*The Synthesis of Diethyl 2-Hydroxyazulene-1, 3-dicarboxylate from Troponoids and Some Reactions of 2-Hydroxyazulene Derivatives**

By Tetsuo NOZOE, Kahei TAKASE and Noboru SHIMAZAKI

(Received June 15, 1964)

It has been reported that 2-chlorotropone and 2-methoxytropone react with ethyl cyanoacetate or malononitrile, in the presence of sodium ethoxide, to give azulene derivatives.[1] On the other hand, 1-oxaazulan-2-one (2*H*-cyclohepta[b]furan-2-one) derivatives have been obtained by the reaction of these tropone derivatives and diethyl malonate or ethyl acetoacetate.[2] We have reexamined these reactions with an interest in the azulene synthesis from troponoids and found that the reaction of 2-chlorotropone or 2-methoxytropone and malonic ester affords a new azulene derivative, 2-hydroxyazulene-1, 3-dicarboxylic ester. Some reactions of this azulene will be described here.

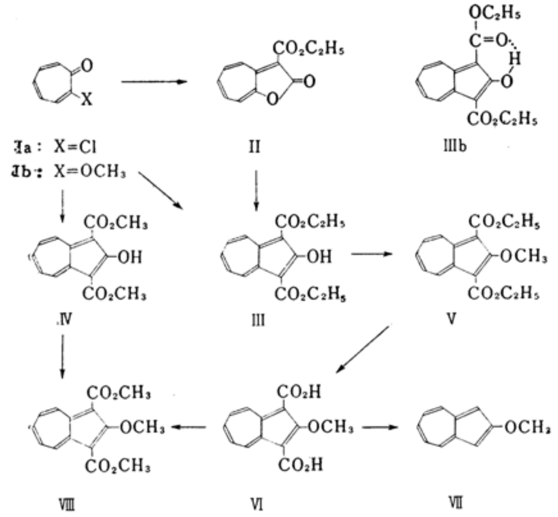
The reaction of 2-chlorotropone (Ia) and diethyl sodiomalonate in dry benzene gave 3-ethoxycarbonyl-1-oxaazulane-2-one (II), as has already been reported.[2] Furthermore, the reaction of 2-chlorotropone (Ia) or 2-methoxy

---

* Presented at the 15th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1962.

[1] T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem. & Ind.*, **1955**, 1257; T. Nozoe, S. Seto, S. Matsumura and Y. Murase, This Bulletin, **35**, 1179 (1962).

[2] S. Seto, *Sci. Repts. Tohoku Univ.*, **I**, **37**, 367 (1953).



tropone (Ib) diethyl malonate, in the presence of one or two molar equivalents of sodium ethoxide, in ethanol also gave II. However, when this reaction was carried out in ethanol by the use of an excess of sodium ethoxide, a yellowish-orange compound (III), $C_{16}H_{16}O_5$, was obtained in place of II. Further, the reaction of 2-methoxytropone with dimethyl malonate by the use of an excess of sodium methoxide in methanol afforded an orange compound (IV), $C_{14}H_{12}O_5$. These products are acidic and gave sparingly soluble sodium salts, red acetates and red *p*-nitrobenzoates. The ultraviolet absorption spectra of III and IV were similar to that of diethyl 2-aminoazulene-1, 3-dicarboxylate,[1] as Fig. 1 shows. These findings suggest that III and IV are the diethyl and dimethyl esters of 2-hydroxyazulene-1, 3-dicarboxylic acid respectively. The structures of III and IV were confirmed by the following evidence. The methylation of III with diazomethane gave diethyl 2-methoxyazulene-1, 3-dicarboxylate (V). The alkaline hydroysis of V, followed by the decarboxylation of the dicarboxylic acid (VI) thereby obtained, gave 2-methoxyazulene (VII).[3] On the other hand, the methylation of IV with diazomethane gave dimethyl 2-methoxy-azulene-1, 3-dicarboxylate (VIII), which was identical with the dimethyl ester of dicarboxylic acid (VI).

