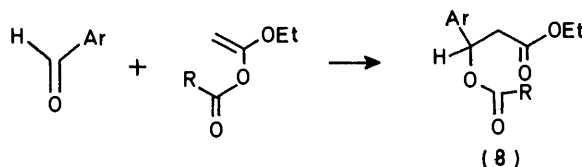
The formation of *cis*- and *trans*-adducts analogous to (7a) was found to be a general reaction of the benzopyranones (1). Treatment of the morpholino-derivative (1a) with the three nitrobenzaldehydes, *m*- and *p*-hydroxybenzaldehyde, *p*-methoxy- and *p*-chloro-benzaldehyde, and furan- and thiophen-2-carbaldehyde in boiling acetic acid, acetonitrile, toluene, or ethanol gave the corresponding dihydrobenzopyranones (7b–j) in yields of 30–100% as isomeric mixtures, some of which were resolved into the *cis*- and *trans*-components. In the case of the *p*-nitrophenyl derivative (7d), obtained as a 1:1 mixture, the *cis*-configuration of the higher melting isomer ( $J_{AB}$  3 Hz) was confirmed and the shape of the molecule determined by X-ray diffraction (see later). From the reaction of 3-piperidinoisocoumarin (1b) with benzaldehyde, the pure *cis*-compound (7k) was isolated; the addition of the piperidino-derivative to *p*-chlorobenzaldehyde and that of the pyrrolidino-analogue (1c) to *p*-nitrobenzaldehyde gave, respectively, *cis*- and *trans*-(7l) and *cis*- and *trans*-(7m), each in quantitative yield.

The formation of the adducts (7) involves bonding of the carbon atom of the aldehyde to one end of the enamine system, shift of the double bond, and transfer of the acyl group from the oxygen atom of the pyranone

to the oxygen atom of the aldehyde; the process is thus formally analogous to the ene synthesis<sup>9</sup> (see Scheme 1),



in which a hydrogen atom migrates. Reactions similar to those discussed here have been reported previously;



(13)

they include the synthesis<sup>10</sup> of the adducts (8) from arenecarbaldehydes and 1-ethoxyvinyl esters, the boron trifluoride-catalysed addition of aldehydes to  $\alpha$ -angelica lactone to yield the  $\gamma$ -lactones (9),<sup>11</sup> the production<sup>12</sup>

<sup>10</sup> H. H. Wasserman and S. H. Wentland, *Chem. Comm.*, 1969, 1216.

<sup>11</sup> T. Mukaiyama, J. Hanna, T. Inoue, and T. Sato, *Chem. Letters*, 1974, 381.

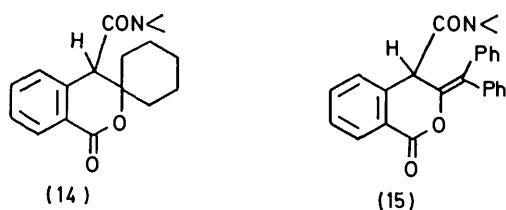
<sup>12</sup> H. H. Wasserman and J. Solodar, *J. Amer. Chem. Soc.*, 1965, 87, 4002.

<sup>8</sup> S. Sternhell, *Quart. Rev.*, 1969, 23, 236.

<sup>9</sup> (a) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, 1943, 76, 27; (b) K. Alder and H. von Brachel, *Annalen*, 1962, 651, 141; (c) review, H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, 8, 556.

of ethyl *o*-acetylphenylacetate (10) from benzyne and 1-ethoxyvinyl acetate, and the formation<sup>13</sup> of the adducts (12) of 4-phenyl-1,2,4-triazoline-3,5-dione with enol esters. In each case the authors postulated a 1,4-dipolar intermediate, such as (11); this suggestion was supported by the isolation of four-membered ring compounds, formed as by-products in the two reactions last mentioned. The present reaction may well proceed in such a multi-stage manner *via* the stabilised intermediates (13), but we have as yet no information concerning the timing of the bond-making and -breaking steps.

Attempts to extend the addition reactions of the morpholinobenzopyranone (1a) to carbonyl compounds other than aromatic aldehydes were only partially successful. The pyranone was recovered after being heated with isobutyraldehyde in acetic acid; however, phenylacetaldehyde afforded a mixture of adducts (7n), from which the pure *cis*-isomer was isolated. Of various ketones tried, *viz.* acetophenone, benzophenone, benzil, and cyclohexanone, only the last reacted to yield the spiro-compound (14). The benzopyranone did not add to the electrophilic carbonyl group of ethyl trifluoroacetate; heating the components yielded a mixture of the amic acid (3), its ethyl ester, and morpholinium trifluoroacetate. Diphenylketen was expected to undergo addition at the carbon-carbon double bond, as this is the normal mode of behaviour of ketens towards olefins in general<sup>14</sup> and enamines in particular.<sup>15</sup> The i.r. spectrum of the product of the reaction of diphenylketen with the morpholinisocoumarin, which was isolated in 85% yield, contained a single high frequency carbonyl band at 1 730 cm<sup>-1</sup>, as well as amide absorption at 1 645 cm<sup>-1</sup>. The spectrum in this region thus closely resembles those of the aldehyde adducts (7) and the product is therefore formulated as the lactone (15). The presence of the cyclic ester grouping was confirmed by a positive hydroxamic acid reaction,\* which was also positive for the isocoumarin (1a) and all the lactones (7) tested. Compound (15) thus results from a rare addition

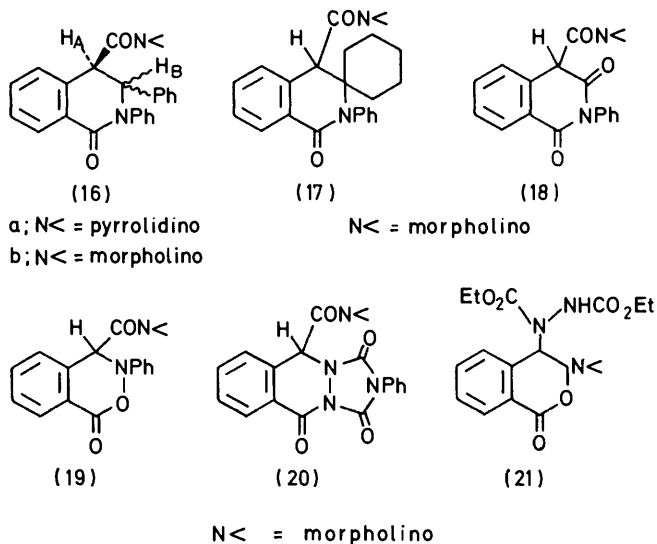


to the carbonyl group of the keten, which also occurs in the dimerisation of keten itself and in certain reactions of bis(trifluoromethyl)keten.<sup>16</sup>

\* The possibility that the positive hydroxylamine-iron(III) chloride reaction might be due to the morpholinocarbonyl group, which would also be present in the alternative adduct, produced by addition to the olefinic double bond of the keten, had to be excluded, since it is stated (F. G. Mann and B. C. Saunders, 'Practical Organic Chemistry,' Longmans, London, 1960, 4th edn., p. 332) that amides may respond to this test. It was found, however, that a control reaction with the dimorpholide of homophthalic acid gave a negative result.

It was found that the partners capable of forming adducts with the isocoumarins (1) were not confined to carbonyl compounds; numerous other systems containing electrophilic multiple bonds undergo the reaction.

Derivatives of isoquinolone were formed by addition to imines. The pyrrolidinoisocoumarin (1c) reacted with benzylideneaniline to give a mixture of the adducts (16a), which showed methine proton doublets with coupling constants of 6 and 7 Hz, tentatively assigned to the *cis*- and *trans*-isomers, respectively. From the reaction of the morpholine analogue (1a) with benzylideneaniline the pure *cis*-isomer, *cis*-(16b), with  $J_{AB}$  5 Hz was isolated; the crude *trans*-compound showed  $J_{AB}$  6 Hz. The isocoumarin (1a) and cyclohexylideneaniline formed the spiro-adduct (17) in 40% yield. The i.r. spectra of the tetrahydroisoquinolones contain carbonyl bands at 1 650 and 1 630 cm<sup>-1</sup>, which are assigned, respectively, to the cyclic and acyclic amide groups. The reaction of compound (1a) with phenyl isocyanate occurred at the carbon-nitrogen double bond rather than at the carbonyl group, since the product, the isoquinolinedione (18), showed cyclic amide carbonyl absorptions



at 1 675 and 1 650, as well as a band at 1 630 cm<sup>-1</sup>, due to the morpholinocarbonyl group. Attempts to bring about addition of the isocoumarin to the imine function of isoquinoline and of dicyclohexylcarbodi-imide and to the electron-deficient cyano-group of 4-cyanopyridine were unsuccessful.

