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THE REACTION OF 2-ARYLSULFONYLOXYTROPONES AND ACTIVE METHYLENE COMPOUNDS

THE FORMATION OF 8-HYDROXY-2H-CYCLOHEPTA[b]FURAN-2-ONE AND 2-AMINO-8H-CYCLOHEPTA[b]FURAN-8-ONE DERIVATIVES

T. NOZOE, K. TAKASE*, M. KATO and T. NOGI

Department of Chemistry, Faculty of Science, Tohoku University, Katahira-2-chome, Sendai, Japan

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Abstract—Reaction of 2-arylsulfonyloxytropones (IV) and active methylene compounds, diethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, malononitrile or cyanoacetamide, in the presence of NaOEt give 8-hydroxy-2H-cyclohepta[b]furan-2-one derivatives (V) and/or 2-amino-8H-cyclohepta[b]furan-8-one derivatives (VII), in addition to azulene derivatives (I) or 2H-cyclohepta[b]furan-2-one derivatives (II), known to be obtained by the reaction of 2-chlorotropones or 2-methoxytropones with active methylene compounds. Relative yields of products are influenced markedly by conditions, *e.g.* base type or molar ratios. The formation of V and VII is characteristic of 2-arylsulfonyloxytropones, not being observed with 2-chlorotropones or 2-methoxytropones. A reaction course involving elimination of the arylsulfonyl group as arenesulfinate ion is presented.

2-HALOTROPONES and 2-methoxytropones are known to react with active methylene compounds, such as diethyl malonate, ethyl acetoacetate, ethyl cyanoacetate or malononitrile, in the presence of bases, such as NaOEt or t-butylamine, giving azulene derivatives (I)[1–3] and/or 2H-cyclohepta[b]furan-2-one (1-oxaazulan-2-one) derivatives (II).[3–6] It has also been found that II or 2H-cyclohepta[b]furan-2-imine derivatives (III) should be reaction intermediates in the formation of azulene derivatives from 2-chlorotropones or 2-methoxytropones.[3,6] From the close parallel of behaviour between 2-halotropones and 2-(*p*-tolylsulfonyloxy)tropones in relation to some amines,[7] it would be expected that 2-arylsulfonyloxytropones (IV) also react with these active methylene compounds in a similar way, giving azulene derivatives (I) or 2H-cyclohepta[b]furan-2-one derivatives (II), and it has been reported[5] that the reaction of 2-(*p*-tolylsulfonyloxy)tropones bearing some alkyl substituents and dimethyl malonate or ethyl acetoacetate in the presence of NaOEt gave 2H-cyclohepta[b]furan-2-one derivatives.

During our study on the synthesis of the azulene derivatives from the troponoid compounds, it has been found that the reaction of 5-acetamido-2-(*p*-tolylsulfonyloxy)-tropone and ethyl cyanoacetate in the presence of NaOEt gave a compound different from the azulene derivatives, in addition to the expected azulene.[8] This is of interest from the view-point of the reaction mechanism, especially the difference in reactivity between 2-chlorotropones and 2-arylsulfonyloxytropones for the formation of the azulene derivatives from the troponoid compounds. This paper describes the reaction of 2-arylsulfonyloxytropones (IV) and some active methylene compounds giving

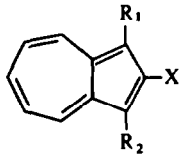
* Address correspondence to this author.

8-hydroxy-2H-cyclohepta[b]furan-2-one derivatives (V) or 2-amino-8H-cyclohepta-[b]furan-8-one derivatives (VII), in addition to the expected azulenes (I) or 2H-cyclohepta[b]furan-2-ones (II).

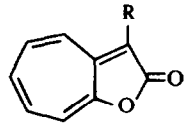
Treatment of tropolone with benzenesulfonyl or *p*-toluenesulfonyl chloride in pyridine gave 2-phenylsulfonyloxy- (IVa) or 2-(*p*-tolylsulfonyloxy)tropone (IVb)[9] respectively in good yields. These 2-arylsulfonyloxytropones (IVa, b) easily reacted with active methylene compounds (diethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, malononitrile, cyanoacetamide) in the presence of NaOEt or t-$BuNH_2$ at room temp., giving the corresponding products. Details of these results are presented below.

The reaction of 2-arylsulfonyloxytropones (IVa, b) *and diethyl malonate or ethyl acetoacetate*

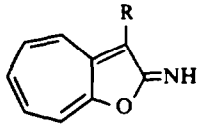
It has been reported that the reaction of 2-halotropone or 2-methoxytropone and diethyl malonate in the presence of bases, such as NaOEt or t-butylamine, gave diethyl 2-hydroxyazulene-1,3-dicarboxylate (Ia)[2] or 3-ethoxycarbonyl-2H-cyclohepta[b]-furan-2-one (IIa).[4,6] and the reaction of these tropones and ethyl acetoacetate gave



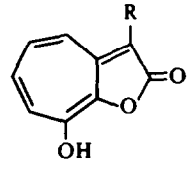
Ia: $R_1 = R_2 = CO_2Et$, X = OH
Ib: $R_1 = R_2 = CO_2Et$, X = NH_2
Ic: $R_1 = R_2 = CN$, X = OH
Id: $R_1 = CO_2Et$, $R_2 = CN$, X = OH
Ie: $R_1 = CO_2Et$, $R_2 = CN$, X = NH_2
If: $R_1 = R_2 = CN$, X = NH_2
Ig: $R_1 = R_2 = CONH_2$, X = NH_2



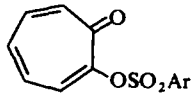
IIa: R = CO_2Et
IIb: R = COMe
IIc: R = CN
IId: R = $COCH_2CO_2Et$



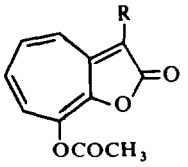
IIIa: R = CO_2Et
IIIb: R = CN
IIIc: R = $CONH_2$



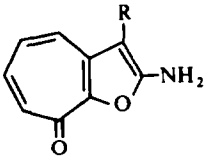
Va: R = CO_2Et
Vb: R = COMe
Vc: R = CN
Vd: R = $CONH_2$
Ve: R = H
Vf: R = $C_6H_4NO_2$ (*p*)
Vg: R = COPh
Vh: R = $COCH_2CO_2Et$
Vi: R = Me



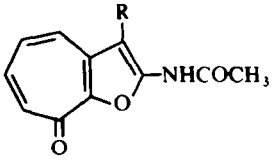
IVa: Ar = Ph
IVb: Ar = $C_6H_4CH_3$ (*p*)



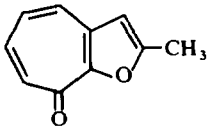
VIa: R = CO_2Et
VIb: R = COMe
VIc: R = CN
VId: R = $CONH_2$
VIe: R = Me



