Tetrahedron. Vol. 27. pp. 3357 to 3368. Pergamon Press 1971. Printed in Great Britain

THE FORMATION OF AZULENE DERIVATIVES FROM 2*H*-CYCLOHEPTA[*b*]FURAN-2-ONE DERIVATIVES

T. NOZOE, K. TAKASE*, T. NAKAZAWA and S. FUKUDA

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

(*Received in Japan* 28 *January* 1971; *Received in the UK for publication* 13 *April* 1971)

Abstract—3-Ethoxycarbonyl- and 3-acetyl-2*H*-cyclohepta[*b*]furan-2-ones react easily with malonitrile. cyanoacetamide. ethyl cyanoacetate and diethyl malonate. in the presence of sodium ethoxide or t-butylamine. giving the corresponding 1.2.3-trisubstituted azulene derivatives. respectively. The structures of these azulene derivatives are determined on the basis of chemical evidence. and spectral data. Considering the structural correlation between the starting 2*H*-cyclohepta[*b*]furan-2-ones and the azulene derivatives obtained. a reasonable reaction course. involving the heptafulvene-type and dihydroazulene-type intermediates. is presented for the formation of azulene derivatives from 2*H*-cyclohepta[*b*]furan-2-ones.

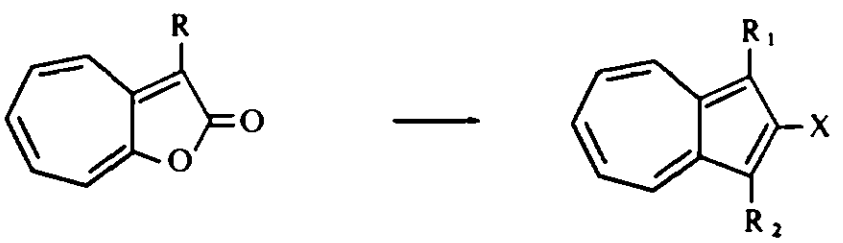
AS DESCRIBED in the previous paper,[1] it has been found that the reaction of 2-methoxy- or 2-chlorotropones and diethyl malonate gave diethyl 2-hydroxyazulene-1,3-dicarboxylate. and it has also been confirmed that 3-ethoxycarbonyl-2*H*-cyclohepta[*b*]-furan-2-one (3-ethoxycarbonyl-1-oxaazulan-2-one) should be the reaction intermediate in this reaction. From these findings. it is presumed that 2*H*-cyclohepta[*b*]-furan-2-one-type compounds should be the intermediate in the azulene-formation reaction[2, 3] from troponoid compounds. In order to confirm this presumption and to make clear the reaction mechanism for the azulene-formation reaction. for which a tentative mechanism have been presented.[2, 3] the reactions of various 2*H*-cyclohepta[*b*]furan-2-one derivatives and the compounds having the reactive methylene group have been examined. and an out-line on part of these results have been reported.[4] This paper will describe the details of the results on the reactions of 3-ethoxycarbonyl- (Ia)[5] and 3-acetyl-2*H*-cyclohepta[*b*]furan-2-ones (Ib)[5] and the compounds having the reactive methylene group. such as. malononitrile. cyanoacetamide. ethyl cyanoacetate or diethyl malonate.

2*H*-Cyclohepta[*b*]furan-2-ones. Ia and Ib. reacted easily with malononitrile. cyanoacetamide. ethyl cyanoacetate and diethyl malonate. in the presence of NaOEt or t-butylamine. at room temperature or under cooling with ice-water. giving the corresponding 1.2.3-trisubstituted azulene derivatives. respectively. The reactions of Ia or Ib and malononitrile or cyanoacetamide each gave a basic azulene derivative. IIa. IIb. IIIa and IIIb. respectively. On the other hand. the reactions of Ia or Ib and ethyl cyanoacetate gave two types of azulene derivatives each. (IVa and V). and (IVb and VI). respectively. in which IVa and IVb are basic azulenes. but V and VI are acidic. In the case of the reaction and diethyl malonate. Ia gave one acidic azulene derivative. namely. diethyl 2-hydroxyazulene-1,3-dicarboxylate (VIIa). as reported.[1] whereas Ib gave two acidic azulene derivatives (VIIb and VIII). The UV and vis. spectra revealed

* Address correspondence to this author.

all these compounds as azulene derivatives. The correlation between the starting 2*H*-cyclohepta[*b*]furan-2-ones and the azulene derivatives obtained are summarized in Table 1. along with the reagents used.

TABLE 1. AZULENE DERIVATIVES OBTAINED ON THE REACTIONS OF 2H-CYCLOHEPTA[*b*]FURAN-2-ONES AND THE ACTIVE METHYLENES[a]



(A) (B)

The active methylenes[a]	2*H*-Cyclohepta[*b*]furan-2-ones (A)	
	Ia: R = $CO_2C_2H_5$	Ib: R = $COCH_3$
	Azulene derivatives (B) (yield %)	
$CH_2(CN)_2$	IIa: $R_1 = CO_2C_2H_5$. $R_2 = CN$. X = NH_2 (94·5)	IIb: $R_1 = COCH_3$. $R_2 = CN$. X = NH_2 (95·6)
$NCCH_2CONH_2$	IIIa: $R_1 = CO_2C_2H_5$. $R_2 = CONH_2$. X = NH_2 (94·3)	IIIb: $R_1 = COCH_3$. $R_2 = CONH_2$. X = NH_2 (93·6)
$NCCH_2CO_2C_2H_5$	IVa: $R_1 = R_2 = CO_2C_2H_5$. X = NH_2 (25·8) V: $R_1 = CO_2C_2H_5$. $R_2 = CN$. X = OH (43·5)	IVb: $R_1 = COCH_3$. $R_2 = CO_2C_2H_5$. X = NH_2 (5·6) VI: $R_1 = CO_2H$. $R_2 = CN$ X = CH_3 (81·2)
		VIIb: $R_1 = COCH_3$. $R_2 = CO_2C_2H_5$. X = OH (34·3)
$CH_2(CO_2C_2H_5)_2$	VIIa: $R_1 = R_2 = CO_2C_2H_5$, X = OH (65·0)	VIII: $R_1 = CO_2H$. $R_2 = CO_2C_2H_5$. X = CH_3 (36·5)

[a] Active methylenes means compounds having reactive methylene groups

Among these azulene derivatives. IIa. IVa and V were identical with ethyl 2-amino-3-cyanoazulene-1-carboxylate. diethyl 2-aminoazulene-1.3-dicarboxylate and ethyl 3-cyano-2-hydroxyazulene-1-carboxylate. respectively. which have been obtained from the reaction of 2-chloro- or 2-methoxytropones with ethyl cyanoacetate.[3] The structures of the other azulene derivatives, IIb, IIIa, IIIb, IVb, VI, VIIb and VIII, were determined on the basis of the chemical evidence described below, as well as the results of elementary analyses and spectral data (Table 2).