The morpholinisocoumarin reacted readily with nitrosobenzene to form the novel heterocycle (19). The

<sup>13</sup> K. B. Wagener, S. R. Turner, and G. Butler, *J. Org. Chem.*, 1972, **37**, 1454.

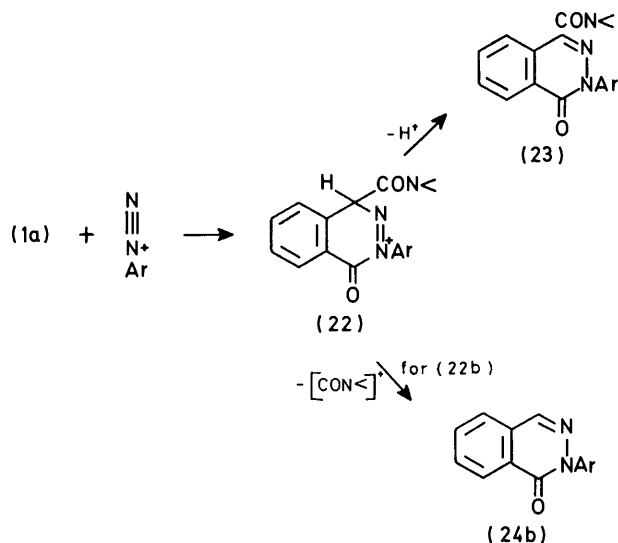
<sup>14</sup> R. N. Lacey, in 'The Chemistry of Alkenes,' ed. S. Patai, Interscience, New York, 1964, p. 1161.

<sup>15</sup> (a) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, *J. Org. Chem.*, 1965, **30**, 2642; (b) R. H. Hasek and J. C. Martin, *ibid.*, 1963, **28**, 1468.

<sup>16</sup> D. C. England and C. G. Krespan, *J. Org. Chem.*, 1970, **35**, 3312. For other examples see R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem. Internat. Edn.*, 1968, **7**, 826.

spectral characteristics of this 3,4-dihydro-1*H*-2,3-benzoxazin-1-one, *i.e.* lactone carbonyl and acyclic amide carbonyl absorptions at 1730 and 1645  $\text{cm}^{-1}$ , respectively, and the appearance of a singlet due to the methine proton, confirm the structure.

The exceptionally reactive enophile 4-phenyl-1,2,4-triazoline-3,5-dione<sup>17</sup> added readily to the morpholinoisocoumarin to give the adduct (20); in contrast, the acyclic azo-compound diethyl azodicarboxylate underwent a Michael addition to the morpholine derivative to form the disubstituted isocoumarin (21), whose i.r. spectrum showed NH absorption and whose electronic spectrum resembled that of its precursor (1a). Addition of the isocoumarin (1a) to the azo-group in arenediazonium salts resulted in the formation of phthalazinones;



N< = morpholino

a; Ar = Ph

b; Ar = *p*-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>

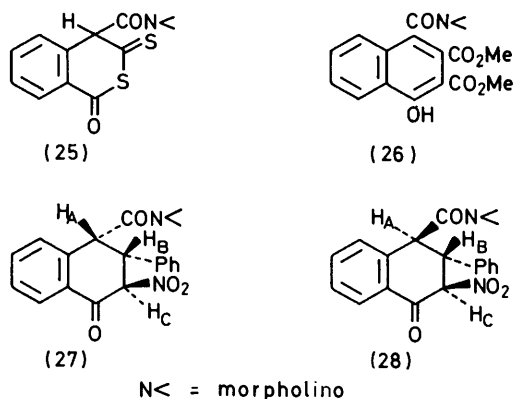
SCHEME 2

these reactions were carried out in the presence of triethylamine. Benzenediazonium fluoroborate and its *p*-nitro-derivative gave compounds (23a and b), respectively. The latter was accompanied by a small amount of the known<sup>18</sup> 1,2-dihydro-2-*p*-nitrophenylphthalazin-1-one (24), formed presumably by loss of morpholinocarbonyl cation from the intermediate (22b) (see Scheme 2).

The last component with a double bond attached to a heteroatom to be investigated was carbon disulphide. This added to compound (1a) to give the yellow 1-oxo-2-benzothiapyran-3-thione (25), representative of another new heterocyclic system. The thione showed absorptions at 1650 and 1640  $\text{cm}^{-1}$ , which are assigned, respectively, to the cyclic and acyclic carbonyl groups.

Simple olefins and acetylenes, such as cyclohexene, styrene, and phenylacetylene, and electron-rich components, *i.e.* enamines and the ynamine 2-diethylaminoprop-1-yne, did not react with the morpholinoisocoumarin (1a).

The action of the electron-deficient dimethyl acetylenedicarboxylate led to an adduct, whose spectral characteristics and acidic character showed it to be the naphthol (26). Of other carbon enophiles investigated, tetracyanoethylene formed a tar, and cinnamionitrile, acrylonitrile, dimethyl maleate, and dimethyl fumarate did not react. The failure of the two last mentioned attempts was disappointing, as the geometry of the products would have indicated whether the additions were stereospecific. The problem was only partially solved by the outcome of an experiment with *trans*- $\beta$ -nitrostyrene. Careful chromatography of the resulting mixture gave only two adducts, (27) and (28), isolated in 10.5 and 3% yield. Their i.r. spectra contained bands due to ring and amide carbonyl groups at 1695 and 1630, and at 1700 and 1600  $\text{cm}^{-1}$ , respectively, and the n.m.r. spectrum of each showed the presence of three adjacent methine protons, of which the central proton H<sub>B</sub>, giving a quartet signal, was at highest field and therefore assigned as a benzylic proton. The most deshielded proton H<sub>C</sub>, which appeared as a doublet, is situated between keto- and nitro-groups. The chemical shift of the doublet due to the remaining proton H<sub>A</sub> was at an intermediate position for each compound. Spin-decoupling experiments indicated that in the major isomer (27), H<sub>A</sub> and H<sub>B</sub> were situated *trans* to each other ( $J_{AB}$  12 Hz), whereas in the other they were *cis*, with  $J_{AB}$  6 Hz. For both isomers  $J_{BC}$  13 Hz, so that the *trans*-geometry of the enophile was maintained in the adducts. However, this result does not prove that the products arise from a kinetically controlled *cis*-addition, as required by a concerted suprafacial-suprafacial mechanism, because the isolated compounds would be thermodynamically preferred to the isomers in which the nitro- and phenyl groups bear the *cis*-relationship.



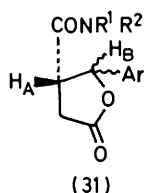
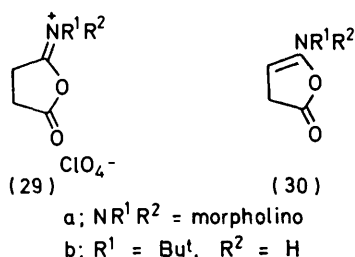
(Indeed, each isomer was recovered when its solution in aqueous sodium hydroxide was acidified.) It was therefore imperative to study the behaviour of *cis*- $\beta$ -nitrostyrene. However, attempts to carry out this reaction were frustrated by our failure to obtain sub-

<sup>17</sup> R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. (C)*, 1967, 1905.

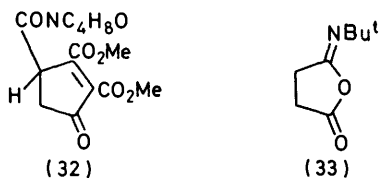
<sup>18</sup> L. Seckles, *Rec. Trav. chim.*, 1924, **43**, 329.

stantial amounts of this compound. The reported<sup>19</sup> irradiation of *trans*- $\beta$ -nitrostyrene gave in our hands a mixture containing only 17% (by n.m.r.) of the labile *cis*-isomer, the remainder being unchanged *trans*-compound; no meaningful results were obtained when the morpholinoisocoumarin was treated with such a mixture.