VIIa: R = CO_2Et
VIIb: R = CN
VIIc: R = $CONH_2$



VIIIa: R = CO_2Et
VIIIb: R = CN



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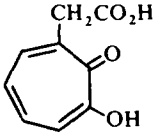

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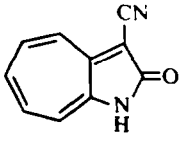

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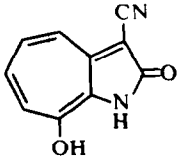
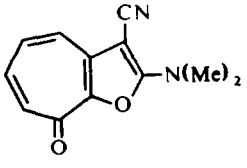


XII



XIII

3-acetyl-2H-cyclohepta[b]furan-2-one (IIb).[4,6] In contrast to these findings, the reaction of IVa, b and diethyl malonate in the presence of NaOEt scarcely gave IIa, but an acidic compound (Va) in a good yield. The reaction of IVa, b and ethyl acetoacetate under similar conditions also gave an acidic compound (Vb), but in this case accompanied by a fairly good yield of IIb. The compounds, Va and Vb, and their acetyl derivatives (VIa and VIb) were identical with 3-ethoxycarbonyl-8-hydroxy-, 3-acetyl-8-hydroxy-, 8-acetoxy-3-ethoxycarbonyl-, and 8-acetoxy-3-acetyl-2H-cyclohepta[b]furan-2-ones respectively, which have been obtained by the condensation reaction of 3-bromotropolone and diethyl malonate or ethyl acetoacetate.[10]

In this reaction, the ratios of the products varied in accordance with the reaction conditions, *i.e.* types or amounts of bases or solvents used. Thus, in the case of the reaction of IVa and ethyl acetoacetate, the yields of Vb increased when excess of NaOEt was used (Table 1). Moreover, Soma *et al.*[11] have also observed that Vb was obtained predominantly when the reaction of IVb and ethyl acetoacetate was carried out in acetone containing a small amount of H_2O in the presence of NaOH.

The reaction of 2-*arylsulfonyloxytropones* (IVa, b) *and ethyl cyanoacetate*

It has been reported that the reaction of 2-halotropone or 2-methoxytropone and ethyl cyanoacetate in the presence of bases (NaOEt or t-butylamine) gave azulene

TABLE 1. THE REACTION OF 2-PHENYLSULFONYLOXYTROPONE (IVa) AND ACTIVE METHYLENE COMPOUNDS IN THE PRESENCE OF NaOEt

Active methylene compound[a]	Molar ratios[b] of NaOEt	Products. %		
		IIa	Va	
	0·5	trace	70	
Diethyl malonate	1·0	trace	83	
	1·5	trace	91	
		IIb	Vb	
Ethyl acetoacetate	1·0	76	9	
	1·5	—	20	Others[c]
		Ib	Vc	VIIa
	0·5	30	—	10
Ethyl cyanoacetate	1·0	24	—	50
	1·5	—	80	—
	2·0	—	78	—
		If	VIIb	
	0·5	48	—	
Malononitrile	1·0	73	—	
	1·5	trace	83	
	2·0	trace	54	

[a] Two molar equivalents of active methylene compounds for IVa were used.
[b] The molar ratios of NaOEt to active methylene compounds.
[c] An acidic substance unidentified was produced.

derivatives (Ib–e) though their relative yields varied in accordance with the amount of the bases used.[1,3] It has also been found that 3-cyano-2H-cyclohepta[b]furan-2-one (IIc) and 3-ethoxycarbonyl-2H-cyclohepta[b]furan-2-imine (IIIa) were formed as intermediates in this reaction.[3] In contrast to these findings, the reaction of IVa, b and ethyl cyanoacetate in the presence of NaOEt gave two new compounds (Vc and VIIa), together with the azulene derivative, Ib.

The compounds, Vc and VIIa, are shown (UV spectra) not to be the azulene derivatives, their structures were determined as follows. Vc is acidic and gave an acetyl derivative (VIc) on acetylation with Ac_2O. The UV spectra of Vc and VIc are similar to those of the 8-hydroxy- and 8-acetoxy-2H-cyclohepta[b]furan-2-ones respectively.[10] The IR spectrum (KBr disk) of Vc shows absorption at 3300–2800, 2220 and 1730 cm^{-1}, corresponding to those of the associated OH and CN groups and the five-membered lactone respectively. On the basis of these spectral data and the results of the elementary analyses, Vc and VIc were assigned the structures of 3-cyano-8-hydroxy- and 8-acetoxy-3-cyano-2H-cyclohepta[b]furan-2-ones respectively. These structures were also supported from the chemical evidence presented below. When Vc was warmed in 75% H_2SO_4, it gave a carbamoyl derivative (Vd), identical with 3-carbamoyl-8-hydroxy-2H-cyclohepta[b]furan-2-one, being synthesized by the treatment of Va with ammonium formate. Moreover, treatment of an acetyl derivative (VId), derived from Vd, with $POCl_3$ gave the acetyl derivative, VIc.

On the other hand, VIIa gave an acetyl derivative (VIIIa) upon acetylation with Ac_2O. The UV spectrum of VIIa is markedly different from those of the azulene

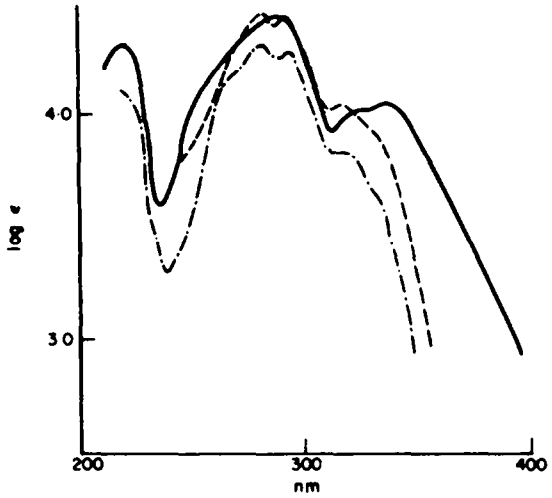


FIG. 1. The UV spectra of VIIa in MeOH (——·——), dioxane (– – – –) and ether (–·–·–).