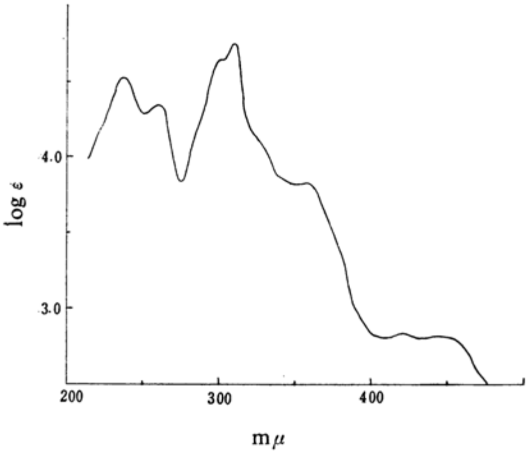


Fig. 1. The ultraviolet absorption spectrum of diethl 2-hydroxyazulene-1, 3-dicarboxylate (III) in methanol.

The above mentioned experiments show without ambiguity that the reaction of 2-chloro- (Ia) or 2-methoxytropone (Ib) and the malonic ester affords the 1-oxaazulan-2-one derivative (II) or 2-hydroxyazulene derivatives (III) according to the amount of the ethoxide used. This evidence indicates that II is a reaction intermediate in the formation of azulene (III) from troponoids (I). This was confirmed by the finding that II easily reacted which diethyl malonate, in the presence of an excess of sodium ethoxide, to give III in a good yield.

It is known[3] that the chlorine atom of diethyl 2-chloroazulene-1, 3-dicarboxylate (IX) is easily replaced by various anionoid reagents. In comparison with IX, the behavior of the methoxyl group of diethyl 2-methoxyazulene-1, 3-dicarboxylate (V) towards some anionoid reagents was examined. The methoxy group of V was replaced by the ethoxyl group when heated with sodium ethoxide, affording diethyl 2-ethoxyazulene-1, 3-dicarboxylate (X). The alkaline hydrolysis of X, followed by the decarboxylation of the dicarboxylic acid thereby obtained, gave 2-ethoxyazulene (XI).[4] When V was heated with alcoholic potassium hydroxide, the methoxy group was replaced by the ethoxyl group, along with the elimination of the ethoxycarbonyl group, to give XI directly. The methoxyl group of V was also replaced by methylamine and by hydrazine to give diethyl-2-methylaminoazulene-1,3-dicarboxylate (XII)[4] and diethyl 2-hydrazinoazulene-1, 3-dicarboxylate (XIII)[4] respectively. Contrary to the case of IX,[3] V did not react with alcoholic ammonia, dimethylamine and aniline.

The efforts to replace the hydroxyl group of III with chlorine were unsuccessful; that is, III was recovered on treatment with thionyl chloride or phosphorous oxychloride. The tosylation of III with *p*-toluenesulfonyl chloride in pyridine gave pyridinium salt (XIV) in place of the *p*-tolylsulfonyloxy derivative. The picrate of XIV was identical with that of

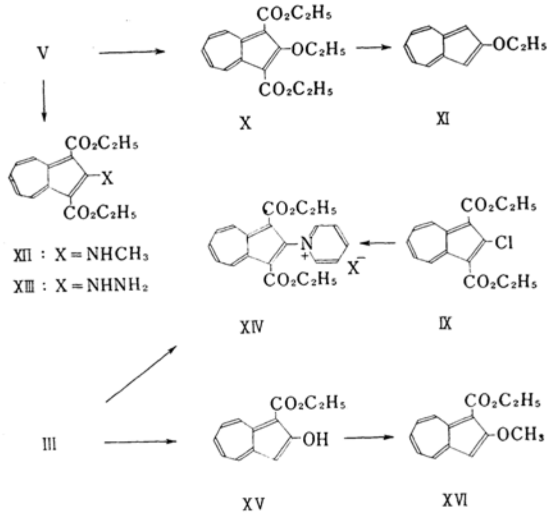
---

[3] T. Nozoe, S. Seto and S. Matsumura, This Bulletin, **35**, 1990 (1962).