*N*-Substituted 5-Amino-2,3-dihydrofuran-2-ones.—It was stated in the preceding paper that treatment of the succinisoimidium perchlorate (29a) with triethylamine gave an intractable tar. However, when the deprotonation was carried out in the presence of *p*-nitrobenzaldehyde, a mixture of two isomeric compounds was obtained; the i.r. spectrum of the mixture showed  $\gamma$ -lactone and amide carbonyl absorptions at 1790 and 1625  $\text{cm}^{-1}$  and the n.m.r. spectrum of the mixture contained signals due to methylene and two sets of adjacent methine protons, the coupling constants of the latter being 8 and 6 Hz in the two isomers. The pure *trans*-isomer ( $J_{AB}$  6 Hz) was isolated after repeated recrystallisation. The spectral data, together with an analysis, indicate that the products are the butyrolactones, *cis*- and *trans*-(31a), respectively, formed by



- a;  $\text{Ar} = p\text{-NO}_2\text{-C}_6\text{H}_4, \text{NR}^1\text{R}^2 = \text{morpholino}$   
 b;  $\text{Ar} = p\text{-ClC}_6\text{H}_4, \text{NR}^1\text{R}^2 = \text{morpholino}$   
 c;  $\text{Ar} = o\text{-NO}_2\text{-C}_6\text{H}_4, \text{NR}^1\text{R}^2 = \text{morpholino}$   
 d;  $\text{Ar} = p\text{-NO}_2\text{-C}_6\text{H}_4, \text{R}^1 = \text{Bu}^t, \text{R}^2 = \text{H}$

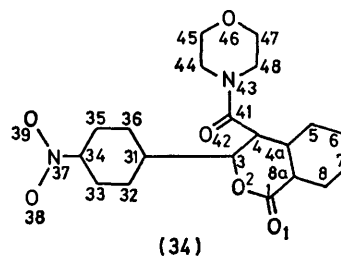


addition of the aldehyde to the unisolable dihydro-morpholinofuranone (30a). This furanone is also generated by the action of acetic anhydride on the monomorpholide of succinic acid, since when the reaction is conducted with the addition of *p*-nitrobenz-

<sup>19</sup> A. A. Dudunskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1961, 182.

aldehyde a mixture of the lactones (31a) is obtained. Deprotonation of the salt (29a) in the presence of *p*-chlorobenzaldehyde gave a mixture of *cis*- and *trans*-(31b), from which the pure *cis*-isomer ( $J_{AB}$  9 Hz) was isolated, and from a similar reaction with *o*-nitrobenzaldehyde a mixture of *cis*- and *trans*-adducts (31c) with  $J_{AB}$  8 and 5 Hz, respectively, was obtained, which yielded the *trans*-isomer on fractional crystallisation. Attempts to trap the butenolide (30a) with phenyl isocyanate, diethyl azodicarboxylate, or carbon disulphide were unsuccessful; dimethyl acetylenedicarboxylate, on the other hand, gave the cyclopentenone (32) in very low yield.

Treatment of a mixture of the secondary succinisoimidium perchlorate (29b) and *p*-nitrobenzaldehyde with triethylamine gave a mixture of two geometrically isomeric products, from which the *cis*-lactone (31d), showing  $J_{AB}$  8 Hz, was isolated. The formation of this compound suggests that in the case of the *t*-butyl derivative, at any rate, the succinisoimide (33) is in equilibrium with the enamine tautomer (30b).



#### X-Ray Crystal Structure of *cis*-3,4-Dihydro-4-morpholinocarbonyl-3-*p*-nitrophenyl-1H-benzopyran-1-one (7d)

*Crystal Data.*— $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_6$ ,  $M = 382.4$ . Monoclinic,  $a = 11.491(2)$ ,  $b = 10.592(1)$ ,  $c = 14.689(2)$  Å,  $\beta = 97.433(4)^\circ$ .  $U = 1773$  Å<sup>3</sup>,  $D_m = 1.426$  g  $\text{cm}^{-3}$  (by flotation in cyclohexane-1,2-dibromoethane),  $Z = 4$ ,  $D_c = 1.432$  g  $\text{cm}^{-3}$ . Space group  $P2_1/c$  ( $C_{2h}^5$ , No. 14).  $\mu(\text{Cu-K}\alpha) = 9.05$   $\text{cm}^{-1}$ .

The compound forms small colourless lath-shaped crystals elongated parallel to  $b$ . One of the largest specimens available, measuring  $0.03 \times 0.37 \times 0.09$  mm, was used for the structure analysis. After a preliminary X-ray photographic survey to determine the space group, refined unit-cell parameters were measured on a Hilger and Watts Y290 automated four-circle diffractometer. Intensity data were also measured on this instrument, using the  $\omega$ - $2\theta$  step scanning mode up to  $\theta \leq 62^\circ$ , the limit of observable data. Three reference reflections were measured after every 50 reflections and the intensity sums of these reference reflections were used to scale the data by interpolation between groups of reference reflections; the overall variation in the reference intensity sum was 2.9%. A total of 2821 independent reflections was measured, of which only 953 were classified as significant using the criterion  $I \geq 3\sigma(I)$ . Over the range  $\theta \leq 30^\circ$  measurements were made for the

$h, k, \pm l$  and  $\bar{h}, k, \pm l$  reflections and weighted averages were used in the analysis; the residual for the 630 reflections measured more than once was 0.104. The poor quality of the data, indicated both by the high residual for the symmetry-related reflections and the low number of significant data, is a consequence of the small size of the crystals available for the analysis. The data were corrected for Lorentz and polarisation effects but not for absorption.

The structure was solved by a weighted multi-resolution tangent formula refinement (MULTAN 74),<sup>20</sup> using 157 reflections with  $|E_h| > 1.88$ . All the non-hydrogen atoms in the molecule were located from an *E* map, calculated using the phase set with the best figures of merit. The structure was refined isotropically by the method of full-matrix least-squares to give a residual of 0.186. Further refinement either by least-squares with the atoms treated anisotropically or by Fourier synthesis methods was unsuccessful and adjustments to the atomic positions did not improve the overall agreement between the observed and calculated structure factors.

The labelling of the atoms in the molecule is shown in formula (34). The Table lists the atomic parameters of

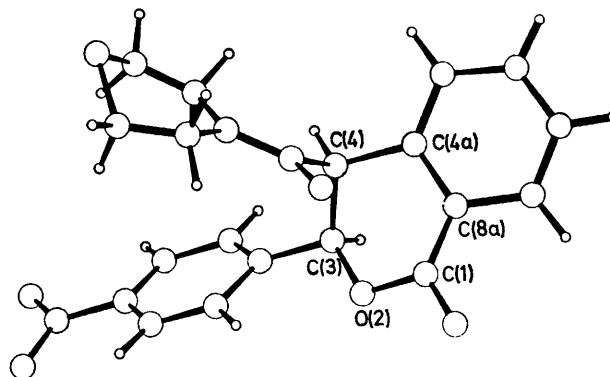
Positional parameters ( $\times 10^3$ ) and isotropic thermal parameters ( $\times 10^3$ ) for the non-hydrogen atoms. The expression used for the temperature parameters was  $\exp(-8\pi^2 U \sin^2 \theta / \lambda^2)$

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
C(1)	618(2)	573(3)	788(2)	34(6)
O(1)	690(1)	655(1)	817(1)	25(4)
O(2)	541(1)	540(2)	850(1)	34(4)
C(3)	465(2)	435(3)	824(2)	36(6)
C(4)	417(2)	442(2)	724(2)	29(6)
C(4a)	519(2)	436(2)	665(2)	32(6)
C(5)	515(3)	372(3)	580(2)	44(7)
C(6)	620(2)	373(3)	541(2)	40(7)
C(7)	720(3)	436(3)	581(2)	54(8)
C(8)	725(2)	496(2)	664(2)	34(6)
C(8a)	619(2)	500(3)	709(2)	40(7)
C(31)	372(2)	435(2)	882(2)	28(6)
C(32)	333(2)	545(3)	927(2)	40(7)
C(33)	248(2)	543(3)	979(2)	48(8)
C(34)	198(2)	425(3)	996(2)	36(6)
C(35)	232(3)	314(3)	960(2)	48(8)
C(36)	318(2)	321(3)	902(2)	35(6)
N(37)	108(2)	418(2)	1 053(2)	50(6)
O(38)	53(2)	319(2)	1 063(1)	57(6)
O(39)	87(2)	515(2)	1 098(1)	51(5)
C(41)	341(2)	563(2)	699(1)	21(5)
O(42)	400(2)	665(2)	694(1)	41(5)
N(43)	227(2)	563(2)	689(1)	39(5)
C(44)	171(4)	685(4)	677(3)	92(12)
C(45)	64(5)	680(6)	695(4)	136(19)
O(46)	-13(2)	578(3)	641(2)	79(7)
C(47)	50(4)	457(5)	672(3)	103(14)
C(48)	159(3)	450(3)	686(2)	67(10)

the non-hydrogen atoms at the end of the isotropic refinement.\* Throughout the structure factor calculations the atomic scattering factors listed by Hanson *et al.*<sup>21</sup> were used and all computations were performed on the CDC 6600 computer at the University of London Computer Centre.