derivatives or 8-hydroxy-2H-cyclohepta[b]furan-2-ones. Although some solvent effects were observed. the absorption curves of VIIa. especially those in aprotic solvents. are similar to that of 2-methyl-8H-cyclohepta[b]furan-8-one (2-methylfuro[2,3-b]-tropone) (IX)[12] (Fig. 1). The UV spectrum of VIIIa was also similar to that of IX. Moreover. the NMR spectrum ($CDCl_3$) of VIIIa reveals a triplet at 1·47 (3H. J = 7·1 Hz), and a quartet at 4·49 ppm (2H, J = 7·1 Hz), and a singlet at 2·52 ppm (3H), corresponding to the protons of the OEt and Ac groups respectively, as well as two multiplets at 6·8–7·4 (3H) and 8·0–8·3 ppm (1H), corresponding to the ring protons, and a broad singlet at 9·75 (1H), corresponding to the NH group. The IR spectra (KBr disk) of VIIa and VIIIa are rather complicated but show absorptions at 3420 and 3220 cm^{-1} and at 3280 cm^{-1}, corresponding to the NH_2 and NH groups, respectively. On the basis of these spectral data and the results of the elementary analyses. VIIa and VIIIa were believed to be 2-amino-3-ethoxycarbonyl- and 2-acetamido-3-ethoxycarbonyl-8H-cyclohepta[b]furan-8-ones respectively. This skeletal structure of VIIa was also supported from the fact that the treatment of VIIa with conc H_2SO_4 gave 8-hydroxy-2H-cyclohepta[b]furan-2-one (Ve) and 3-carboxymethyltropolone (X) which have been obtained by the acidic treatment of Va or Vb.[10] When VIIa was warmed in an alcoholic alkaline solution it gave Vc quantitatively: the mechanism of this conversion will be discussed later.

In the reaction of IVa. b and ethyl cyanoacetate. the relative yields of the products. Ib. Vc and VIIa. varied markedly in accordance with the amounts of NaOEt. (Table 1). Thus. when the reaction was carried out in the presence of an equimolar or less amount of NaOEt for ethyl cyanoacetate. VIIa was obtained as major product. together with azulene Ib. whereas in the presence of excess NaOEt. Vc was produced in a good yield. When t-butylamine was used as base neither Vc nor VIIa was obtained. but only Ib in good yield.

The reaction of 2-*arylsulfonyloxytropones* (IVa. b) *and malononitrile or cyanoacetamide*

It has been reported that the reaction of 2-halotropone or 2-methoxytropone and malononitrile in the presence of bases (NaOEt or t-butylamine) gave 2-amino-1,3-

dicyanoazulene (If).[1] and reaction of these tropones and cyanoacetamide gave 2-amino-1,3-dicarbamoylazulene (Ig) or 3-cyanocyclohepta[b]pyrrol-2(1H)-one (XI).[13] It has also been found that 3-cyano- (IIIb) and 3-carbamoyl-2H-cyclohepta[b]furan-2-imine (IIIc) were formed as reaction intermediates.[3] In contrast to these findings. the reaction of IVa. b and malononitrile or cyanoacetamide in the presence of NaOEt gave products which were different from azulene derivatives (If or Ig) or 2H-cyclohepta[b]furan-2-imine (IIIb or IIIc), in addition to the expected azulenes. Thus, the reaction of IVa, b and malononitrile in the presence of an equimolar amount of NaOEt for malononitrile or in the presence of t-butylamine gave only azulene If, whereas it gave another compound (VIIb) in a good yield in the presence of excess NaOEt (Table 1). The reaction of IVa, b and cyanoacetamide in the presence of excess NaOEt gave VIIc and an acidic compound (XII), together with azulene derivative Ig.

The structures of VIIb and VIIc are assumed to be 2-amino-3-cyano- and 2-amino-3-carbamoyl-8H-cyclohepta[b]furan-8-ones respectively. from the findings to be presented below. as well as their elementary analyses. The UV spectra of VIIb and VIIc are similar to that of VIIa. Their IR spectra (KBr disk) are rather complicated but that of VIIb shows absorptions at 3300 and 3040. and at 2220 cm^{-1}. corresponding to those of the NH_2 and CN groups respectively, and that of VIIc shows absorptions at 3340 and 3165 cm^{-1}. corresponding to that of the NH_2 group. When warmed in conc H_2SO_4. VIIb gave VIIc. and when heated in 75% H_2SO_4 at 140°. both VIIb and VIIc gave the tropolone derivative. X. Moreover. upon acetylation with Ac_2O and methylation with dimethyl sulfate. VIIb gave N-acetyl derivative (VIIIb) and N.N-dimethyl derivative (XIII) respectively. The UV spectra of these derivatives are similar to that of IX. Moreover, the alkaline treatment of XIII resulted in hydrolysis, giving Vc. together with dimethylamine.

The compound. XII. was identical with the compound which has been obtained by the condensation of 2-amino-3-bromotropone and ethyl cyanoacetate and represented as 1.3-dihydrocyclohepta[b]pyrrole-2.8-dione.[14] However. the adequate structure, 3-cyano-8-hydroxycyclohepta[b]pyrrol-2(1H)-one, was given for this compound on the basis of the UV spectra.*

The observation described above shows that the reaction of 2-arylsulfonyloxytropones (IVa. b) and active methylene compounds. such as diethyl malonate. ethyl acetoacetate. ethyl cyanoacetate. malononitrile or cyanoacetamide. in the presence of NaOEt. gave 8-Hydroxy-2H-cyclohepta[b]furan-2-one derivatives (Va. Vb and Vc) or 2-amino-8H-cyclohepta[b]furan-8-one derivatives (VIIa. VIIb and VIIc). This behaviour of IVa. b is apparently different from those of 2-halotropones and 2-methoxytropones and is thought to be characteristic of 2-arylsulfonyloxytropones.

A reasonable reaction course for the formation of 8-hydroxy-2H-cyclohepta[b]-furan-2-ones (Va–c) and 2-amino-8H-cyclohepta[b]furan-8-ones (VIIa–c) by reaction of 2-arylsulfonyloxytropones (IVa. b) and active methylene compounds is presented in Chart 1. The carbanions which are produced from the active methylene compounds should attack IVa, b at the 7-position to give an addition-type intermediate (A). In this intermediate elimination can take place through two different paths (a and b). In a. the arylsulfonyloxyl group is eliminated *via* a protonated intermediate (B) to give a tropone-type intermediate (C). which subsequently cyclizes to 2H-cyclohepta[b]-

* This result will be reported separately.