[4] The compounds which have been derived from diethyl 2-chloroazulene-1, 3-dicarboxylate (IX) have been reported[3] as oil.

the compound obtained by the treatment of IX with pyridine.[5] This is because the initially formed tosylate reacted with pyridine to give XIV.

Diethyl 2-aminoazulene-1, 3-dicarboxylate was brominated easily to give the 6-bromo derivative,[1] but the bromination of III ended only in its recovery. Nitrosation and azo-coupling reaction on III also recovered the starting material.



For the synthesis of 2-hydroxyazulene, the hydrolysis of III was examined. The alkaline hydrolysis of III gave ethyl 2-hydroxyazulene-1-carboxylate (XV), which afforded an acetate and a *p*-nitrobenzoate, along with an oily substance which changed to a black substance which was insoluble organic solvents. The methylation of XV gave ethyl 2-methoxyazulene-1-carboxylate (XVI). The acid hydrolysis of III gave only an insoluble black substance. The formation of these insoluble matters is assumed to be due to the polymerization of the unstable 2-hydroxyazulene which is formed. In the infrared spectra, III shows two absorptions (1675 and 1639 cm^{-1}) and due to an ester carbonyl, while its methyl ether (IV), shows only one absorption (1984 cm^{-1}). This evidence indicates that III exists as an intramolecular hydrogen-bonded structure (IIIa), which enhances the stability of this compound.

Experimental[6]

Diethyl 2-Hydroxyazulene-1, 3-dicarboxylate (III).—*a) From 2-Chlorotropone (Ia).*—To a sodium ethoxide solution prepared from sodium (700 mg.) and absolute ethanol (50 ml.), diethyl malonate (2.4 g.) and Ia (700 mg.) were added, and the mixture was allowed to stand for 40 hr. at room temerature; the reaction mixture then turned into a gelatinous orange mass. Water was added, and the sodium salts thereby separated out were collected and dissolved in glacial acetic acid. This solution was diluted with water and extracted with chloroform. The solvent was evaporated and the residue was recrystallized from ethanol to give III (700 mg.) as orangish yellow needles, m. p. 95∼96°C.

Found: C, 66.60; H, 5.42. Calcd. for $C_{16}H_{16}O_5$: C, 66.67; H, 5.55%.

λ_{max}^{MeOH} mμ (log ε); 237 (4.53), 260 (4.34), 310 (4.75), 360 (3.83), 420 (2.84).

Acetate.—m. p. 129.5∼130°C, red needles (from ethanol).

Found: C, 65.55; H, 5.67. Calcd. for $C_{18}H_{18}O_5$: C, 65.44; H, 5.49%.

λ_{max}^{MeOH} mμ (log ε); 235 (4.53), 270 (4.40), 300 (4.69), 335 (3.80), 365 (3.89), 480 (2.83).

p-Nitrobenzoate. — m. p. 180∼181°C, red needles (from ethanol).

Found: C, 63.18; H, 4.59; N, 3.34. Calcd. for $C_{23}H_{19}O_8N$: C, 63.15; H, 4.38; N, 3.20%.

λ_{max}^{MeOH} mμ (log ε); 233 (4.59), 267 (4.53), 300 (4.81), 333 (3.91), 365 (3.93), 460 (2.88), 480 (2.91).

b) From 2-Methoxytropone (Ib). — To a sodium ethoxide solution prepared from sodium (11.6 g.) and absolute ethanol (300 ml.), diethyl malonate (48 g.) and Ib (13.6 g.) were added, and the mixture was allowed to stand for 40 hr. at room temperature. When the reaction mixture was then treated as in a), III (15.8 g.) was obtained as orangish yellow needles, m.p. 95∼96°C.

c) From 2-Ethoxycarbonyl-1-oxaazulan-2-one (II).—To a sodium ethoxide solution prepared from sodium (230 mg.) and absolute ethanol (20 ml.), diethylmalonate (800 mg.) and II (500 mg.) were added. The mixture was treated as in a), and III (430 mg.) was obtained as organish yellow needles, m. p. (95∼96°C).