\* A list of observed and calculated structure factors is contained in Supplementary Publication No. SUP 22328 (17 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

*Description of the Structure.*—The Figure is a drawing of the molecule viewed along the normal to the plane defined by the atoms C(4), C(4a), and C(8a) and clearly shows the *cis*-configuration of the hydrogen atoms at C(3) and C(4). The pyran ring has a distorted twist conformation, lying approximately midway between two boat conformations in which the bow and stern are C(3) and C(8a), and C(1) and C(4), respectively; the asymmetry parameter,<sup>22</sup>  $\Delta C_2^{C(1) - C(8a)} = 6.2^\circ$ . The two boat conformations are approximately related by a two-fold axis through O(2) and C(4a). Alternatively, the distortions of the pyran ring can be described in terms of the deviations of O(2), 0.47 Å, and C(3), 0.95 Å, from the least-squares plane through the remaining four ring atoms, maximum deviation 0.04 Å for C(8a); O(1)



Structure of compound (7d) viewed along the normal to the plane defined by C(4), C(4a), and C(8a)

is displaced by  $-0.29$  Å from this plane. The benzene ring fused to the pyran ring is planar and the dihedral angle between these two planes is  $3.6^\circ$ .

The geometry of the equatorially situated *p*-nitrophenyl group at C(3), although not well defined, appears to contain a planar phenyl ring with the nitro group slightly twisted out in order to minimise non-bonded interactions between the oxygen atoms and the *ortho*-hydrogen atoms of the ring. The axially substituted *N*-morpholinecarbonyl group at C(4) is even less well defined, but the geometry about the nitrogen atom appears to be planar, indicating  $\pi$ -electron interaction between this atom and the carbonyl group.

There are no significantly short intermolecular interactions.

#### EXPERIMENTAL

I.r. spectra refer to Nujol mulls;  $^1\text{H}$  n.m.r. spectra were determined for deuteriochloroform solutions at 90 MHz.

*Attempted Acylation and Alkylation of the Morpholinobenzopyranone (1a).*—A mixture of (1a) (2.3 g), acetyl chloride (0.78 g), and acetic acid (10 ml) was refluxed for 10 min. Concentration of the mixture gave homophthalic anhydride (0.94 g, 63%). A similar result was obtained

<sup>20</sup> G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

<sup>21</sup> H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

<sup>22</sup> W. L. Duax and D. A. Norton, 'Atlas of Steroid Structures,' Plenum, New York, 1975.

when acetic anhydride (1.2 g) was used. There was no reaction with benzoyl chloride; prolonged heating with methyl iodide gave the amic acid (3) (32%).

**3,4-Dihydro-4-(*p*-dimethylaminophenyl)methylene-1H-2-benzopyran-1,3-dione (4a).**—A mixture of the morpholino-benzopyranone (1a) (0.58 g), *p*-dimethylaminobenzaldehyde (0.37 g, 1 mol. equiv.), and acetic acid (3 ml) was refluxed for 10 min and then cooled, whereupon the product (0.63 g, 66%) crystallised as red needles, m.p. 167–169° (lit.,<sup>6</sup> 169°),  $\nu_{\max}$  1 740 and 1 710  $\text{cm}^{-1}$ ,  $\delta$  8.3–7.4 (9 H, m, Ar and CH) and 3.28 (s, 2 Me). The same compound (1.3 g, 45%) was obtained from a similar reaction of the piperidino-derivative (1b) (2.29 g) and *p*-dimethylaminobenzaldehyde (1.49 g) in acetic acid (10 ml).

**4-Cinnamylidene-3,4-dihydro-1H-2-benzopyran-1,3-dione (4b)** (0.25 g, 9%), m.p. 220–221° (decomp.) (lit.,<sup>6</sup> 218°),  $\nu_{\max}$  1 760 and 1 730  $\text{cm}^{-1}$ ,  $\delta$  8.63–7.3 (m), crystallised from the solution obtained by refluxing a mixture of the benzopyranone (1a) (2.31 g), cinnamaldehyde (1.32 g, 1 mol. equiv.), and acetonitrile (10 ml) for 1 h.

**3-(*o*-Carboxyphenyl)-2H-1-benzopyran-2-one (6).**—A mixture of the benzopyranone (1a) (2.31 g), salicylaldehyde (1.22 g, 1 mol. equiv.), and acetic acid (20 ml) was refluxed for 1 h and then cooled, whereupon the acid (1.86 g, 54%) crystallised. It had m.p. 271–273° (from acetic acid),  $\nu_{\max}$  1 730 and 1 670  $\text{cm}^{-1}$ ,  $\delta$  8.2–6.9 (m) (Found: C, 71.9; H, 3.8.  $\text{C}_{16}\text{H}_{10}\text{O}_4$  requires C, 72.2; H, 3.8%).

**Addition of the Benzopyranones (1) to Aldehydes.**—A benzopyranone was refluxed with an aldehyde (1 mol. equiv.) in the stated solvent for the stated time. On cooling, the product usually crystallised either as a mixture or as one isomer; if it did not, ether was added to incipient turbidity. The first fraction was collected and recrystallised. The original filtrate was evaporated *in vacuo* and the residue was recrystallised.

(a) Reaction of the morpholino-derivative (1a) (2.31 g) and benzaldehyde in acetic acid (10 ml) for 1 h gave the less soluble *cis*-3,4-dihydro-4-morpholinocarbonyl-3-phenyl-1H-2-benzopyran-1-one (7a) (0.7 g, 21%), m.p. 257–258.5° (from acetic acid),  $\nu_{\max}$  1 730 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.35–6.7 (9 H, m, Ar), 5.93 (d, CH) and 4.78 (d, CH) (*J* 3 Hz), and 4.1–2.35 (8 H, m, morpholino) (Found: C, 71.1; H, 5.8; N, 4.2.  $\text{C}_{20}\text{H}_{19}\text{NO}_4$  requires C, 71.2; H, 5.7; N, 4.2%) and the more soluble *trans*-isomer (0.7 g, 21%), m.p. 214–214.5° (from ethanol),  $\nu_{\max}$  1 723 and 1 630  $\text{cm}^{-1}$ ,  $\delta$  8.4–7.0 (9 H, m, Ar), 5.92 (d, CH) and 4.97 (d, CH) (*J* 11 Hz), and 4.0–2.4 (8 H, m, morpholino) (Found: C, 71.3; H, 5.6; N, 4.2%).

(b) Reaction of the morpholino-derivative (1a) (2.31 g) and *o*-nitrobenzaldehyde in acetonitrile (10 ml) for 30 min gave a 3:7 mixture of (by n.m.r.) *cis*- and *trans*-3,4-dihydro-4-morpholinocarbonyl-3-*o*-nitrophenyl-1H-2-benzopyran-1-one (7b) (3.5 g, 92%), m.p. 175–220°,  $\nu_{\max}$  1 740 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.3–7.1 (8 H, m, Ar), 6.39 (d, CH) and 5.3 (d, CH) (*J* 3 Hz), 6.6 (d, CH) and 5.33 (d, CH) (*J* 9 Hz), and 4.2–3.2 (8 H, m, morpholino) (Found: C, 62.7; H, 4.9; N, 7.3.  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_6$  requires C, 62.8; H, 4.8; N, 7.3%). Two crystallisations from ethanol–acetic acid yielded the *trans*-isomer, m.p. 219–220°,  $\delta$  8.3–7.1 (8 H, m, Ar), 6.62 (d, CH) and 5.33 (d, CH) (*J* 9 Hz), and 4.2–3.2 (8 H, m, morpholino).