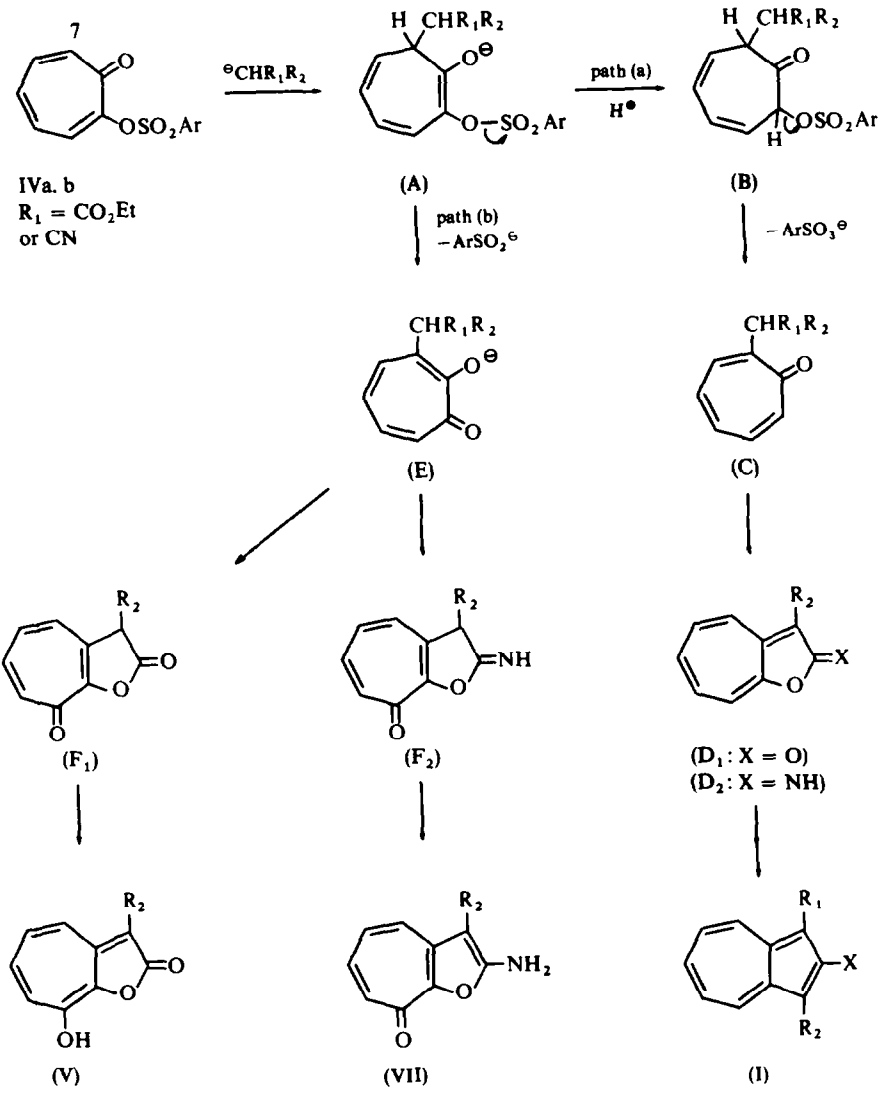


CHART 1. A reasonable reaction course for the formation of 8-hydroxy-2H-cyclohepta[b]furan-2-one derivatives (V) and 2-amino-8H-cyclohepta[b]furan-8-one derivatives. (VII).

furan 2-ones (D_1) or 2-cyclohepta[b]furan-2-imines (D_2). In the reaction with diethyl malonate or ethyl acetoacetate, IIa (D_1: $R_2 = CO_2Et$) or IIb (D_1: $R_2 = COMe$) was obtained as the products. whereas in the reaction with ethyl cyanoacetate or cyanoacetamide. the intermediates (D_1 or D_2) react subsequently with another molecule of the active methylene compounds to give azulene derivatives (Ib or Ig).[6]

On the other hand. in path b the arylsulfonyl group of the intermediate (A) is eliminated as arenesulfinate ion by the aid of a strong base to produce a tropolonate-type intermediate (E). The elimination of arenesulfinate ion was confirmed from the fact that *p*-tolyl *p*-toluenethiolsulfonate. which was a disproportionation product of *p*-toluenesulfinic acid.[15] was isolated from the reaction mixture of IVb and diethyl

malonate or ethyl cyanoacetate. The CO_2Et or CN group in the intermediate (E) can participate in ring formation to give a lactone-type (F_1) or an imidolactone-type intermediate (F_2), which enolize to the stable products, 8-hydroxy-2H-cyclohepta[b]-furan-2-one derivatives (Va–c) or 2-amino-8H-cyclohepta[b]furan-8-one derivatives (VIIa–c).

Path a involves a step in which protonation takes place (A → B), whereas path b does not involve a protonation step; consequently the reaction takes place through path a under less basic conditions (t-butylamine) to give 2H-cyclohepta[b]furan-2-one derivatives (IIa, IIb) or azulene derivatives (Ib, Ig), whereas the reaction takes place through path b under more basic conditions (excess NaOEt) to give 8-hydroxy-2H-cyclohepta[b]furan-2-one derivatives (Va–c) or 2-amino-8H-cyclohepta[b]furan-8-one derivatives (VIIa–c).

In the reaction of IVa, b and ethyl cyanoacetate, both types of intermediates (F_1' and F_2') can be produced from the tropolonate-type intermediate (E') by the ring formation with the CO_2Et or CN group; consequently the two products (Vc and VIIa) can be produced (Chart 2). In practice, both Vc and VIIa were obtained, but their relative yields were markedly influenced by amounts of NaOEt (Table 1). This finding can be explained as below. In the intermediate E', the cyclization in which the CN group participates takes place more easily to give the intermediate F_2'; consequently the formation of VIIa is a faster reaction. However, since VIIa easily loses its proton of the NH_2 group by the action of a strong base, the reverse reaction

$$(\text{VIIa} \rightarrow F_2' \rightarrow E')$$

easily takes place in the presence of excess NaOEt. On the other hand, although the cyclization in which the CO_2Et participates to give intermediate F_1' takes place more

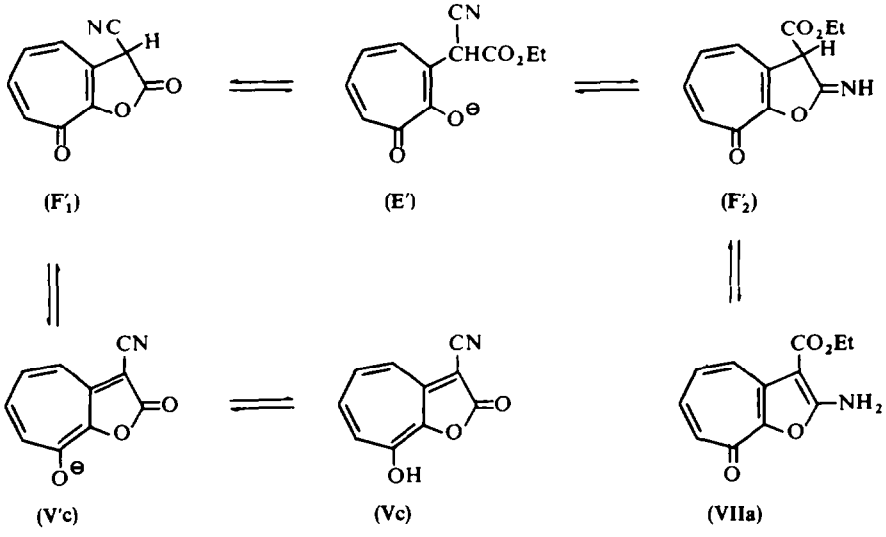


CHART 2. The reaction of 2-arylsulfonyloxytropones (Va, b) and ethyl cyanoacetate.

slowly, compound Vc can change to its stable anion (Vc')* in the presence of NaOEt. As a result the kinetically controlled product, VIIa, is predominantly produced in the presence of an equimolar amount of NaOEt, whereas the thermodynamically controlled product, Vc, is obtained predominantly in the presence of excess NaOEt. That VIIa can be changeable to Vc under basic conditions was supported from the fact that VIIa gave Vc quantitatively upon being warmed in an alcoholic alkaline solution.