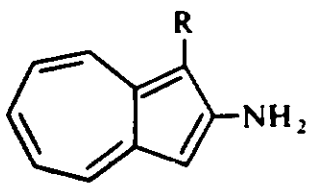
The azulene. IIb. gave an azulene derivative (IXa) when heated in concentrated HBr or 85% H_3PO_4 at about 100°C. This azulene, IXa, was also obtained from IIa on treatment with acid in a similar way to IIb. or on alkaline hydrolysis followed by decarboxylation. The IR spectrum of IXa shows absorptions at 3510. 3400 and 3280 cm^{-1}. and at 2212 cm^{-1}. corresponding to the NH_2 and CN groups. respectively. From these findings. IXa was assigned the structure of 2-amino-1-cyanoazulene. and consequently the structure of IIb was determined to be 1-acetyl-2-amino-3-cyanoazulene. The azulenes. IIIa and IIIb. were assigned the structures of ethyl

2-amino-3-carbamoylazulene-1-carboxylate and 1-acetyl-2-amino-3-carbamoylazulene, respectively, from the fact that, when heated in 85% H_3PO_4 or in 75% H_2SO_4, both gave 2-amino-1-carbamoylazulene (IXb), which was derived from IXa upon heating in 75% H_2SO_4. The azulene, IVb, was assumed to be ethyl 3-acetyl-2-aminoazulene-1-carboxylate from its basic properties (giving a picrate), as well as its IR spectra (Table 2).

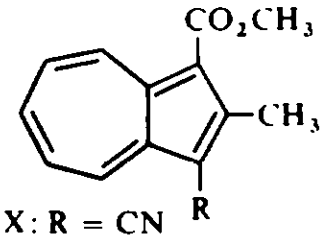
TABLE 2. THE INFRARED SPECTRAL DATA OF THE AZULENE DERIVATIVES

Compound	Absorption ν_{max}^{KBr}: cm^{-1}
IIa	3470, 3355 (NH_2); 2217 (CN); 1669 (CO)[3]
IIb	3410, 3300, 3215 (NH_2); 2203 (CN); 1621 (CO)
IIIa	3390, 3355, 3175 (NH_2); 1681, 1637 (CO)
IIIb	3470, 3330, 3205 (NH_2); 1639, 1610 (CO)
IVa	3500, 3310 (NH_2); 1660 (CO)[3]
IVb	3450, 3320 (NH_2); 1650, 1630 (CO)
V	3100 (OH); 2200 (CN); 1655 (CO)[3]
VI	3100 ~ 2600, 1655, 909 (CO_2H); 2232 (CN)
VIIa	1675, 1639 (CO)[1]
VIIb	1626 (CO)
VIII	3050 ~ 2300, 1647, 920 (CO_2H); 1692 (CO)

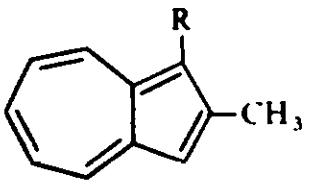
The azulene, VI, was revealed to be a carboxylic acid from the IR spectral data, and from the fact that it gave a methyl ester (X) on treatment with CH_2N_2. Upon heating in H_3PO_4 at about 100°C or upon heating at its melting point, VI gave a neutral azulene derivative (XIa), with evolution of CO_2. The IR spectrum of XIa shows an absorption at 2212 cm^{-1}, corresponding to the CN group. Moreover, on being heated in 75% H_2SO_4, XIa afforded two kinds of azulene derivatives (XIb) and (XII). On comparison of the IR spectra and on admixture of their trinitrobenzolates, the latter azulene, XII, was identical with 2-methylazulene.[6] The IR spectrum of the other azulene, XIb, shows absorptions at 3400, 3205 and 1639 cm^{-1}, corresponding to the carbamoyl group and no absorption due to the CN group. Moreover, XIb



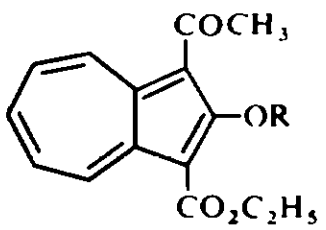
IXa: R = CN
IXb: R = $CONH_2$



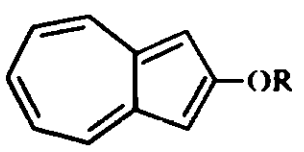
X: R = CN
XV: R = $CO_2C_2H_5$



XIa: R = CN
XIb: R = $CONH_2$
XII: R = H
XVI: R = $CO_2C_2H_5$



XIIIa: R = CH_3
XIIIb: R = $COCH_3$



XIVa: R = CH_3
XIVb: R = C_2H_5

reproduced XIa upon heating in $POCl_3$, whereas it gave XII upon heating in conc. H_2SO_4. These findings indicated that XIa and XIb were 1-cyano-2-methylazulene and 1-carbamoyl-2-methylazulene, respectively, and consequently VI was assigned the structure of 3-cyano-2-methylazulene-1-carboxylic acid.

The azulene, VIIb, being a weakly acidic substance, gave a monomethyl derivative (XIIIa) and a monoacetyl derivative (XIIIb) on treatment with CH_2N_2 or Ac_2O, respectively. The IR spectrum of XIIIa shows absorptions at 1689 and 1639 cm^{-1}, corresponding to the conjugated carbonyl groups, and that of XIIIb shows an absorption at 1767 cm^{-1} due to the enol or phenol acetate, as well as absorptions at 1673 and 1642 cm^{-1}, corresponding to the conjugated carbonyl groups. Moreover, the NMR spectrum of VIIb reveals a triplet at 1·48 (3H, $J = 7$ Hz) and a quarter at 4·48 (2H, $J = 7$ Hz), a singlet at 2·66 (3H, s), and a broad singlet at 11·98 ppm (1H), corresponding to the protons of the EtO, Ac and OH groups, respectively, as well as three multiplets at 7·57 (3H), 8·90 (1H) and 9·66 ppm (1H), corresponding to the ring protons, and that of XIIIa reveals a triplet at 1·47 (3H, $J = 7$ Hz) and a quartet at 4·48 (2H, $J = 7$ Hz), and two singlets at 2·70 (3H) and 4·17 ppm (3H), corresponding to the protons of the EtO, Ac, and MeO groups, as well as three multiplets at 7·72 (3H), 9·49 (1H) and 9·88 ppm (1H), corresponding to the ring protons. From these findings, as well as the IR data (Table 2), VIIb was assigned the structure of ethyl 3-acetyl-2-hydroxyazulene-1-carboxylate, and XIIIa and XIIIb were its methyl ether and acetyl derivative, respectively. When heated in 100% H_3PO_4, the methyl ether, XIIIa, gave a mixture of 2-methoxyazulene (XIVa)[1, 7] and 2-ethoxyazulene (XIVb).[1, 7] The formation of XIVb is presumed to be due to the replacement of the OMe group in XIIIa with EtOH or its equivalent species produced on deethoxycarbonylation. It is known that the OMe group at the 2-position of azulene derivative could be replaced with the OEt.[1]

The acidic azulene, VIII, was revealed to be a carboxylic acid from its IR spectra (Table 2), and from the fact that it gave a methyl ester (XV) on treatment with CH_2N_2. When heated in 85% H_3PO_4 or 75% H_2SO_4, VIII afforded 2-methylazulene (XII), with evolution of CO_2. Alkaline hydrolysis followed by decarboxylation, VIII also gave XII. On the other hand, when heated at about 200°C in the absence of solvent, VIII afforded a neutral azulene derivative (XVI), whose IR spectrum shows absorptions at 1690 and 1678 cm^{-1}. Alkaline hydrolysis of XVI gave a carboxylic acid, which afforded XII upon heating at its melting point. Treatment of XVI in H_3PO_4 at about 100°C also gave XII. From these findings, XVI was assigned the structure of ethyl 2-methylazulene-1-carboxylate, and consequently, VIII was assigned the structure of 3-ethoxycarbonyl-2-methylazulene-1-carboxylic acid.