(c) Reaction of the morpholino-derivative (1a) (2.31 g) and *m*-nitrobenzaldehyde in acetonitrile (10 ml) for 1.5 h gave *cis*-3,4-dihydro-4-morpholinocarbonyl-3-*m*-nitrophenyl-1H-2-benzopyran-1-one (7c) (1.3 g, 34%), m.p. 231–234°

(from acetic acid),  $\nu_{\max}$  1 730 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.55–7.2 (8 H, m, Ar), 6.13 (d, CH) and 4.91 (d, CH) (*J* 3 Hz), and 4.1–2.8 (8 H, m, morpholino) (Found: C, 62.8; H, 4.8; N, 7.2%).

(d) Reaction of the morpholino-derivative (2.31 g) and *p*-nitrobenzaldehyde in acetic acid (20 ml) for 10 min gave the less soluble *cis*-3,4-dihydro-4-morpholinocarbonyl-3-*p*-nitrophenyl-1H-2-benzopyran-1-one (7d) (1.9 g, 50%), m.p. 249.5–250.5° (from acetic acid),  $\nu_{\max}$  1 730 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.57–7.25 (8 H, m, Ar), 6.18 (d, CH) and 4.95 (d, CH) (*J* 3 Hz), and 4.0–3.0 (8 H, m, morpholino) (Found: C, 62.6; H, 4.7; N, 7.2%), and the more soluble *trans*-isomer (1.9 g, 50%), m.p. 209–210° (from aqueous ethanol),  $\nu_{\max}$  1 722 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.5–7.1 (8 H, m, Ar), 6.14 (d, CH) and 5.04 (d, CH) (*J* 11 Hz), and 4.3–3.1 (8 H, m, morpholino) (Found: C, 62.6; H, 4.7; N, 7.1%). When the reaction was carried out in refluxing toluene for 5 min, a 40% yield of a mixture of *cis*- and *trans*-(7d) was obtained.

(e) Reaction of the morpholino-derivative (2.31 g) with *m*-hydroxybenzaldehyde in acetonitrile (10 ml) for 35 min gave *cis*-3,4-dihydro-3-*m*-hydroxyphenyl-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7e) (1.05 g, 30%), m.p. 244–247° (from acetic acid),  $\nu_{\max}$  3 320, 1 720, and 1 635  $\text{cm}^{-1}$ ,  $\delta$  7.7–6.67 (8 H, m, Ar), 5.88 (d, CH) and 4.72 (d, CH) (*J* 3 Hz), and 4.1–2.5 (8 H, m, morpholino) (Found: C, 67.7; H, 5.4; N, 4.0.  $\text{C}_{20}\text{H}_{19}\text{NO}_5$  requires C, 67.9; H, 5.4; N, 4.0%).

(f) Reaction of the morpholino-derivative (2.31 g) with *p*-hydroxybenzaldehyde in acetonitrile (10 ml) for 15 min gave *trans*-3,4-dihydro-3-*p*-hydroxyphenyl-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7f) (2.5 g, 71%), m.p. 226–227° (from acetic acid–ethanol),  $\nu_{\max}$  3 330, 1 745, and 1 635  $\text{cm}^{-1}$ ,  $\delta$  9.36–6.7 (8 H, m, Ar), 5.86 (d, CH) and 4.94 (d, CH) (*J* 10 Hz), and 4.25–3.0 (8 H, m, morpholino) (Found: C, 67.5; H, 5.5; N, 4.0%).

(g) Reaction of the morpholino-derivative (2.31 g) with *p*-methoxybenzaldehyde in ethanol (10 ml) for 4 h gave a 1:2 mixture (by n.m.r.) of *cis*- and *trans*-3,4-dihydro-3-*p*-methoxyphenyl-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7g) (2.5 g, 75%), m.p. 180–229°,  $\nu_{\max}$  1 710 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.28–7.06 (8 H, m, Ar), 5.90 (d, CH) and 4.96 (d, CH) (*J* 11 Hz), 5.85 (d, CH) and 4.70 (d, CH) (*J* 3 Hz), and 4.3–3.2 (8 H, m, morpholino) (Found: C, 68.6; H, 5.8; N, 3.8.  $\text{C}_{21}\text{H}_{21}\text{NO}_5$  requires C, 68.7; H, 5.8; N, 3.8%). Crystallisation from ethanol yielded the *cis*-isomer, m.p. 229–229.5°,  $\delta$  8.19–6.92 (8 H, m, Ar), 5.8 (d, CH) and 4.8 (d, CH) (*J* 3 Hz), 3.80 (s, OMe), and 3.8–3.24 (8 H, m, morpholino).

(h) Reaction of the morpholino-derivative (2.31 g) and *p*-chlorobenzaldehyde in acetic acid (20 ml) for 4 h gave a 3:2 mixture (by n.m.r.) of *cis*- and *trans*-3-*p*-chlorophenyl-3,4-dihydro-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7h) (3.4 g, 92%), m.p. 200–223°,  $\nu_{\max}$  1 720 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.32–7.0 (8 H, m, Ar), 5.93 (d, CH) and 4.95 (d, CH) (*J* 11 Hz), 5.93 (d, CH) and 4.75 (d, CH) (*J* 3 Hz), and 4.12–2.65 (8 H, m, morpholino) (Found: C, 64.5; H, 4.8; N, 3.7.  $\text{C}_{20}\text{H}_{18}\text{ClNO}_4$  requires C, 64.6; H, 4.9; N, 3.8%).

(i) Reaction of the morpholino-derivative (2.31 g) with furan-2-carbaldehyde in acetonitrile (10 ml) for 30 min gave a 1:1 mixture (by n.m.r.) of *cis*- and *trans*-3-furan-2-yl-3,4-dihydro-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7i) (2.46 g, 75%), m.p. 174–196°,  $\nu_{\max}$  1 730 and 1 635  $\text{cm}^{-1}$ ,  $\delta$  8.32–7.15 (7 H, m, Ar and furyl), 6.63 (d, CH) and 6.52 (d, CH) (*J* 3 Hz), 6.03 (d, CH) and 5.31 (d, CH) (*J* 12 Hz),

and 4.35—3.45 (8 H, m, morpholino) (Found: C, 66.0; H, 5.5; N, 4.2.  $C_{18}H_{17}NO_5$  requires C, 66.1; H, 5.2; N, 4.3%).

(j) Reaction of the morpholino-derivative (2.31 g) with thiophen-2-carbaldehyde in acetonitrile (10 ml) for 20 min gave a 4 : 7 mixture (by n.m.r.) of *cis*- and *trans*-3,4-dihydro-4-morpholinocarbonyl-3-(2-thienyl)-1H-2-benzopyran-1-one (7j) (1.6 g, 47%), m.p. ca. 180°,  $\nu_{\max}$  1 730 and 1 640  $cm^{-1}$ ,  $\delta$  8.3—7.0 (7 H, m, Ar and thienyl), 6.25 (d, CH) and 5.04 (d, CH) ( $J$  10 Hz), 6.24 (d, CH) and 4.87 (d, CH) ( $J$  4 Hz), and 4.0—3.3 (8 H, m, morpholino) (Found: C, 62.8; H, 5.0; N, 4.0; S, 8.9.  $C_{18}H_{17}NO_4S$  requires C, 63.0; H, 5.0; N, 4.1; S, 9.3%).