Dimethyl 2-Hydroxyazulene-1, 3-dicarboxylate (IV).—To a sodium methoxide solution prepared from sodium (3.95 g.) and absolute methanol (85 ml.), dimethyl malonate (12 g.) and 2-methoxytropone (4.23 g.) were added, and the mixture was allowed to stand for 40 hr. at room temperature. The reaction mixture was treated as described in the above experiment, and IV (4.90 g.) was obtained as reddish orange needles or yellowish orange needles, m. p. 144∼145°C, after recrystallization from ethyl acetate.

Found: C, 64.87; H, 4.49. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65%.

λ_{max}^{MeOH} mμ (log ε); 238 (4.49), 260 (4.31), 310 (4.74), 356 (3.82), 450 (2.86).

Acetate. — m. p. 151∼153°C, red needles (from ethyl acetate).

Found: C, 63.71; H, 4.75. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67%.

λ_{max}^{MeOH} mμ (log ε); 233 (4.52), 268 (4.40), 300 (4.70), 335 (3.81), 350 (3.78), 363 (3.89), 410 (2.55), 475 (2.85).

p-Nitrobenzoate. — m. p. 221∼222°C, red needles (from dimethylformamide).

---

[5] T. Nozoe and M. Oyama, to be published.

[6] All melting points are uncorrected.

Found: C, 62.14; H, 3.60; N, 3.59. Calcd. for $C_{21}H_{15}O_8N$: C, 61.61; H, 3.69; N, 3.42%.

λ_{max}^{MeOH} mμ; 233, 266, 300, 363, 410, 470.

Diethyl 2-Methoxyazulene-1, 3-dicarboxylate (V).—To a suspension of III (1.50 g.), in ether (5 ml.), an ethereal solution of diazomethane (20 ml.) was added, and the mixture was stirred for 3 hr. while being cooled with ice-water. The solvent was evaporated and the oily residue was passed through a short column of amlumina with ether to give V (1.50 g.) as a red oil.

Found: C, 67.08; H, 5.98. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00%.

λ_{max}^{MeOH} mμ (log ε); 235 (4.50), 265 (4.27), 305 (4.66), 345 (3.77), 480 (2.50).

2-Methoxyazulene-1, 3-dicarboxylic Acid (VI).—To a solution of V (600 mg.) in ethanol (8 ml.), a 2 N potassium hydroxide solution (6 ml.) was added, the mixture was then heated under reflux for 4 hr. The reaction mixture was acidified with 6 N hydrochloric acid to give VI (440 mg.) as orange micro crystals, m. p. 205~208°C.

Found: C, 63.50; H, 4.04. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.09%.

2-Methoxyazulene (VII).—The heating of VI (400 mg.) at about 200°C to effect decarboxylation, followed by sublimation under reduced pressure, gave a violet sublimate. This was recrystallized from methanol to give VII (80 mg.) as violet plates, m. p. 79~80°C; VII was identified with an authentic specimen3) by admixture and by a comparison of the infrared spectrum.

Dimethyl 2-Methoxyazulene-1, 3-dicarboxylate (VIII).—*a) From Dimethyl 2-Hydroxyazulene-1,3-dicarboxylate (IV).*—To a suspension of IV (300 mg.) in ether (2 ml.), an ethereal solution of diazomethane (10 ml.) was added; the mixture was then stirred for 3 hr. while being cooled with ice-water. The residual oil obtained by the evaporation of the solvent was passed through a short column of alumina with ether and recrystallized from methanol to give VIII (280 mg.) as red needles, m. p. 69~70°C, reported3) m. p. 61~62°C.

Found: C, 65.86; H, 4.91. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15%.