During the studies on the structural elucidation of the azulene derivatives described above, it was found that the substituents at the 1- and 3-positions of the azulene nucleus showed an interesting behavior toward acidic treatment, that is, the acetyl, ethoxycarbonyl and carboxyl groups were easily eliminated upon heating in strong acid, whereas the CN and carbamoyl groups were resistant to elimination. Moreover, the CN group was hydrolyzed to the carbamoyl group upon heating in H_2SO_4, but did not show any change in HBr or H_3PO_4.

As results of the structural determination on the azulene derivatives were obtained, it was revealed that the azulene derivatives bearing the various substituents at the 1-, 2- and 3-positions of the azulene nucleus were easily produced from 2H-cyclo-

hepta[*b*]furan-2-one derivatives in good yield. Moreover, it was also confirmed that 2H-cyclohepta[*b*]furan-2-one-type compounds should be the reaction intermediate in the azulene-formation reaction from troponoid compounds.

Considering the structural correlation between the starting 2H-cyclohepta[*b*]furan-2-ones and the azulene derivatives, a reasonable reaction course for the formation of azulene derivatives from 2H-cyclohepta[*b*]furan-2-ones can be presented. (Chart 1).

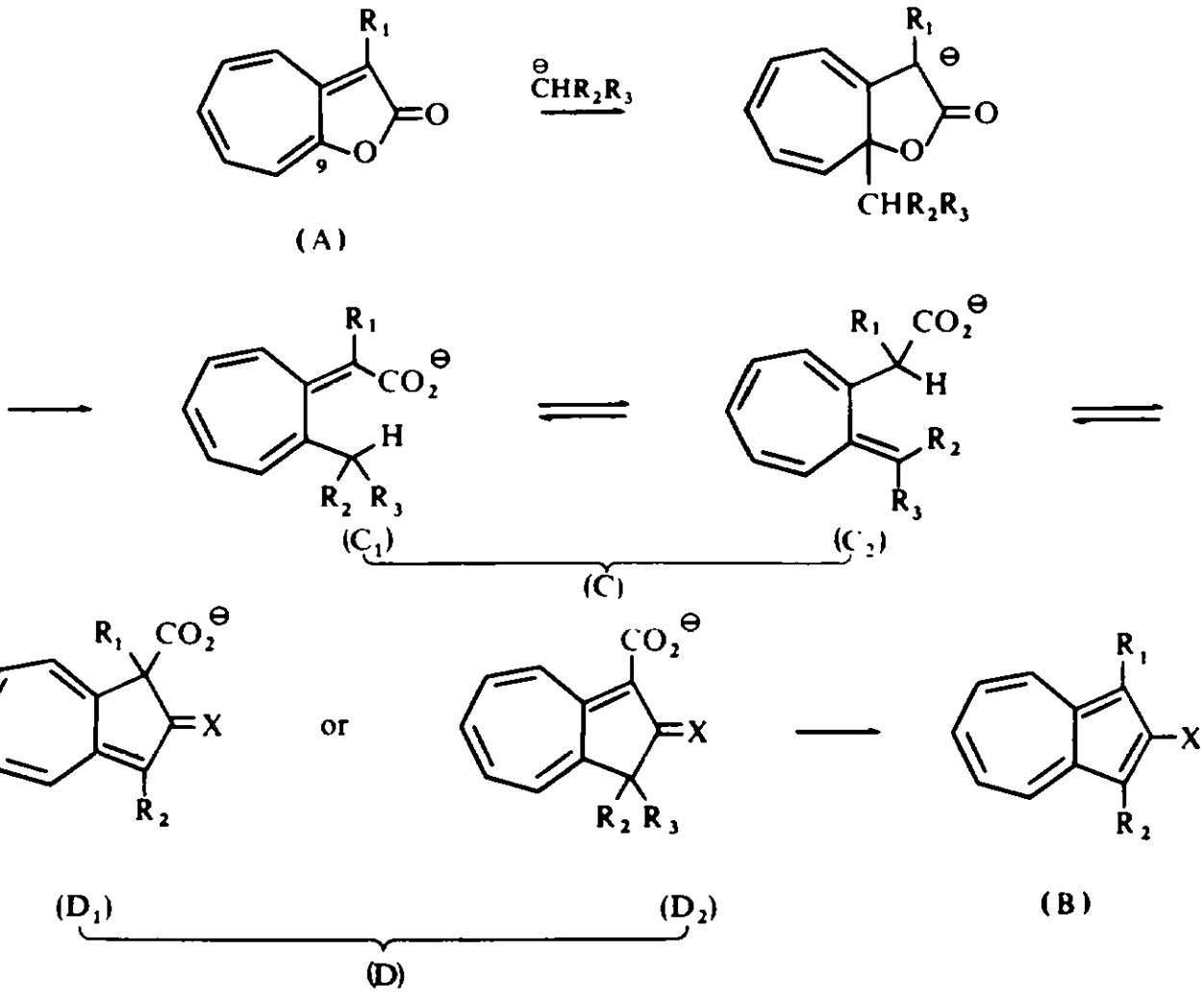


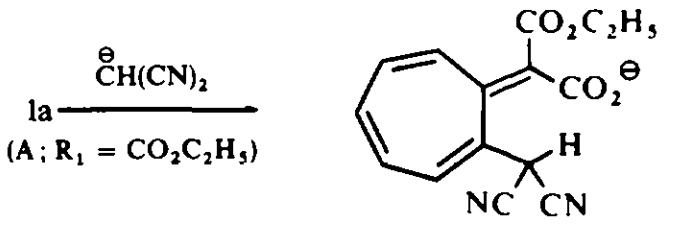
CHART 1. The reaction course for the formation of azulene derivatives (B) from 2H-cyclohepta[*b*]furan-2-one derivatives (A)

The carbanions, $R_2—\overset{\ominus}{C}H—R_3$, being produced from malononitrile, cyanoacetamide, ethyl cyanoacetate or diethyl malonate, attack 2H-cyclohepta[*b*]furan-2-ones (A) at the 9-position, and the lactone ring opens to give a heptafulvene-type intermediate (C), which should exist in the tautomers (C_1) and (C_2). The position at which the carbanions attack was confirmed from the observation on the formation of azulene derivatives from 2H-cyclohepta[*b*]furan-2-ones bearing the substituent at the seven-membered ring; these results will be reported separately.