In the reaction of IVa, b and malononitrile, the tropolonate-type intermediate (E'') can cyclize to give only one kind of imidolactone-type intermediate (F_2''), which enolizes to VIIb (Chart 3). VIIb is easily soluble in alkali and thus is thought to exist in the form of the anion (E'') in an alkaline medium.

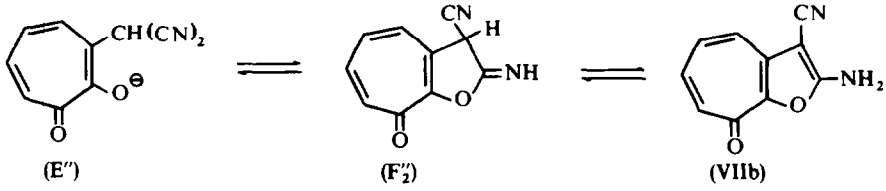
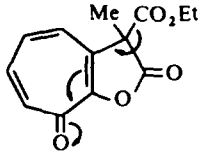


CHART 3. The reaction of 2-arylsulfonyloxytropones (IVa, b) and malononitrile.

2-Arylsulfonyloxytropones, IVa, b, also reacted with some active methylene compounds related to diethyl malonate or ethyl acetoacetate in the presence of NaOEt, giving 8-hydroxy-2H-cyclohepta[b]furan-2-one derivatives. Thus, the reaction of IVa, b and ethyl *p*-nitrophenylacetate easily gave 3-(*p*-nitrophenyl)-8-hydroxy-2H-cyclohepta[b]furan-2-one (Vf) in a good yield. The reaction with ethyl benzoylacetate also gave 3-benzoyl derivative (Vg).[11] On the other hand, the reaction of IVa, b and diethyl acetonedicarboxylate gave a small amount of 3-(ω-ethoxycarbonylacetyl)-8-hydroxy-2H-cyclohepta[b]furan-2-one (Vh), together with a fairly good amount of 3-(ω-ethoxycarbonylacetyl)-2H-cyclohepta[b]furan-2-one (IId).[16] The structures of Vf–h (and their acetyl derivatives) were determined by elementary analyses and UV spectral data their UV spectra are similar to those of 8-hydroxy-2H-cyclohepta[b]-furan-2-ones and their acetyl derivatives respectively.



G

The reaction of IVa, b and diethyl methylmalonate under similar conditions gave 3-methyl-8-hydroxy-2H-cyclohepta[b]furan-2-one (Vi). The UV spectra of Vi and its acetyl derivate (VIe) are consistent with this structure. This compound is thought to be formed as a result of the elimination of the ethoxycarbonyl group from the lactone-type intermediate (G), which has no enolizable proton.

* 8-Hydroxy-2H-cyclohepta[b]furan-2-ones are monobasic acids (enolic OH).[10]

EXPERIMENTAL

All m.ps are uncorrected. UV spectra were measured on a Hitachi EPS-3 spectrophotometer and IR spectra were recorded on a Shimazu IR-27 infracord.

2-Phenylsulfonyloxytropone (IVa). Into a stirred solution of tropolone (2·4 g) in dry pyridine (12 ml) was added dropwise freshly distilled benzenesulfonyl chloride (4·0 g) at 0°. after which the mixture was allowed to stand for 12 hr at room temp and poured into H_2O. Crystals were collected. washed with H_2O and dried in *vacuo*. Recrystallization from EtOH gave IVa (4·81 g). colorless needles; m.p. 98–99°. (Found C. 59·93: H. 3·84 .$C_{13}H_{10}O_4S$ requires: C. 59·53; H. 3·84%).

The reaction of IVa. b *and diethyl malonate.* Into a stirred solution of IVb (1·38 g. 0·005 mol) and diethyl malonate (1·60 g. 0·01 mol) in anhyd EtOH (10 ml) was added 1M NaOEt solution (10 ml) at 0°. After being stirred for an additional 3 hr. the mixture was allowed to stand overnight. poured into H_2O and shaken with C_6H_6. The C_6H_6 layer was washed with water. dried (Na_2SO_4) and evaporated. giving crude crystals (30 mg. m.p. 99–104°). recrystallized from ether to give IIa. yellow needles; m.p. 129–130°; (lit..[4] 129–130°). The aqueous layer was acidified with 6N HCl and crystals thereby formed were collected and recrystallized from EtOH to give Va (1·10 g). yellow needles; m.p. 224–225°; (lit..[10] 225°). The aqueous filtrate was extracted with $CHCl_3$ and dried (Na_2SO_3). Evaporation of solvent left an oil, which partially crystallized on standing. Crystals were collected and recrystallized from EtOH to give *p*-tolyl *p*-toluenethiolsulfonate (450 mg). colorless needles; m.p. 76–78°; (lit..[16] 78–79°). (Found: C. 60·52; H. 5·15. $C_{14}H_{14}S_2O_2$ requires: C. 60·43; H. 5·07%).

Similar treatments of a solution of IVa (524 mg. 0·002 mol) and diethyl malonate (640 mg. 0·004 mol) in anhyd EtOH (15 ml) with each 2, 4, and 6 ml of 1M NaOEt solution gave 320, 370, and 400 mg of Va respectively, together with a small amount of IIa. Moreover, similar treatment of a solution of IVb (552 mg) and diethyl malonate (320 mg) in anhyd EtOH (15 ml) with 1M NaOEt solution (6 ml) also gave 365 mg of Va.

Reaction of IVa. b *and ethyl acetoacetate.* Into a stirred solution of IVb (1·38 g. 0·005 mol) and ethyl acetate (1·30 g. 0·01 mol) in anhyd EtOH (15 ml) was added 1M NaOEt solution (10 ml) at 0°. After being stirred for an additional 2 hr. the mixture was allowed to stand overnight at room temp and poured into H_2O. Crystals were collected, washed with H_2O, dried in *vacuo* and recrystallized from EtOH, giving IIb (420 mg). yellow needles; m.p. 208–209°; (lit..[4] 206–207°). The aqueous filtrate was acidified with 6N HCl and crystals collected and recrystallized from EtOH. giving Vb (450 mg). yellow needles; m.p. 285°; (lit..[10] 285°).