λ_{max}^{MeOH} mμ (log ε); 235 (4.45), 267 (4.29), 305 (4.71), 340 (3.83), 410 (2.39), 470 (2.69).

b) From 2-Methoxyazulene-1,3-dicarboxylic Acid (VI).—To a suspension of VI (200 mg.) in ether (2 ml.), an ethereal solution of diazomethane (10 ml.) was added, and the mixture was stirred for 3 hr. while being cooled with ice-water. When the reaction mixture was treated as in a), VIII (150 mg.) was obtained as red needles, m. p. 69~70°C.

Diethyl 2-Ethoxyazulene-1, 3-dicarboxylate (X).—A mixture of V (400 mg.) and a 1 M sodium ethoxide solution (3 ml.) was heated under reflux for 3 hr. The reaction mixture was diluted with water and extracted with chloroform. The solvent was removed, and residue was passed through a short column of alumina with ether to give X (150 mg.) as red plates, m. p. 47~49°C.4)

Found: C, 69.72; H, 6.51. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37%.

2-Ethoxyazulene (XI).—*a) From Diethyl 2-Ethoxyazulene-1, 3-dicarboxylate (X).*—To a solution of X (200 mg.) in ethanol (4 ml.), a 2 N potassium hydroxide solution (2 ml.) was added, and the mixture was heated under reflux for 4 hr. The reaction mixture was acidified with 6 N hydrochloric acid to give 2-ethoxyazulene-1,3-dicarboxylic acid (150 mg.) as orange micro crystals, m. p. 200~205°C. This acid (130 mg.) was heated to effect decarboxylation and then sublimed at reduced pressure. The sublimate was passed through a short column of alumina with ether and recrystallized from ethanol to give XI (50 mg.) as violet plates, m. p. 76~77°C.4)

Found: C, 83.61; H, 6.81. Calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02%.

λ_{max}^{MeOH} mμ (log ε); 238 (4.08), 276 (4.78), 284 (4.85), 315 (3.77), 340 (3.58), 355 (3.75), 370 (3.69), 395 (2.67), 410 (2.64), 440 (2.44).

b) From Diethyl 2-Methoxyazulene-1,3-dicarboxylate (V).—To a solution of potassium hydroxide (400 ml.) in ethanol (10 ml.), V (600 mg.) was added, and the mixture was heated under reflux for 8 hr. The reaction mixture was diluted with water, neutralized with 6 N hydrochloric acid, and extracted with ether. The ether extract was chromatographed through an alumina column, and the evaporated of the solvent from the effluent left crystals, which were recrystallized from ethanol to give XI (100 mg.) as violet plates, m. p. 76~77°C.

Diethyl 2-(Methylamino)azulene-1, 3-dicarboxylate (XII).—A mixture of V (300 mg.), a 40% aqueous methylamine solution (2 ml.) and ethanol (2 ml.) was heated under reflux for 2 hr. The reaction mixture was diluted with water, neutrallized with 6 N hydrochloric acid, and extracted with chloroform. The solvent was evaporated and the residual oil was passed through a short column of alumina with ether to give XII (210 mg.) as orange plates, m. p. 48~50°C.4)

Found: C, 68.16; H, 5.97; N, 4.29. Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36; N, 4.65%.

λ_{max}^{MeOH} mμ (log ε); 230 (4.15), 255 (4.30), 280 (4.28), 324 (4.67), 410 (3.87), 460 (3.35).

Picrate.—m. p. 113~114°C, orange micro prisms (from ethanol).

Found: C, 52.32; H, 3.83; N, 10.38. Calcd. for $C_{23}H_{22}O_{11}N_4$: C, 52.07; H, 4.15; N, 10.56%.