In the intermediate (C), cyclization takes place easily, in the presence of base, between the methine carbon and the functional groups in the other side-chain, giving dihydroazulene-type intermediate (D). This cyclization should be catalyzed with base by means of the abstraction of the methine proton and probably be reversible as ester condensation generally is. Among the four possible sets of modes for cyclization of the intermediate (C), the one in which the carboxyl or carbamoyl groups would participate can not take place, because of lesser reactivity of these groups

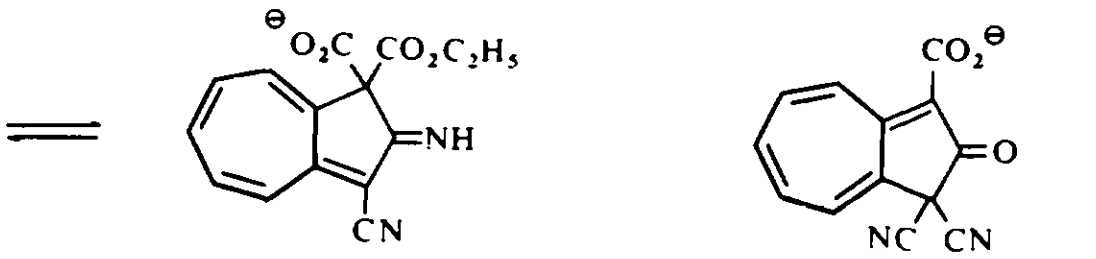
toward nucleophiles. Elimination of a functional group at the geminally substituted carbon in the intermediate (D) gives azulene derivatives (B); this could be catalyzed by base. The structures of the azulene derivatives produced should be affected by such factors as the mode of cyclization of the intermediate (C) and the ease of elimination of the substituents in the intermediate (D). Consequently, by following the reaction course described above. the azulene derivatives obtained practically should be limited.

The general consideration on the azulene-formation reaction described above can be applicable to the examples in this study. Some of them will now be described. The reaction of 3-ethoxycarbonyl-2H-cyclohepta[*b*]furan-2-one (Ia) and malononitrile should produce the heptafulvene-type intermediate (Ca) (Chart 2). Between



(Ca)

(C; $R_1 = CO_2C_2H_5$. $R_2 = R_3 = CN$)



(Da) (Db)

(D_1: $R_1 = CO_2C_2H_5$. $R_2 = CN$. X = NH) (D_2; $R_2 = R_3 = CN$. X = O)

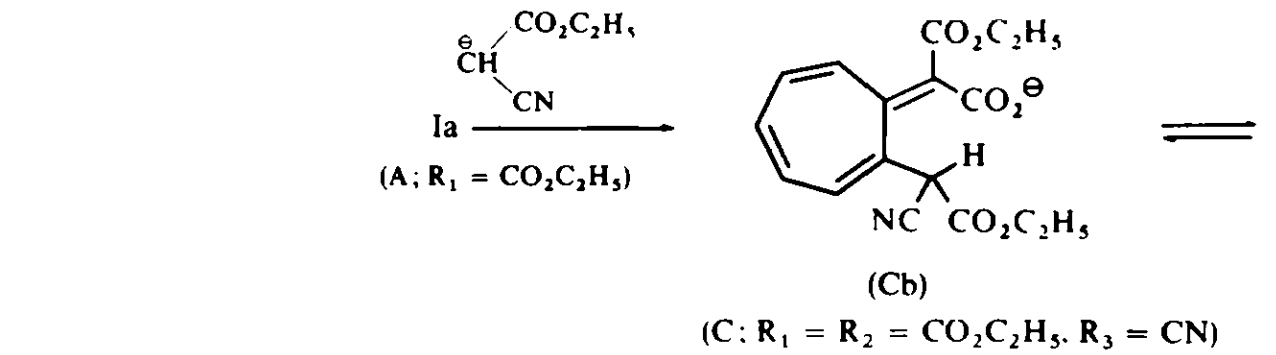
IIa

(B: $R_1 = CO_2C_2H_5$. $R_2 = CN$. $X = NH_2$)

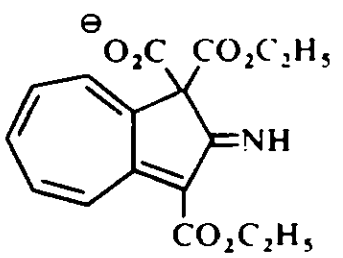
CHART 2. The reaction of 3-ethoxycarbonyl-2H-cyclohepta[*b*]furan-2-one (Ia) and malononitrile

the two possible dihydroazulene-type intermediates (Da) and (Db), the former. in which the CN group participates in cyclization, should be produced predominantly and decarboxylation gives the azulene (IIa). The reaction of IIb and malononitrile. and those of IIa or IIb and cyanoacetamide should follow a similar reaction course.

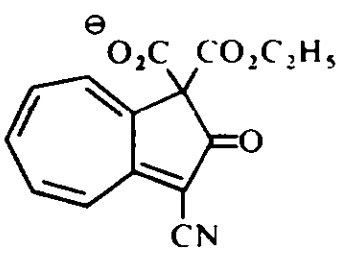
In the reaction of Ia and ethyl cyanoacetate, as shown in Chart 3, the heptafulvene-type intermediate (Cb) may be possible to give three dihydroazulene-type intermediates



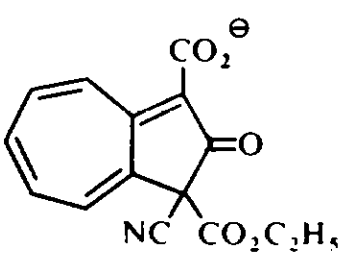
(Cb)
(C: $R_1 = R_2 = CO_2C_2H_5$. $R_3 = CN$)



(Dc)
(D_1; $R_1 = R_2 = CO_2C_2H_5$. X = NH)



(Dd)
(D_1; $R_1 = CO_2C_2H_5$. R_2 = CN. X = O)



(De)
(D_2; $R_2 = CO_2C_2H_5$. R_3 = CN. X = O)

IVa
(B; $R_1 = R_2 = CO_2C_2H_5$. $X = NH_2$)

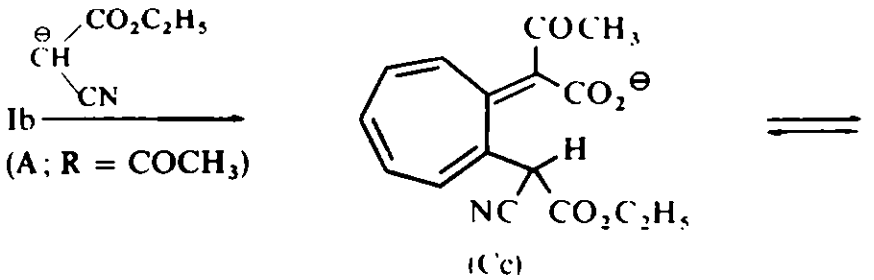
V
(B; $R_1 = CO_2C_2H_5$. R_2 = CN. X = OH)

CHART 3. The reaction of 3-ethoxycarbonyl-2H-cyclohepta[*b*]furan-2-one (Ia) and ethyl cyanoacetate

(Dc). (Dd) and (De) by cyclization between the methine carbon and the ethoxycarbonyl or CN groups. Among these. (Dc) and (Dd) give azulene derivatives (IVa) and (V). respectively. by decarboxylation. The azulene derivatives. being expected to be formed from the intermediate (De). could not be obtained. The reaction of Ia and diethyl malonate is of a similar type.