Similar treatment of a solution of IVa (1·31 g. 0·005 mol) and ethyl acetoacetate (1·30 g) in anhyd EtOH (15 ml) with 10 ml of 1M NaOEt gave IIb (720 mg) and Vb (92 mg), and that with 15 ml of 1M NaOEt gave IIb (610 mg) and Vb (204 mg).

The reaction of IVa. b *and ethyl cyanoacetate.* (a) *In the presence of an equimolar amount of NaOEt.* Into a stirred solution of IVa (524 mg. 0·002 mol) and ethyl cyanoacetate (452 mg. 0·004 mol) in anhyd EtOH (15 ml) was added 1M NaOEt solution (4 ml) at 0°. After being stirred for an additional 3 hr. the mixture was allowed to stand overnight at room temp and then diluted with H_2O. Crystals were collected. washed with H_2O. dried in *vacuo* and extracted with hot C_6H_6. Evaporation of solvent from the C_6H_6 soluble part left crystals (140 mg. m.p. 86–95°). which were recrystallized from EtOH to give Ib. orange prisms; m.p. 96–97; (lit..[1] 96°). IR spectrum is identical with that of an authentic sample.[1] The residue which was slightly soluble in C_6H_6 was recrystallized from dimethylformamide to give VIIa (260 mg). yellow needles; m.p. 251°. (Found: C. 61·35; H. 4·81; N. 5·86. $C_{12}H_{11}O_4N$ requires: C. 61·80; H. 4·75; N. 6·01%). λ_{max}(MeOH) nm (log ε); 220 (4·33). 288 (4·41). 323 (4·03). 338 (4·06).

Similar treatment of a solution of IVb (1·38 g. 0·005 mol) and ethyl cyanoacetate (1·15 g. 0·01 mol) in anhyd EtOH (15 ml) with 1M NaOEt solution (10 ml) gave Ib (480 mg) and VIIa (450 mg). From the aqueous filtrate, *p*-tolyl *p*-toluenethiolsulfonate (30 mg, m.p. 76–78°) was obtained in similar manner to IVb and diethyl malonate.

(b) *In the presence of an excess amount of NaOEt.* Into a stirred solution of IVa (524 mg. 0·002 mol) and ethyl cyanoacetate (425 mg. 0·004 mol) in anhyd EtOH (15 ml) was added 1M NaOEt (6 ml) at 0°. After being stirred for 3 hr. the mixture was allowed to stand overnight at room temp. diluted with H_2O and acidified with 6N HCl. Crystals thereby formed were collected and recrystallized from dimethylformamide to give Vc (300 mg). yellow needles; m.p. over 300°. (Found: C. 63·77; H. 2·91; N. 7·46. $C_{10}H_5O_3N$ requires: C. 64·17; H. 2·69; N. 7·48%). λ_{max}(MeOH) nm (log ε); 223 (4·42). 288 (4·36). 354 (4·15).

(c) *In the presence of t-butylamine.* A mixture of IVa (524 mg), ethyl cyanoacetate (452 mg) and t-butylamine (60 mg) in anhyd EtOH (15 ml) was stirred for 3 hr and allowed to stand overnight at room temp.

The mixture was diluted with H_2O and crystals thereby formed were collected, washed with H_2O, dried in *vacuo* and recrystallized from EtOH, giving Ib (449 mg), orange prisms; m.p. 96–97°. Similar treatment of a mixture of IVb (1·38 g), ethyl cyanoacetate (1·12 g) and t-butylamine (120 mg) in anhyd EtOH (15 ml) also gave Ib (1·02 g, m.p. 96–97°).

8-*Acetoxy*-3-*cyano*-2H-*cyclohepta*[b]*furan*-2-*one* (VIc). A mixture of Vc (300 mg), Ac_2O (2·5 ml) and pyridine (0·5 ml) was warmed at about 70° for 2 hr, and poured into ice water, giving crude crystals (290 mg, m.p. 180–185°), recrystallized from EtOH to give VIc, yellow needles; m.p. 186–188°. (Found: C, 62·63; H, 3·06; N, 6·27. $C_{12}H_7O_4N$ requires: C, 62·89; H, 3·08; N, 6·11%). λ_{max}(MeOH) nm (log ε); 225 (4·31), 266 (4·35), 400 (4·30).

3-*Carbamoyl*-8-*hydroxy*-2H-*cyclohepta*[b]*furan*-2-*one* (Vd). (a) *From* Vc. A solution of Vc (200 mg) in conc H_2SO_4 (3 ml) was heated at about 70° for 1 hr, and poured into ice water. Crystals thereby formed were collected and recrystallized from dimethylformamide to give Vd (150 mg), yellow needles; m.p. 289°. (Found: C, 58·84; H, 3·84; N, 6·64. $C_{10}H_7O_4N$ requires: C, 58·54; H, 3·44; N, 6·83%). λ_{max}(MeOH) nm (log ε); 220 (4·39), 290 (4·39), 380 (4·14).

(b) *From* Va. A mixture of Va (400 mg) and ammonium formate (200 mg) was heated at 190° for 2 hr under N_2, and poured into H_2O. Crystals thereby formed were collected and recrystallized from dimethylformamide to give Vd (135 mg), yellow needles; m.p. 289°.

8-*Acetoxy*-3-*carbamoyl*-2H-*cyclohepta*[b]*furan*-2-*one* (VId). The treatment of Vd with Ac_2O in similar manner for the preparation of VIc from Vc gave VId, yellow needles; m.p. 212–213°. (Found: C, 58·22; H, 3·93; N, 5·39. $C_{12}H_9O_5N$ requires: C, 58·30; H, 3·67; N, 5·67%). λ_{max}(MeOH) nm (log ε); 225 (4·44), 276 (4·34), 400 (4·22).

The treatment of VId *with* $POCl_3$. A mixture of VId (200 mg) and $POCl_3$ (5 ml), containing pyridine (0·5 ml), was heated at about 70° for 3 hr, after which the mixture was cooled and poured into ice water. Crystals thereby formed were collected and recrystallized from EtOH to give VIc (130 mg), yellow needles; m.p. 186–188°.