(k) Reaction of the piperidino-derivative (1b) (0.61 g) and benzaldehyde in acetic acid (3 ml) for 2 min gave *cis*-3,4-dihydro-3-phenyl-4-piperidinocarbonyl-1H-2-benzopyran-1-one (7k) (0.45 g, 54%), m.p. 229—230° (from acetic acid),  $\nu_{\max}$  1 730 and 1 635  $cm^{-1}$ ,  $\delta$  8.3—7.2 (9 H, m, Ar), 5.9 (d, CH) and 4.83 (d, CH) ( $J$  3 Hz), and 3.7—2.9 (4 H, m) and 1.7—1.1 (6 H, m) (piperidino) (Found: C, 75.6; H, 6.5; N, 4.0.  $C_{21}H_{21}NO_3$  requires C, 75.2; H, 6.3; N, 4.2%).

(l) Reaction of the piperidino-derivative (2.29 g) with *p*-chlorobenzaldehyde in acetic acid (20 ml) for 15 min gave a mixture of *cis*- and *trans-p-chlorophenyl*-3,4-dihydro-4-piperidinocarbonyl-1H-2-benzopyran-1-one (7l) (3.62 g, 100%), m.p. 214—250°,  $\nu_{\max}$  1 720 and 1 630  $cm^{-1}$  (Found: C, 67.8; H, 5.4; N, 3.7.  $C_{21}H_{20}ClNO_3$  requires C, 68.2; H, 5.5; N, 3.8%). Repeated crystallisation from ethanol yielded the *cis*-isomer, m.p. 260°,  $\delta$  8.3—6.5 (8 H, m, Ar), 5.91 (d, CH) and 4.79 (d, CH) ( $J$  3 Hz), and 3.8—2.7 (4 H, m) and 1.9—1.0 (6 H, m) (piperidino); from the mother liquors the *trans*-isomer was obtained; it had m.p. 214—215.5°,  $\delta$  8.25—7.1 (8 H, m, Ar), 5.96 (d, CH) and 5.0 (d, CH) ( $J$  11 Hz), and 4.1—2.8 (4 H, m), and 2.0—1.0 (6 H, m) (piperidino).

(m) Reaction of the pyrrolidino-derivative (1c) (0.585 g) with *p*-nitrobenzaldehyde in acetic acid (5 ml) for 10 min gave the less soluble *cis*-3,4-dihydro-3-*p*-nitrophenyl-4-pyrrolidinylcarbonyl-1H-2-benzopyran-1-one (7m) (0.26 g, 41%), m.p. 259—259.5° (from ethanol),  $\nu_{\max}$  1 726 and 1 632  $cm^{-1}$ ,  $\delta$  8.55—7.3 (8 H, m, Ar), 6.1 (d, CH) and 4.66 (d, CH) ( $J$  3 Hz), and 3.8—3.1 (m) and 1.9—1.4 (m) (8 H, pyrrolidinyl) (Found: C, 66.0; H, 5.1; N, 7.5.  $C_{20}H_{18}N_2O_5$  requires C, 65.6; H, 5.0; N, 7.7%) and the more soluble *trans*-isomer (0.3 g, 49%), m.p. 209—209.5° (from chloroform-ether),  $\nu_{\max}$  1 730 and 1 635  $cm^{-1}$ ,  $\delta$  8.5—7.1 (8 H, m, Ar), 6.14 (d, CH) and 4.83 (d, CH) ( $J$  11 Hz), and 3.9—3.0 (m) and 2.2—1.5 (m) (8 H, pyrrolidinyl) (Found: C, 65.7; H, 5.0; N, 7.5%).

(n) Reaction of the morpholino-derivative (2.31 g) with phenylacetaldehyde in acetic acid (10 ml) for 1 h, followed by two recrystallisations of the first fraction from acetic acid, gave *cis*-3-benzyl-3,4-dihydro-4-morpholinocarbonyl-1H-2-benzopyran-1-one (7n) (1.0 g, 28%), m.p. 212—212.5°,  $\nu_{\max}$  1 720 and 1 735  $cm^{-1}$ ,  $\delta$  8.3—7.0 (9 H, m, Ar), 5.22 (m, CH) and 4.47br (d, CH) ( $J$  4 Hz), and 4.0—3.0 (m,  $CH_2$  and morpholino) (Found: C, 71.7; H, 5.9; N, 3.9.  $C_{21}H_{21}NO_4$  requires C, 71.8; H, 6.0; N, 4.0%).

3',4'-Dihydro-4'-morpholinocarbonylspiro[cyclohexane-3'(1H)-2'-benzopyran-1'-one] (14).—A solution of the morpholinoisocoumarin (1a) (2.31 g) and cyclohexanone (1.02 g) in acetic acid (10 ml) was heated for 9 days; the product (0.6 g, 18%) crystallised on cooling. It had m.p. 269—271°,  $\nu_{\max}$  1 710 and 1 635  $cm^{-1}$ ,  $\delta$  8.3—7.1 (4 H, m, Ar), 4.26 (s, CH), 4.1—3.52 (8 H, m, morpholino), and

2.4—1.0 (10 H, m, cyclohexane) (Found: C, 69.7; H, 7.1; N, 4.3.  $C_{18}H_{23}NO_4$  requires C, 69.3; H, 7.0; N, 4.3%).

Reaction of the Morpholino-derivative (1a) with Ethyl Trifluoroacetate.—A mixture of (1a) (2.31 g) and the ester (25 ml) was refluxed for 3 h and then cooled, whereupon the amic acid (3) (0.4 g) separated. The filtrate was treated with ether to give morpholinium trifluoroacetate (0.4 g), m.p. 87.5—89° (from benzene),  $\nu_{\max}$  2 530 and 1 675  $cm^{-1}$  (Found: C, 36.4; H, 5.0; F, 28.3; N, 7.0.  $C_6H_9F_3NO_3$  requires C, 36.0; H, 4.55; F, 28.45; N, 7.0%). On standing, the mother liquor deposited *N*-*o*-ethoxycarbonylphenylacetylmorpholine (0.5 g), m.p. 142—143° (from chloroform-ether),  $\nu_{\max}$  1 715 and 1 640  $cm^{-1}$  (Found: C, 64.5; H, 7.0; N, 5.0.  $C_{15}H_{19}NO_4$  requires C, 64.9; H, 6.9; N, 5.05%).

3-Diphenylmethylene-3,4-dihydro-4-morpholinocarbonyl-1H-2-benzopyran-1-one (15).—Addition of diphenylketen (1.94 g, 1 mol. equiv.) to a solution of (1a) (2.31 g, 0.01M) in acetonitrile (20 ml) resulted in the immediate precipitation of the product (3.6 g, 85%), m.p. 230.5° (from acetic acid),  $\nu_{\max}$  1 730 and 1 635  $cm^{-1}$ ,  $\delta$  8.3—6.8 (14 H, m, Ar), 5.6 (s, CH), and 4.1—2.8 (8 H, m, morpholino) (Found: C, 76.5; H, 5.5; N, 3.2.  $C_{27}H_{23}NO_4$  requires C, 76.2; H, 5.5; N, 3.3%).

Reaction of Benzopyranones (1) with Imines.—(a) A mixture of the pyrrolidinyl derivative (1c) (2.15 g, 0.01M), benzylideneaniline (1.81 g, 1 mol. equiv.), and acetonitrile (10 ml) was refluxed for 30 min and then cooled, whereupon a mixture of *cis*- and *trans*-1,2,3,4-tetrahydro-2,3-diphenyl-4-pyrrolidinylcarbonylisoquinolin-1-one (16a) (1.6 g, 40%) separated; it had m.p. ca. 137°,  $\nu_{\max}$  1 650 and 1 625  $cm^{-1}$ ,  $\delta$  8.4—6.5 (14 H, m, Ar), 5.45 (d, CH) and 4.62 (d, CH) ( $J$  7 Hz), 5.32 (d, CH) and 4.28 (d, CH) ( $J$  6 Hz), and 3.82—3.1 (4 H, m) and 2.0—1.4 (4 H, m) (pyrrolidinyl) (Found: C, 79.0; H, 5.9; N, 7.0.  $C_{26}H_{24}N_2O_4$  requires C, 78.8; H, 6.1; N, 7.1%).