The third example is the reaction of 3-acetyl-2*H*-cyclohepta[*b*]furan-2-ones (Ib) and ethyl cyanoacetate; this gave 2-methylazulene derivative (VI). In this case. the dihydroazulene-type intermediate (Dh) should be formed predominantly by cyclization between the methine carbon and the acetyl carbonyl of the heptafulvene-type intermediate (Cc). (Chart 4). Elimination of the ethoxycarbonyl and OH groups from (Dh) gives the azulene (VI). The azulene (IVb) being expected to be produced from the intermediate (Df) was also obtained, but the azulene being expected to be produced from the intermediate (Dg) could not be isolated. The reaction of Ib and diethyl malonate should follow a similar course.

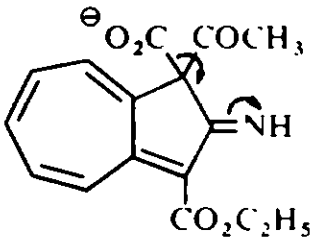
In these examples, it was found that the CN, ethoxycarbonyl and Ac groups participated in cyclization of the heptafulvene-type intermediate (C) to form the dihydroazulene-type intermediate (D) and the carboxyl and ethoxycarbonyl groups could eliminate from the intermediate (D) to give azulenes.



(A; R = $COCH_3$)

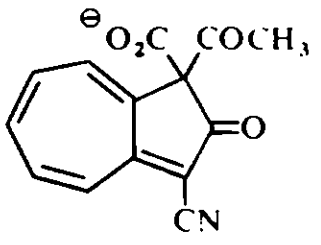
(C)

(C; R_1 = $COCH_3$, R_2 = $CO_2C_2H_5$, R_3 = CN)



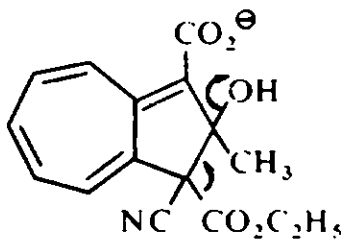
(Df)

(D_1: R_1 = $COCH_3$, R_2 = $CO_2C_2H_5$, X = NH)



(Dg)

(D_1; R_1 = $COCH_3$, R_2 = CN, X = O)



(Dh)

(D_2; R_2 = $CO_2C_2H_5$, R_3 = CN, X = OH, CH_3)

IVb

(B; R_1 = $COCH_3$, R_2 = $CO_2C_2H_5$, X = NH_2)

VI

(B; R_1 = CO_2H, R_2 = CN, X = CH_3)

CHART 4. The reaction of 3-acetyl-2H-cyclohepta[*b*]furan-2-one (Ib) and ethyl cyanoacetate

EXPERIMENTAL

All m.ps are uncorrected. The UV and vis. spectra were measured on a Hitachi EPS-3 spectrophotometer and IR spectra on a Shimadzu IR-27 infracord. The NMR spectra were determined with a Varian A-60 spectrometer in $CDCl_3$ containing TMS.

3-*Ethoxycarbonyl*-2H-*cyclohepta*[b]*furan*-2-*one* (Ia). This was prepared by a modification of the method reported.[5] A solution of 2-chlorotropone (560 mg), diethyl malonate (1·28 g) and t-butylamine in anhyd. EtOH (5 ml) was allowed to stand for 2 days in a refrigerator. Crystals separated and were collected to give Ia (480 mg), yellow needles; m.p. 129 ~ 130 °; (lit[5] 129 ~ 130°). The filtrate was diluted with H_2O, extracted with $CHCl_3$, dried (Na_2SO_4), solvent evaporated and the oily residue triturated with ether, giving Ia (160 mg); m.p. 127 ~ 9°.

3-*Acetyl*-2H-*cyclohepta*[b]*furan*-2-*one* (Ib). Modification of the method reported.[5] To a solution of 2-chlorotropone (4·64 g) and ethyl acetoacetate (8·60 g) in anhyd. EtOH (21 ml) was added 1M NaOEt (36·6 ml), and the mixture stirred for 2 hr (0°), and allowed to stand for 2 days in a refrigerator. Addition of H_2O separated crystals. Ib (5·25 g); m.p. 204 ~ 5°. Recrystallization from glacial AcOH afforded yellow needles; m.p. 206 ~ 7°. (lit.[5], 206–7°). A similar result was obtained with t-butylamine in place of NaOEt.

Ethyl 2-*amino*-3-*cyanoazulene*-1-*carboxylate* (IIa). A mixture of Ia (654 mg), malononitrile (297 mg) and t-butylamine (440 mg) in anhyd EtOH (18 ml) was stirred for 3 hr and allowed to stand for 2 days at room temperature. H_2O was added and crystals recrystallized from EtOH, giving IIa (680 mg), orange scales; m.p. 171 ~ 2° (lit.[3], 167–8°).

Similar results by NaOEt in place of t-butylamine or C_6H_6 in place of EtOH.

N-Acetyl derivative. Orange needles (from dioxane); m.p. 214 ~ 5°. (Found: C. 67·69; H. 4·70; N. 9·82. Calcd. for $C_{16}H_{14}O_3N_2$: C. 68·07; H. 5·00; N. 9·92%). λ_{max}: nm (log ε); 265 (4·35), 312 (4·74), 322 (4·82), 375 (3·98), 482 (2·59).

1-*Acetyl*-2-*amino*-3-*cyanoazulene* (IIb). A mixture of Ib (564 mg), malononitrile (300 mg) and t-butylamine (440 mg) in anhyd. EtOH (20 ml) was treated as described above. Crystals (602 mg); m.p. 250 ~ 5°, obtained were recrystallized from ethyl acetate to give IIb, orangish yellow needles; m.p. 254 ~ 5°. (Found: C, 74·22; H, 4·67; N, 13·21. Calcd. for $C_{13}H_{10}ON_2$: C, 74·27; H, 4·79; N, 13·33%). λ_{max}(MeOH): nm (log ε); 226 (4·20), 245 (4·33), 274 (4·37), 318 (4·70), 329 (4·79), 377 (3·75), 391 (3·75), 460 (3·45).

Ethyl 2-*amino*-3-*carbamoylazulene*-1-*carboxylate* (IIIa). To a NaOEt solution prepared from Na (300 mg) and anhyd. EtOH (25 ml), cyanoacetamide (504 mg) and Ia (654 mg) were added, and the mixture treated as described for IIa. Crystals (730 mg); m.p. 228 ~ 9°, obtained were recrystallized from dioxane to give IIIa (730 mg), yellowish-orange needles; m.p. 228–9°. (Found: C, 64·97; H, 5·21; N, 10·64. Calc. for $C_{14}H_{14}O_3N_2$: C, 65·10; H, 5·46; N, 10·85%) λ_{max}(MeOH): nm (log ε); 247 (4·51), 270 (4·33), 314 (3·68), 324 (4·73), 370 (3·86), 392 (3·85), 457 (3·38).