Diethyl 2-(Hydrazino)azulene-1, 3-dicarboxylate (XIII).—To a solution of V (600 ml.) in ethanal (2 ml.), 80% hydrazine hydrate (2 ml.) was added, and the mixture was heated at 100°C for 3 min. The crystals thereby formed were collected and recrystallized from ethanol to give XIII (500 mg.) as yellow needles m. p. 108~109°C.4)

Found: C, 63.67; H, 5.86; N, 9.29. Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.00; N, 9.27%.

λ_{max}^{MeOH} mμ (log ε); 246 (4.35), 273 (4.41), 316 (4.73), 363 (3.88).

Acetate.—m. p. 129~130°C (reported3) m. p. 132°C), yellow needles (from methanol).

Found: C, 62.85; H, 5.58; N, 7.90. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%.

***N*-(1, 3-Diethoxycarbonylazulen-2-yl)pyridinium *p*-Toluenesulfonate (XIV).**—To a solution of III (600 mg.) in pyridine (3 ml.), *p*-toluenesulfonyl chloride (600 mg.) was added, and the mixture was stirred for 3 hr. while being cooled with ice-water. The mixture diluted with water and extacted with chloroform. The solvent was evaporated, and the residue was recrystallized from ethanol to give XIV (680 mg.) as red needles, m. p. 184~185°C.

Found: C, 64.46; H, 4.81; N, 2.64. Calcd. for $C_{28}H_{27}O_7NS$: C, 64.48; H, 5.22; N, 2.69%.

λ_{max}^{MeOH} mμ (log ε); 228 (4.57), 269 (4.45), 296 (4.67), 320 (3.90), 356 (4.04), 470 (3.02).

***N*-(1, 3-Diethoxycarbonylazulen-2-yl) pyridinium Picrate.**—To a solution of XIV (50 mg.) in ethanol (2 ml.), a saturated alcoholic picric acid solution (1 ml.) was added to give picrate (60 mg.) as orange micro-prisms, m. p. 212~213°C.

Found: C, 55.75; H, 3.69; N, 9.59. Calcd. for $C_{27}H_{22}O_{11}N_4$: C, 56.05; H, 3.81; N, 9.68%.

Ethyl 2-Hydroxyazulene-1-carboxylate (XV).—A mixture of III (300 mg.) and a 2 N potassium hydroxide solution (2 ml.) in ethanol (8 ml.) was heated under reflux for 3 hr. The reaction mixture was then diluted with water, acidified with 6 N hydrochloric acid, and extracted with ether. The oily material obtained by the evaporation of the solvent was dissolved in benzene and chromatographed through a silica gel column. The evaporation of the solvent from the effluent left crystals, which were recrystallized from ethanol gave XV (150 mg.) as red needles, m. p. 75~76°C.

Found: C, 72.15; H, 5.64. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%.

λ_{max}^{MeOH} mμ (log ε); 293 (4.72), 304 (4.80), 350 (3.75), 450 (2.56), 490 (2.42).

p-Nitrobenzoate.—m. p. 191~193°C, reddish violet needles (from benzene).

Found: C, 66.06; H, 4.01; N, 3.74. Calcd. for $C_{20}H_{15}O_6N$: C, 65.75; H, 4.14; N, 3.83%.

Ethyl 2-Methoxyazulene-1-carboxylate (XVI).—To a suspension of XV (50 mg.) in ether, an ethereal solution of diazomethane (1 ml.) was added, and the mixture was stirred for 3 hr. while being cooled with ice-water. The solvent was evaporated, and the residue was passed through a short column of alumina with benzene to give XVI (50 mg.) as red needles, m. p. 64~65°C.

Found: C, 72.97; H, 5.66. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13%.

A part of the expenses for the present series of experiments were defrayed by a grant-in-aid for Scientific Research from the Sankyo Co., Ltd., and from the Upjohn Co., Ltd. The infrared spectra were measured by using a Shimadzu infrared spectrophotometer IR-27 purchased by a grant-in-aid for Scientific Research from the Toyo Rayon Co., Ltd. The authors wish to express their deep gratitude for these contributions.

Department of Chemistry
Faculty of Science
Tohoku University
Katahira-cho, Sendai