(b) A similar reaction of the morpholino-derivative (1a) (2.31 g) with benzylideneaniline in acetonitrile (15 ml) for 4.5 h gave *cis*-1,2,3,4-tetrahydro-4-morpholinocarbonyl-2,3-diphenylisoquinolin-1-one (16b) (1.8 g, 77%), m.p. 265—267° (from ethanol),  $\nu_{\max}$  1 650 and 1 630  $cm^{-1}$ ,  $\delta$  8.35—6.55 (14 H, m, Ar), 5.57 (d, CH) and 4.91 (d, CH) ( $J$  5 Hz), and 4.0—2.7 (8 H, m, morpholino) (Found: C, 75.1; H, 5.9; N, 6.6.  $C_{26}H_{24}N_2O_3$  requires C, 75.1; H, 6.0; N, 6.6%). Evaporation of the mother liquors and repeated crystallisation of the combined residues from aqueous methanol gave a crude solid, whose n.m.r. spectrum,  $\delta$  5.24(d) and 4.45(d) ( $J$  6 Hz), indicated that it was essentially the *trans*-isomer.

(c) Reaction of the morpholino-derivative (2.31 g) with cyclohexylideneaniline (1.74 g) in acetonitrile (12 ml) for 1.5 h gave 1',2',3',4'-tetrahydro-4'-morpholinocarbonyl-2'-phenylspiro[cyclohexane-3'-isoquinolin-1'-one] (17) (1.6 g, 40%), m.p. 298—300° (from ethanol),  $\nu_{\max}$  1 645 and 1 630  $cm^{-1}$ ,  $\delta$  8.4—7.2 (9 H, m, Ar), 5.19 (s, CH), 4.6—3.6 (8 H, m, morpholino), and 2.4—0.9 (10 H, m, cyclohexane) (Found: C, 74.1; H, 6.9; N, 6.8.  $C_{25}H_{28}N_2O_3$  requires C, 74.2; H, 7.0; N, 6.9%).

1,2,3,4-Tetrahydro-4-morpholinocarbonyl-2-phenylisoquinoline-1,3-dione (18).—A mixture of (1a) (2.31 g), phenyl isocyanate (1.19 g, 1 mol. equiv.), and acetonitrile (10 ml) was heated under reflux for 3 h and then cooled; the product (1.1 g, 31%) separated. It had m.p. 208—209.5° (from benzene),  $\nu_{\max}$  1 675, 1 650, and 1 630  $cm^{-1}$ ,  $\delta$  8.25—6.7 (9 H, m, Ar), 5.87 (s, CH), and 4.3—3.0 (8 H, m, morpho-



lino) (Found: C, 69.0; H, 5.2; N, 8.0.  $C_{20}H_{18}N_2O_4$  requires C, 68.7; H, 5.2; N, 8.0%).

**3,4-Dihydro-4-morpholinocarbonyl-3-phenyl-1H-2,3-benzoxazin-1-one** (19).—Refluxing a mixture of the morpholino-compound (1a) (2.31 g), nitrosobenzene (1.07 g, 1 mol. equiv.), and acetonitrile (10 ml) for 20 min gave the benzoxazinone (1.6 g, 47%), m.p. 150–152° (from ethanol),  $\nu_{\max}$  1 730 and 1 645  $cm^{-1}$ ,  $\delta$  8.1–6.6 (9 H, m, Ar), 6.53 (s, CH), and 3.9–3.0 (8 H, m, morpholino) (Found: C, 67.5; H, 5.5; N, 8.2.  $C_{19}H_{18}N_2O_4$  requires C, 67.4; H, 5.4; N, 8.3%).

**2,3,5,10-Tetrahydro-10-morpholinocarbonyl-2-phenyl-1H-s-triazolo[1,2-b]phthalazine-1,3,5-trione** (20).—The morpholinobenzopyranone (1.16 g) was added to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.88 g, 1 mol. equiv.) in acetonitrile (10 ml), whereupon the product (1.78 g, 87%) separated immediately; it had m.p. 225–226° (from acetonitrile),  $\nu_{\max}$  1 800, 1 735, and 1 640  $cm^{-1}$ ,  $\delta$  8.5–7.0 (9 H, m, Ar), 6.83 (s, CH), and 4.65–3.2 (8 H, m, morpholino) (Found: C, 61.6; H, 4.5; N, 13.6.  $C_{21}H_{18}N_4O_5$  requires C, 62.0; H, 4.5; N, 13.8%).

**Addition of Diethyl Azodicarboxylate to the Morpholinobenzopyranone** (1a).—A solution of equimolecular amounts (0.01M) of the components in acetonitrile (10 ml) was refluxed for 45 min; the cooled solution deposited yellow 4-(NN'-diethoxycarbonylhydrazino)-3-morpholino-1H-2-benzopyran-1-one (21) (2.65 g, 65%), m.p. 165–166° (from ethanol-ether),  $\nu_{\max}$  3 300, 1 760, 1 740, and 1 710  $cm^{-1}$ ,  $\lambda_{\max}$  (EtOH) 233, 300, and 355 nm,  $\delta$  8.3–7.3 (4 H, m, Ar), 7.49br (s, NH), 4.18 (q,  $CH_2$ ), 6.22 (q,  $CH_2$ ), 3.55–2.8 (8 H, m, morpholino), and 1.24 (2 overlapping t, 2 Me) (Found: C, 56.3; H, 5.8; N, 10.2.  $C_{19}H_{23}N_3O_7$  requires C, 56.3; H, 5.7; N, 10.4%).

**Reaction of the Morpholinobenzopyranone with Arene-diazonium Salts.**—(a) Benzenediazonium fluoroborate (1.92 g, 1 mol. equiv.) was added to a stirred solution of the pyranone (1a) (2.31 g, 0.01M) and triethylamine (3.03 g, 3 mol. equiv.) in acetonitrile (20 ml). After 5 min, water (50 ml) was added, whereupon 1,2-dihydro-4-morpholinocarbonyl-2-phenylphthalazin-1-one (23a) (1.2 g, 37%) separated. It had m.p. 177° (from ethanol),  $\nu_{\max}$  1 660 and 1 640  $cm^{-1}$ ,  $\delta$  8.65–6.8 (9 H, m, Ar) and 4.3–3.0 (8 H, m, morpholino) (Found: C, 67.9; H, 5.1; N, 12.4.  $C_{18}H_{17}N_3O_3$  requires C, 68.0; H, 5.1; N, 12.5%).

(b) A similar experiment with *p*-nitrobenzenediazonium fluoroborate (1.18 g, 0.005M) gave 1,2-dihydro-4-morpholinocarbonyl-2-*p*-nitrophenylphthalazin-1-one (23b) (1.0 g, 53%), m.p. 211–212° (from aqueous ethanol),  $\nu_{\max}$  1 680 and 1 660  $cm^{-1}$ ,  $\delta$  8.3–7.18 (8 H, m, Ar) and 3.82 (8 H, s, morpholino) (Found: C, 59.9; H, 5.0; N, 14.6.  $C_{18}H_{16}N_4O_5$  requires C, 60.0; H, 5.1; N, 14.7%). The combined mother liquors yielded 1,2-dihydro-2-*p*-nitrophenylphthalazin-1-one (24b) (0.1 g, 75%), m.p. 259–261° (from ethanol) (lit.<sup>18</sup> 258–259°),  $\nu_{\max}$  1 670  $cm^{-1}$ .

**3,4-Dihydro-4-morpholinocarbonyl-1-oxo-1H-2-benzothiopyran-3-thione** (25).—A solution of the morpholino-derivative (1a) (4.62 g) in carbon disulphide (20 ml) was stirred for 3 days, during which time the yellow product (2.2 g, 37%) gradually separated. It had m.p. 242° (from acetic acid-ethanol),  $\nu_{\max}$  1 650 and 1 640  $cm^{-1}$ ,  $\delta$  8.6–7.5 (4 H, m, Ar) and 5.0–3.2 (9 H, m, CH and morpholino) (Found: C, 54.9; H, 4.0; N, 4.4; S, 21.3.  $C_{14}H_{13}NO_3S_2$  requires C, 54.7; H, 4.3; N, 4.6; S, 20.9%).