1-*Acetyl*-2-*amino*-3-*carbamoylazulene* (IIIb). To a NaOEt prepared from Na (300 mg) and anhyd. EtOH (20 ml), cyanoacetamide (500 mg) and Ib (564 mg) were added, and the mixture was treated as described for IIa. Crystals (640 mg); m.p. 236 ~ 8°, recrystallized from dioxane to give IIIb, yellowish-orange needles; m.p. 238 ~ 9°. (Found: C, 66·73; H, 5·74; N, 10·70. Calc. for $C_{13}H_{12}O_2N_2 \cdot \frac{1}{2} - C_4H_8O_2$: C, 66·16; H, 5·92; N, 10·29%. λ_{max} (MeOH): nm (log ε); 253 (4·24), 286 (4·37), 312 (4·70), 332 (4·76), 375 (3·87), 470 (3·80).

Diethyl 2-*aminoazulene*-1.3-*dicarboxylate* (IVa) *and ethyl* 3-*cyano*-2-*hydroxyazulene*-1-*carboxylate* (V). To NaOEt prepared from Na (220 mg) and anhyd. EtOH (30 ml), ethyl cyanoacetate (520 mg) and Ia (500 mg) were added, and the mixture stirred for 2 hr and allowed to stand for 2 days at room temperature. H_2O was added, and the Na salt separated out. The salt was dissolved in glacial AcOH and the solution diluted with H_2O extracted ($CHCl_3$) and dried over Na_2SO_4. Evaporation gave crystals (140 mg); m.p. 188 ~ 190°, recrystallized from dimethylformamide to give V, orange needles; m.p. 189 ~ 190°, (lit.[3], 189°).

The filtrate of the Na salt was extracted with $CHCl_3$. Evaporation of solvent left crystals, recrystallized from EtOH to give IVa (170 mg), orange prisms; m.p. 95 ~ 6°. (lit.[3], 96°). The aqueous extraction layer was acidified with 6N HCl and extracted with $CHCl_3$. Evaporation of solvent followed by recrystallization from dimethylformamide gave V (100 mg): 189 ~ 190°.

Ethyl 3-*acetyl*-2-*aminoazulene*-1-*carboxylate* (IVb) *and* 3-*cyano*-2-*methylazulene*-1-*carboxylic acid* (VI). To a mixture of Ib (2·25 g) and ethyl cyanoacetate (2·71 g) in anhyd. EtOH (48 ml) was added 1M NaOEt solution (48 ml), and the mixture stirred for 4 hr and allowed to stand for 2 days at room temp. The mixture was diluted with H_2O (200 ml) and extracted with $CHCl_3$ dried over Na_2SO_4 sulfate, the solvent evaporated and the residue recrystallized from EtOH to give IVb (170 mg), orangish-yellow prisms; m.p. 85 ~ 6°. (Found: C, 70·38; H, 5·78; N, 5·13. Calc. for $C_{15}H_{15}O_3N$: C, 70·02; H, 5·88; N, 5·44%). λ_{max} (MeOH); nm (log ε); 228 (4·18), 250 (4·38), 282 (4·52), 320 (4·64), 332 (4·76), 337 (3·86), 390 (3·86), 463 (3·64). *Picrate*: Reddish orange scales (from EtOH); m.p. 131 ~ 2°. (Found: C, 52·16; H, 3·80; N, 11·21%. Calcd for $C_{21}H_{18}O_{10}N_4$: C, 51·85; H, 3·73; N, 11·52%). The aqueous layer was acidified with 6N HCl and crystals collected to give VI (2·05 g); m.p. 270° (decomp.). Recrystallization from dimethylformamide afforded orangish red micro-needles; m.p. 273 (dec.). (Found: C, 73·68; H, 4·18; N, 6·33. Calc. for $C_{13}H_9O_2N$: C, 73·92; H, 4·30; N, 6·63%. λ_{max} (MeOH): nm (log ε); 235 (4·56), 261 (4·23), 295 (4·62), 305 (4·68), 343 (3·71), 371 (3·71), 505 (2·58).

Ethyl 3-*acetyl*-2-*hydroxyazulene*-1-*carboxylate*(VIIb) *and* 3-*ethoxycarbonyl*-2-*methylazulene*-1-*carboxylic acid* (VIII). To a mixture of Ib (3·39 g) and diethyl malonate (5·76 g) in anhyd. EtOH (80 ml) was added 1M NaOEt (72 ml), and the mixture stirred for 5 hr and allowed to stand for 2 days at room temp. The mixture was diluted with H_2O (250 ml), acidified with 6N HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was shaken twice with 2N K_2CO_3 (25 ml × 2). The organic layer was dried (Na_2SO_4) and solvent evaporated, giving yellow crystals (1·60 g); m.p. 138 ~ 145°. Recrystallization from EtOH gave VIIb (1·00 g), yellow needles; m.p. 146 ~ 9°, 150 ~ 1° by further recrystallization from EtOH. (Found: C, 70·17; H, 4·92. Calc. for $C_{15}H_{14}O_4$: C, 69·75; H, 5·46%). λ_{max} (MeOH) nm (log ε); 245 (4·38), 278 (4·50), 323 (4·52), 335 (4·56), 460 (3·68).

Acetyl derivative (XIIIb). Red prisms (from C_6H_6); m.p. 103 ~ 4°. (Found: C, 68·31; H, 5·31. Calc. for $C_{17}H_{16}O_5$: C, 67·99; H, 5·37%. λ_{max} (MeOH): nm (log ε); 237 (4·58), 280 (4·58), 306 (4·57), 375 (3·93), 421 (3·34).

The carbonate layer was acidified with 6N HCl and crystals collected. Recrystallization from EtOAc gave VIII (1·70 g), pale red micro-needles; m.p. 172 ~ 3°. (Found: C, 70·15; H, 5·13. Calc. for $C_{15}H_{14}O_4$: C, 69·75; H, 5·46%). λ_{max} (MeOH): nm (log ε): 236 (4·37), 271 (4·18), 306 (4·73), 343 (3·57), 372 (3·60), 500 (2·47).