2-*Acetamido*-3-*ethoxycarbonyl*-8H-*cyclohepta*[b]*furan*-8-*one* (VIIIa). A mixture of VIIa (375 mg) and Ac_2O (3 ml) was refluxed for 3 hr and allowed to stand overnight at room temp. Crystals thereby formed were collected and recrystallized from EtOH to give VIIIa (370 mg), colourless needles; m.p. 158–160°. (Found: C, 61·19; H, 4·42; N, 4·93. $C_{14}H_{13}O_5N$ requires: C, 61·09; H, 4·76; N, 5·09%). UV (MeOH): λ_{max}nm (log ε); 258 (4·25), 310 (3·74), 335 (3·60).

The treatment of VIIa *with conc* H_2SO_4. A mixture of VIIa (1·00 g) and conc H_2SO_4 (2 ml) was warmed at about 100° for 1 hr, and poured into ice water. Crystals thereby formed were collected and recrystallized from EtOH to give Ve (930 mg), yellow prisms; m.p. 233–234°; (lit.,[10] 223°). The aqueous filtrate was extracted with ether, giving X (20 mg), yellow needles; m.p. 173°; (lit.,[10] 174°). IR spectra of these compounds are identical with those of authentic samples[10].

The alkaline treatment of VIIa. A mixture of VIIa (1·00 g), EtOH (10 ml) and 2N NaOH solution (8 ml) was refluxed for 2 hr. After being cooled, the solution was acidified with 6N HCl, affording Vc (1·72 g), yellow crystals; m.p. over 300°.

The reaction of IVa, b *and malononitrile.* (a) *In the presence of an equimolar amount of* NaOEt. Into a stirred solution of IVa (524 mg, 0·002 mol) and malononitrile (264 mg, 0·004 mol) in anhyd EtOH (15 ml) was added 1M NaOEt solution (4 ml) at 0°. After being stirred for an additional 3 hr, the mixture was allowed to stand overnight at room temp and diluted with H_2O. Crystals thereby formed were collected and washed with H_2O and hot EtOH to give If (282 mg), yellow microcrystals; m.p. over 300°. IR spectrum is identical with that of an authentic sample.[1] Similar treatment of a solution of IVb (1·38 g, 0·005 mol) and malononitrile (660 mg, 0·01 mol) in anhyd EtOH (15 ml) with 1M NaOEt solution (10 ml) also gave If (450 mg), yellow micro-crystals; m.p. over 300°.

(b) *In the presence of an excess amount of* NaOEt. Into a stirred solution of IVa (524 mg, 0·002 mol) and malononitrile (264 mg, 0·004 mol) in anhyd. EtOH (15 ml) was added 1M NaOEt solution (6 ml) at 0°. After being stirred for an additional 3 hr, the mixture was poured into H_2O and a small amount of precipitate was filtered off. The aqueous filtrate was neutralized carefully with N HCl under cooling. Crystals thereby formed were collected and recrytallized from dimethylformamide to give VIIb (300 mg), yellow micro-crystals; m.p. over 300°. (Found: C, 63·91; H, 3·24, N, 14·61. $C_{10}H_6O_2N_2$ requires: C, 64·51; H, 3·25; N, 15·05%). λ_{max}(MeOH) nm (log ε): 220 (4·49), 253 (4·11), 287 (4·46), 324 (4·06), 336 (4·07).

(c) *In the presence of t-butylamine.* A solution of IVa (524 mg), malononitrile (264 mg) and t-butylamine (60 mg) in anhyd EtOH (15 ml) was stirred for 4 hr, allowed to stand overnight at room temp and diluted with H_2O. Crystals thereby formed were collected, washed with H_2O, and hot EtOH, giving If (370 mg).

yellow micro-crystals; m.p. over 300°. Similar treatment of a solution of IVb (1·38 g), malononitrile (660 mg) and t-butylamine (120 mg) in anhyd EtOH (15 ml) also gave If (895 mg), yellow micro-crystals; m.p. over 300°.

2-Acetamido-3-cyano-8H-cyclohepta[b]furan-8-one (VIIIb). A mixture of VIIb (120 mg), Ac_2O (0·5 ml) and pyridine (0·1 ml) was heated at about 70° for 2 hr. Crystals thereby formed were collected and recrystallized from EtOH to give VIIIb (120 mg), yellow needles; m.p. 282–283°. (Found: C, 60·49; H, 3·70; N, 11·79. $C_{12}H_8O_3N_2 \cdot \frac{1}{2}H_2O$ requires: C, 60·76; H, 3·82; N, 11·81%). λ_{max}(MeOH) nm (log ε); 223 (4·11), 283 (4·38), 304 (3·95), 322 (3·82).

3-Cyano-2-dimethylamino-8H-cyclohepta[b]furan-8-one (XIII). Into a stirred solution of VIIb (1·10 g) in a 10% NaOH aq (5 ml) was added dropwise dimethyl sulfate (2 ml) at 0°. After being stirred for an additional 3 hr, the mixture was allowed to stand overnight at room temp, diluted with H_2O and extracted with $CHCl_3$. Evaporation of solvent left orange crystals, recrystallized from EtOH–$CHCl_3$ (1:1), giving XIII (620 mg), orangish yellow needles; m.p. 203–204°. (Found: C, 67·54; H, 4·61; N, 12·91. $C_{12}H_{10}O_2N_2$ requires: C, 67·28; H, 4·71; N, 13·08%). λ_{max}(MeOH) nm (log ε); 221 (4·43), 260 (4·23), 290 (4·35), 345 (4·09).

The reaction of IVa, b *and cyanoacetamide.* Into a stirred solution of IVa (1·05 g, 0·004 mol) and cyanoacetamide (673 mg, 0·008 mol) in anhyd EtOH (20 ml) was added 1M NaOEt solution (8 ml) after which the mixture was stirred for 12 hr at room temp and diluted with H_2O. Crystals thereby formed were collected and fractionally recrystallized from dimethylformamide. The less soluble part gave Ig (302 mg), yellow-micro-crystals; m.p. over 280°, identified by the comparison of the IR spectrum with an authentic sample.[13] The readily soluble part gave VIIc (27 mg), yellow micro-crystals; m.p. over 300°. (Found: C, 58·37; H, 4·11; N, 13·76. $C_{10}H_8O_3N_2$ requires: C, 58·82; H, 3·95; N, 13·72%). λ_{max}(MeOH) nm (log ε); 230 (4·16), 255 (3·95, sh), 292 (4·25), 322 (4·18), 346 (3·94). The aqueous filtrate was acidified with 6N HCl and crystals thereby formed were collected and washed with hot EtOH, giving XII (370 mg), yellow crystals; m.p. over 300°, identified by comparison of the IR spectrum with that of an authentic sample.[14]

Similar treatment of a solution of IVb (1·38 g, 0·005 mol) and cyanoacetamide (840 mg, 0·01 mol) in anhyd EtOH (15 ml) with 1M NaOEt solution (10 ml) gave Ig (183 mg), VIIc (91 mg) and XII (460 mg).