**2,3-Bismethoxycarbonyl-4-morpholinocarbonyl-1-naphthol** (26).—Refluxing a mixture of (1a) (2.31 g), dimethyl

acetylenedicarboxylate (1.42 g, 1 mol. equiv.), and acetic acid (10 ml) for 15 min gave the naphthol (1.25 g, 33%), m.p. 211° (from methanol),  $\nu_{\max}$  1 730, 1 660, and 1 642  $cm^{-1}$ ,  $\delta$  8.6–7.6 (4 H, m, Ar), 4.05 (s, Me), 4.02 (s, Me), and 4.45–3.0 (8 H, m, morpholino) (Found: C, 61.3; H, 5.2; N, 3.6.  $C_{19}H_{19}NO_7$  requires C, 61.1; H, 5.1; N, 3.8%). The compound dissolved in aqueous alkali and was recovered on acidification.

**Addition of trans- $\beta$ -Nitrostyrene to the Morpholinobenzopyranone** (1a).—Equimolecular (0.01M) amounts of the components were refluxed in acetonitrile (10 ml) for 5 h; the resulting solution deposited trans,trans-1,2,3,4-tetrahydro-4-morpholinocarbonyl-2-nitro-3-phenyl-naphthalen-1-one (27) (0.4 g, 10.5%), m.p. 267–269° (from ethanol),  $\nu_{\max}$  1 695 and 1 630  $cm^{-1}$ ,  $\delta$  8.35–7.0 (9 H, m, Ar), 6.34 (d,  $H_C$ ), 5.1 (d,  $H_A$ ), 4.6 (q,  $H_B$ ) ( $J_{AB}$  12,  $J_{BC}$  13 Hz), and 4.2–3.0 (8 H, m, morpholino) (Found: C, 66.3; H, 5.4; N, 7.3.  $C_{21}H_{20}N_2O_5$  requires C, 66.3; H, 5.3; N, 7.4%). Chromatography of the mother liquors on silica gel with 9 : 1 ethyl acetate-light petroleum (b.p. 40–60°) as eluant gave the cis,trans-isomer (28) (0.1 g, 3%), m.p. 207–208°,  $\nu_{\max}$  1 700 and 1 630  $cm^{-1}$ ,  $\delta$  8.4–7.2 (9 H, m, Ar), 7.02 (d,  $H_C$ ), 5.01 (d,  $H_A$ ), 4.6 (q,  $H_B$ ) ( $J_{AB}$  6,  $J_{BC}$  13 Hz), and 4.2–3.4 (8 H, m, morpholino) (Found: C, 66.2; H, 5.2; N, 7.5%).

**Tetrahydrofuran-2-ones** (31).—(a) Tetrahydro-5-morpholinofuran-2-one perchlorate (29a) (5.37 g, 0.02M) was added in small portions to a stirred solution of *p*-nitrobenzaldehyde (3.02 g, 1 mol. equiv.) and triethylamine (4.04 g, 2 mol. equiv.) in acetonitrile (30 ml). The resulting solution was stirred for 15 min and then treated with water (60 ml), whereupon a mixture of cis- and trans-tetrahydro-4-morpholinocarbonyl-5-*p*-nitrophenylfuran-2-one (31a) (4.6 g, 75%) separated as a solid. It had m.p. 144–175°,  $\nu_{\max}$  1 790 and 1 625  $cm^{-1}$ ,  $\delta$  8.35 and 7.7 (4 H, Ar), 6.12 (d,  $H_B$ ,  $J$  6 Hz), 6.15 (d, CH,  $J$  9 Hz), 4.44 (m,  $H_A$ ), and 4.0–3.0 (10 H, m,  $CH_2$  and morpholino) (Found: C, 56.2; H, 5.1; N, 8.7.  $C_{15}H_{16}N_2O_6$  requires C, 56.3; H, 5.0; N, 8.8%). Repeated crystallisation from ethanol gave the trans-isomer, m.p. 213–215°,  $\delta$  8.4 (2 H, d) and 7.68 (2 H, d) (Ar), 6.12 (d,  $H_B$ ,  $J$  6 Hz), 4.42 (m,  $H_A$ ), and 4.0–3.1 (10 H, m,  $CH_2$  and morpholino).

(b) A solution of the monomorpholide of succinic acid (1.87 g) and *p*-nitrobenzaldehyde (1.51 g) in acetic anhydride (15 ml) was refluxed for 30 min and then evaporated *in vacuo*. When the gummy residue was triturated with ethanol, a mixture of cis- and trans-(31a) (1.2 g, 38%), identified by its i.r. spectrum, was obtained.

(c) Reaction of the morpholino perchlorate (29a) (5.37 g) with a solution of *p*-chlorobenzaldehyde (2.81 g) and triethylamine (2.02 g) in acetonitrile (20 ml) gave a mixture of cis- and trans-5-*p*-chlorophenyltetrahydro-4-morpholinocarbonylfuran-2-one (31b) (3.1 g, 50%), m.p. 140–181°,  $\nu_{\max}$  1 765 and 1 620  $cm^{-1}$ , from which the cis-isomer was isolated by repeated crystallisation from ethanol. It had m.p. 184–185°,  $\delta$  7.53–7.3 (4 H, Ar), 5.79 (d,  $H_B$ ,  $J$  9 Hz), 4.25 (m,  $H_A$ ), and 4.0–3.0 (10 H, m,  $CH_2$  and morpholino) (Found: C, 57.8; H, 5.4; N, 4.4.  $C_{15}H_{16}ClNO_4$  requires C, 58.2; H, 5.2; N, 4.5%).

(d) A similar reaction of (29a) (8.05 g) with *o*-nitrobenzaldehyde gave a crude solid [ $\delta_{HB}$  6.28 (d,  $J$  5 Hz) and 6.06 (d,  $J$  8 Hz)], which after four crystallisations from aqueous ethanol gave trans-tetrahydro-4-morpholinocarbonyl-5-*o*-nitrophenylfuran-2-one (31c) (0.96 g, 10%), m.p. 188–190°,  $\nu_{\max}$  1 790 and 1 635  $cm^{-1}$ ,  $\delta$  8.25–7.6 (4 H, m, Ar),

6.41 (d,  $H_B$ ,  $J$  5 Hz), 4.7 (m,  $H_A$ ), and 4.0—2.8 (10 H, m,  $CH_2$  and morpholino) (Found: C, 55.8; H, 5.1; N, 8.6.  $C_{15}H_{16}N_2O_6$  requires C, 56.3; H, 5.0; N, 8.8%).

(e) A similar reaction of 5-*t*-butylammoniotetrahydrofuran-2-one perchlorate (29b) (4.3 g) with *p*-nitrobenzaldehyde gave *cis*-4-*t*-butylcarbonyltetrahydro-5-*p*-nitrophenylfuran-2-one (31d) (1.44 g, 47%), m.p. 206—209° (from aqueous ethanol),  $\nu_{max}$  1 790 and 1 660  $cm^{-1}$ ,  $\delta$  8.25 (d) and 7.56 (d) (4 H, Ar), 6.4br (s, NH), 6.07 (d,  $H_B$ ,  $J$  8 Hz), 4.0—3.7 (m,  $H_A$ ), 3.2 (t,  $CH_2$ ), and 1.03 (9 H, s,  $Bu^t$ ) (Found: C, 59.0; H, 6.0; N, 9.1.  $C_{16}H_{18}N_2O_5$  requires C, 58.8; H, 5.9; N, 9.2%).

2,3-Bismethoxycarbonyl-4-morpholinocarbonylcyclopent-2-enone (32).—The perchlorate (29a) (5.37 g) was added to a solution of dimethyl acetylenedicarboxylate (2.84 g) and

triethylamine (2.02 g) in ether (40 ml) and the mixture was stirred for 45 min. The ethereal layer was decanted and evaporated leaving the *cyclopentenone* (0.03 g, 0.5%), m.p. 179—180° (from chloroform-ether),  $\nu_{max}$  1 780, 1 750, 1 695, and 1 640  $cm^{-1}$ ,  $\delta$  4.5—3.2 (8 H, m, morpholino), 3.8 (s, Me), 3.63 (s, Me), and 3.0—2.4 (3 H, m, CH and  $CH_2$ ) (Found: C, 54.5; H, 5.7; N, 4.5.  $C_{14}H_{17}NO_7$  requires C, 54.2; H, 5.5; N, 4.5%).

We thank the Governors of Chelsea College for a Research Studentship (to R. L. M.) and the Ministry of Higher Education and Scientific Research of the Government of Iraq for a Research Scholarship (to M. M. M.).

[7/2220 Received, 20th December, 1977]