2-*Amino*-1-*cyanoazulene* (IXa). (a) *From* 1-*acetyl*-2-*amino*-3-*cyanoazulene* (IIb). A mixture of IIb (200 mg)

and conc. HBr (2 ml) was heated at about 100° for 30 min. After cooling, the mixture was diluted with H_2O and neutralized with 2N KOH. Crystals were collected (140 mg); m.p. 151 ~ 3°. and recrystallized from EtOH to give IXa. orange scales; m.p. 156 ~ 7°. (Found: C. 78·53; H. 4·49; N. 16·32. Calc. for $C_{11}H_8N_2$: C. 78·55; H. 4·79; N. 16·66%). λ_{max} (MeOH) nm (log ε); 243 (4·01). 298 (4·80). 310 (4·87). 360 (3·85). 394 (3·79). N-*Acetyl derivative*: Red silky needles (from EtOH); m.p. 225 ~ 6°. (Found: C. 74·38; H. 4·82; N. 12·86. Calc. for $C_{13}H_{10}ON_2$: C. 74·27; H. 4·79; N. 13·33%). λ_{max} (MeOH) nm (log ε); 233 (4·45). 300 (4·83). 310 (4·90). 353 (3·93). 369 (3·99). 520 (2·62). *Picrate*: Dark red needles from EtOH); m.p. 146 ~ 7°. (Found: C. 51·40; H. 2·80; N. 17·39. Calc. for $C_{17}H_{11}O_7N_5$: C. 51·39; H. 2·79; N. 17·63%). A similar treatment of IIb (100 mg) with 85% H_3PO_4 (1 ml) also gave IXa (40 mg); 156 ~ 7°.

(*b*) *From ethyl 2-amino-3-cyanoazulene-1-carboxylate* (IIa) *on heating in acid.* The treatment of IIa (100 mg) with concentrated HBr (1 ml) in a similar manner as described in (a) gave IXa (60 mg). orange scales; m.p. 156 ~ 7°.

(*c*) *From* IIa *by alkaline hydrolysis.* A mixture of IIa (480 mg). 2N KOH (3 ml) and EtOH (7 ml) was refluxed for 2 hr. dissolved in H_2O and acidified with 6N HCl. giving 2-amino-3-cyanoazulene-1-carboxylic acid (440 mg); m.p. 212° (decomp.). Recrystallization from dioxane afforded orangish yellow needles; m.p. 212° (decomp.). This acid (100 mg) was heated at about 200° and sublimed under a reduced pressure. Sublimates were recrystallized from EtOH to give IXa (40 mg). orange scales; m.p. 156 ~ 7°.

2-*Amino-1-carbamoylazulene* (IXb). (*a*) *From 2-amino-1-cyanoazulene* (IXa). A mixture of IXa (100 mg) and 75% H_2SO_4 (1 ml) was heated at about 100° for 30 min. The mixture was diluted with H_2O and shaken with $CHCl_3$. and the aqueous layer neutralized with $NaHCO_3$. Crystals were collected (50 mg); m.p. 184 ~ 6°. recrystallized from EtOH to give IXb. reddish orange scales; m.p. 186 ~ 7°. (Found: C. 70·58; H. 5·28; N. 14·79. Calc. for $C_{11}H_{10}ON_2$: C. 70·95; H. 5·41; N. 15·05%). λ_{max} (MeOH): nm (log ε); 305 (4·71). 314 (4·75). 362 (3·79). 380 (3·75).

(*b*) *From ethyl 2-amino-3-carbamoylazulene-1-carboxylate* (IIIa). The treatment of IIIa (200 mg) with 75% H_2SO_4 or 85% H_3PO_4 as in (a) gave IXb (90 mg). reddish orange scales; m.p. 186 ~ 7°.

(*c*) *From 1-acetyl-2-amino-3-carbamoylazulene* (IIIb). The treatment of IIIb (200 mg) with 75% H_2SO_4 or 85% H_3PO_4 as in (a) gave IXb (100 mg). reddish orange scales; m.p. 186 ~ 7°.

Methyl 3-cyano-2-methylazulene-1-carboxylate (X). To a suspension of VI (527 mg) in a mixture of dioxane (20 ml) and MeOH (5 ml). an ethereal solution of CH_2N_2 (8 ml) was added and the mixture stirred for 2 hr (0°). The solvent was evaporated and the residue recrystallized from MeOH to give X (440 mg). red needles; m.p. 137 ~ 8°. (Found: C. 75·09; H. 5·14; N. 6·45. Calc. for $C_{14}H_{11}O_2N$: C. 74·65; H. 4·92; N. 6·22%). λ_{max}(MeOH): nm (log ε); 235 (4·62). 262 (4·36). 294 (4·62). 305 (4·73). 342 (3·89). 370 (3·88). 497 (2·73).

1-*Cyano-2-methylazulene* (XIa). (*a*) *Treatment of 3-cyano-2-methylazulene-1-carboxylic acid* (VI) *with acid.* A mixture of VI (100 mg) and 85% H_3PO_4 (1 ml) was heated at about 100° for 30 min. poured into H_2O and extracted with $CHCl_3$. After evaporation of $CHCl_3$. the residue was dissolved in C_6H_6 and passed through a short column of alumina. C_6H_6 was evaporated and the residue recrystallized from cyclohexane to give XIa (75 mg). violet needles; m.p. 114 ~ 5°. (Found: C. 86·06; H. 5·09; N. 8·24. Calc. for $C_{12}H_9N$: C. 86·20; H. 5·43; N. 8·38%). λ_{max} (MeOH): nm (log ε); 229 (4·31). 287 (4·69). 298 (4·72). 349 (3·81). 366 (3·69). 530 (2·50).

(b) *Decarboxylation of* VI *on heating.* A sample of VI (200 mg) was heated at 200° for 30 min then sublimed under reduced press. The sublimate (70 mg); m.p. 110 ~ 4°. was recrystallized from cyclohexane to give XIa. violet needles; m.p. 114 ~ 5°.

Treatment of XIa *or* VI *with Sulfuric Acid.* A mixture of XIa (90 mg) and 75% H_2SO_4 (1 ml) was heated at 100° for 30 min. poured into H_2O and extracted with $CHCl_3$. After evaporation of $CHCl_3$. the residue was dissolved in C_6H_6 and chromatographed on alumina. The first fraction with C_6H_6 gave blue oil (10 mg). identified as 2-methylazulene (XII)[6] IR and m.m.p. of trinitrobenzolate; m.p. 140°. The second fraction with C_6H_6 gave XIa (30 mg). The third fraction eluted with EtOAc gave pale violet crystals, recrystallized from EtOH to give 1-carbamoyl-2-methylazulene (XIb) (35 mg). pale violet plates; m.p. 225 ~ 6°. (Found: C. 77·49; H. 6·28; N. 7·30. Calc. for $C_{12}H_{11}ON$: C. 77·81; H. 5·99; N. 7·56%). λ_{max} (MeOH): nm (log ε); 240 (4·40). 281 (4·43). 312 (4·58). 465 (2.61). Similar treatment of XIb (30 mg) with 75% H_2SO_4 gave XII (10 mg). together with recovery of XIb (15 mg). Similar treatment of VI (400 mg) with 75% H_2SO_4 (4 ml) also gave a mixture of XII (70 mg). XIa (150 mg) and XIb (45 mg).

Treatment of XIb *with phosphorous oxychloride.* A mixture of XIb (100 mg) and $POCl_3$ (0·5 ml) was heated at 110° for 1 hr. poured into an ice-water and extracted with $CHCl_3$. The solvent was evaporated. and the residue dissolved in C_6H_6 and passed through an alumina column. Evaporation of the solvent from effluent gave XIa (50 mg). violet needles; m.p. 114 ~ 5°.