Treatment of VIIb *or* VIIc *with* H_2SO_4. (a) A mixture of VIIb (200 mg) and conc H_2SO_4 (1 ml) was warmed at about 100° for 3 hr and poured into H_2O, giving VIIc (198 mg), yellow micro-crystals; m.p. over 300°.

(b) A mixture of VIIc (100 mg) and 75% H_2SO_4 (1 ml) was heated at 140° for 1 hr, cooled and poured into ice water. Crystals thereby formed were collected to give recovery of starting material, VIIc (79 mg). The aqueous filtrate was extracted with ether to give X (14 mg), yellow needles; m.p. 173°.

Treatment of XIII *with alkali.* A solution of XIII (1·15 g) in a mixture of EtOH (10 ml) and 4N NaOH aq (5 ml) was refluxed for 2 hr; a gentle stream of N_2 gas was passed through this solution and then through a 0·5N HCl solution in another flask. After completion, the alkaline solution was acidified with 6N HCl, giving Vc (0·85 g), yellow crystals; m.p. over 300°. The aqueous HCl solution was made alkaline with N NaOH and extracted with C_6H_6. Picric acid was added to the C_6H_6 and the solution concentrated to small volume, giving dimethylamine picrate (80 mg), yellow needles; m.p. 157–158°.

3-(p-Nitrophenyl)-8-hydroxy-2H-cyclohepta[b]furan-2-one (Vf). Into a stirred solution of IVa (1·05 g) and ethyl *p*-nitrophenylacetate (1·67 g) in anhyd EtOH (15 ml) was added 1M NaOEt (8 ml) at 0°. After being stirred for an additional 3 hr, the mixture was allowed to stand overnight and poured into H_2O. The sodium salts thereby separated out were collected and dissolved in DMF and the solution acidified with 6N HCl. Crystals thereby formed were collected and recrystallized from DMF to give Vf (1·05 g), yellowish orange crystals; m.p. 310°. (Found: C, 63·79; H, 3·47; N, 4·75. $C_{15}H_9O_5N$ requires: C, 63·61; H, 3·20; N, 4·95%). λ_{max}(MeOH) nm (log ε); 224 (4·17), 275 (4·13), 354 (3·70), 420 (4·19). Similar treatment of a solution of IVb (1·38 g) and ethyl *p*-nitrophenylacetate (2·09 g) in anhyd EtOH (15 ml) with 1M NaOEt (10 ml) also gave Vf (1·05 g).

The reaction of IVa, b *and diethyl acetonedicarboxylate.* Into a stirred solution of IVa (2·62 g) and diethyl acetonedicarboxylate (4·04 g) in anhyd EtOH (10 ml) was added 1M NaOEt (20 ml) at 0°. After being stirred for an additional 4 hr, the mixture was diluted with H_2O, and crystals thereby formed were collected and recrystallized from EtOH to give IId (1·38 g), yellow plates; m.p. 125–126°; (lit.,[18] 126°). The aqueous filtrate was acidified with 6N HCl and extracted with $CHCl_3$. The solvent was evaporated and the residue recrystallized from EtOH to give Vh (233 mg), yellow needles; m.p. 209°. (Found: C, 61·42; H, 4·38. $C_{14}H_{12}O_6$ requires: C, 60·87; H, 4·38%). λ_{max}(MeOH) nm (log ε); 224 (4·41), 295 (4·43), 310 sh (4·26), 390 (4·15). Similar treatment of a solution of IVb (1·38 g) and diethyl acetonedicarboxylate (2·02 g) in anhyd EtOH (10 ml) with 1M NaOEt (10 ml) gave IId (850 mg) and Vh (250 mg).

3-*Methyl*-8-*hydroxy*-2H-*cyclohepta*[b]*furan*-2-*one* (Vi). Into a stirred solution of IVa (524 mg) and diethyl methylmalonate (700 mg) in anhyd EtOH (15 ml) was added 1M NaOEt (4 ml) at 0°, after which the mixture was allowed to stand overnight at room temp. poured into H_2O, acidified with 6N HCl and extracted with $CHCl_3$. The solvent was evaporated and the residue recrystallized from EtOH to give Vi (89 mg), orange prisms; m.p. 248°. (Found: C, 68·20; H, 4·59. $C_{10}H_8O_3$ requires: C, 68·18; H, 4·58%). λ_{max}(MeOH) nm (log ε); 222 (4·22), 278 (4·26), 310 (3·73), 373 (4·17), 387 (4·70). Similar treatment of a solution of IVb (1·38 g) and diethyl methylmalonate (1·74 g) in EtOH (10 ml) with 1M NaOEt (10 ml) gave Vi (200 mg).

8-*Acetoxy*-2H-*cyclohepta*[b]*furan*-2-*one derivatives from* Vf–i. These derivatives were obtained by the acetylation of the corresponding 8-hydroxy-2H-cyclohepta[b]furan-2-ones with Ac_2O in the presence of a small amount of pyridine. (a) 3-(p-*Nitrophenyl*)-8-*acetoxy*-2H-*cyclohepta*[b]*furan*-2-*one*, reddish orange crystals (from AcOH); m.p. 213–215°. (Found: C, 62·65; H, 3·64; N, 4·29. $C_{17}H_{11}O_6N$ requires: C, 62·77; H, 3·41; N, 4·31%). λ_{max}(MeOH) nm (log ε); 230 (4·36), 270 (4·27), 416 (4·38).

(b) 3-*Benzoyl*-8-*acetoxy*-2H-*cyclohepta*[b]*furan*-2-*one*, yellow needles (from EtOH); m.p. 152–154°. (Found: C, 70·17; H, 3·96. $C_{18}H_{12}O_5$ requires: C, 70·13; H, 3·92%). λ_{max}(MeOH) nm (log ε); 227 (4·42), 258 (4·43), 288 (4·17), 423 (4·42).

(c) 3-ω-*Ethoxycarbonylacetyl*)-8-*acetoxy*-2H-*cyclohepta*[b]*furan*-2-*one*, orange needles (from EtOH); m.p. 155–157°. (Found: C, 59·85; H, 4·32. $C_{16}H_{14}O_7$ requires: C, 60·38; H, 4·43%), λ_{max} (MeOH) nm (log ε); 237 (4·13), 285 (4·23), 310 (3·89), 425 (4·36).

(d) 3-*Methyl*-8-*acetoxy*-2H-*cyclohepta*[b]*furan*-2-*one*, orange needles (from EtOH); m.p. 153–155°. (Found: C, 65·94; H, 4·48. $C_{12}H_{10}O_4$ requires: C, 66·05; H, 4·62%). λ_{max} (MeOH) nm (log ε); 225 (4·25), 257 (4·41), 374 (4·27).

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