Ethyl 3-acetyl-2-methoxyazulene-1-carboxylate (XIIIa). To a solution of VIIb (130 mg) in a mixture of MeOH (2 ml) and ether (5 ml), an ethereal solution of CH_2N_2 (3 ml) was added and the mixture stirred for 3 hr at 0°. After evaporation of solvent, the residue was dissolved in C_6H_6 and passed through alumina. Evaporation of the solvent left an oil, which solidified on standing. Recrystallization from MeOH gave XIIIa (115 mg), orange needles; m.p. 65 ~ 6°. (Found: C, 70·28; H, 5·98. Calc. for $C_{16}H_{16}O_4$: C, 70·57; H, 5·92%). λ_{max} (MeOH) nm (log ε); 240 (4·40), 281 (4·43), 312 (4·58), 465 (2·61).

Treatment of XIIIa *with phosphoric acid.* A mixture of XIIIa (400 mg) and 100% H_3PO_4 (4 ml) was heated at 100° for 30 min, poured into ice-water and extracted with $CHCl_3$. The solvent was evaporated and the residue dissolved in cyclohexane and chromatographed on alumina. The first fraction gave reddish violet needles (66 mg); m.p. 76 ~ 7°, and the second gave reddish violet needles (56 mg); m.p. 79 ~ 80°. They were identified with 2-ethoxyazulene (XIVb)[1,7] and 2-methoxyazulene (XIVa)[1,7], respectively. IR and m.mp.

Ethyl methyl 2-methylazulene-1,3-dicarboxylate (XV). To a suspension of VIII (100 mg) in a mixture of EtOAc (4 ml) and MeOH (1 ml), an ethereal solution of CH_2N_2 (1·4 ml) was added and was stirred for 2 hr at 0°. After evaporation of solvent, the residue was dissolved in C_6H_6 and passed through alumina. The solvent was evaporated from the effluent and the residue recrystallized from EtOAc to give XV (60 mg), reddish violet needles; m.p. 92 ~ 3°. (Found: C, 70·55; H, 5·33. Calc. for $C_{16}H_{16}O_4$: C, 70·57; H, 5·92%). λ_{max} (MeOH): nm (log ε); 237 (4·56), 272 (4·44), 295 (4·63), 305 (4·73); 343 (3·96), 371 (3·99), 490 (2·95).

2-*Methylazulene* (XII) *from* VIII. (a) *by acidic treatment.* A mixture of VIII (100 mg) and 85% H_3PO_4 (1 ml) was heated at 100° for 30 min, poured into ice-water and the residue dissolved in C_6H_6 and passed through alumina. Evaporation of solvent from the effluent gave XII (40 mg), blue oil, trinitrobenzolate; m.p. 140°. Similar treatment of VIII (100 mg) with 75% H_2SO_4 (1 ml) gave XII (50 mg).

(b) *By alkaline hydrolysis followed by decarboxylation.* A mixture of VIII (370 mg), N KOH aq. (5 ml) and EtOH (6 ml) was refluxed for 4 hr. Acidification of the mixture with 6N HCl afforded 2-methylazulene-1,3-dicarboxylic acid (300 mg), pale reddish violet crystals; m.p. 250 ~ 3° (decomp.). This acid (200 mg) was heated at about 230° for 30 min and then sublimed under reduced press. The sublimates were treated on an alumina column as above, affording XII (60 mg) as a blue oil.

Ethyl 2-methylazulene-1-carboxylate (XVI). A sample of VII (1·20 g) was heated at about 200° for 30 min and then sublimed under reduced press., affording a reddish oil. This was dissolved in C_6H_6 and passed through alumina to give XVI (430 mg), reddish violet oil. (Found: C, 78·56; H, 6·53. Calc. for $C_{14}H_{14}O_2$: C, 78·48; H, 6·59%). λ_{max} (MeOH): nm (log ε); 233 (4·32), 292 (4·64), 303 (4·67), 355 (3·79), 374 (3·65), 530 (2·53). Trinitrobenzolate: Orangish red needles (from EtOH); m.p. 97 ~ 8°. (Found: C, 55·75; H, 3·85; N, 9·55. Calc. for $C_{20}H_{17}O_8N_3$: C, 56·21; H, 4·01; N, 9·83%).

2-*Methylazulene* (XII) *from* XVI. (a) *by alkaline hydrolysis followed by decarboxylation.* A mixture of XVI (210 mg), N KOH aq (6 ml) and EtOH (10 ml) was refluxed for 4 hr and acidified with 6N HCl, giving 2-methylazulene-1-carboxylic acid (165 mg), pale red crystals; m.p. 160° (decomp.). (Found: C, 77·61; H, 5·68. Calc. for $C_{12}H_{10}O_2$: C, 77·40; H, 5·41%). ν_{max}^{KBr}: 3200 ~ 2300, 1639, 932 (CO_2H).

This acid (100 mg) was heated at its m.p. to effect decarboxylation and sublimed under reduced press. The sublimates were dissolved in C_6H_6 and passed through alumina. Evaporation of solvent from effluent gave XII (50 mg), blue oil, trinitrobenzolate; m.p. 140°.

(b) *By acidic treatment.* A mixture of XVI (100 mg) and 85% H_3PO_4 (1 ml) was heated at 100° for 30 min, poured into water and extracted with $CHCl_3$. An oil obtained by evaporation of solvent was treated on an alumina column as above, affording XII (50 mg) as a blue oil.

Acknowledgements—This research has been financially supported by grants of the Japanese Ministry of Education and of Sankyo Co., Ltd.

REFERENCES

[1] T. Nozoe, K. Takase and N. Shimazaki, *Bull. Chem. Soc. Japan* **37**, 1644 (1964)

[2] T. Nozoe, *Croat. Chem. Acta* **29**, 207 (1957); *Experientia Suppl.* VII, 306 (1957); T. Nozoe, K. Takase, H. Matsumura, T. Asao, K. Kikuchi and S. Ito, *Dai-Yuki-Kagaku* (*Comprehensive Organic Chemistry*), *Vol.* **13**, pp. 178–213, 439–533. Asakura Publishing Co., Tokyo (1960)

[3] T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem. and Ind.* 1257 (1955); T. Nozoe, S. Seto, S. Matsumura and Y. Murase, *Bull. Chem. Soc. Japan* **35**, 1179 (1962)

[4] T. Nozoe, S. Seto, K. Takase, S. Matsumura and T. Nakazawa, *J. Chem. Soc. Japan* (*Nippon Kagaku Zasshi*) **86**, 346 (1965)

[5] S. Seto. *Sci. Repts. Tohoku Univ., Ser. I* **37**, 367 (1953)
[6] Pl. A. Plattner and J. Wyss, *Helv. Chim. Acta* **24**, 483 (1941); Hs. H. Gunthard and Pl. A. Plattner, *Ibid.* **32**, 284 (1949); T. Nozoe and A. Sato, to be published.
[7] T. Nozoe, S. Seto and S. Matsumura, *Bull. Chem. Soc. Japan* **35**, 1990 (1962)