The Synthesis of 7-Isopropyl-2,4-dimethylazulene (Se-Guaiazulene) from 4-Isopropyltropolone

Tetsuo Nozoe, Kahei Takase,* and Satoko Fukuda
Department of Chemistry, Faculty of Science, Tohoku University, Katahira-2-chome, Sendai

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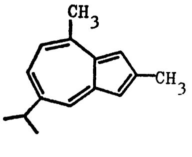
7-Isopropyl-2,4-dimethylazulene (Se-guaiazulene) (I) was synthesized from 4-isopropyl-7-methyltropolone (II), which had itself been derived from 4-isopropyltropolone. The tropolone, II, was then converted to 3-acetyl-5-isopropyl-8-methyl-2*H*-cyclohepta[*b*]furan-2-one (VI) *via* the *p*-tolylsulfonyloxytropone derivative derived from II. The application of the azulene synthesis to VI gave 3-cyano-7-isopropyl-2,4-dimethylazulene-1-carboxylic acid (VII), from which I was obtained by the removal of the carboxyl and cyano groups.

Since the discovery of the method for synthesizing azulenoid compounds from troponoid compounds,[1)] a number of 2-amino- and 2-hydroxyazulene derivatives have been synthesized directly from troponoid compounds.[2)] Moreover, as has been described in one of our previous papers,[3)] it has been found that the reaction of 4-acetyl-2*H*-cyclohepta[*b*]furan-2-one (3-acetyl-1-oxaazulan-2-one) with ethyl cyanoacetate or diethyl malonate gave 2-methylazulene derivatives. This finding suggests that 2-alkylazulene derivatives can be easily synthesized from troponoid compounds *via* 3-acyl-2*H*-cyclohepta[*b*]furan-2-ones. As an example of the application of this method to the synthesis of azulenoid compounds from troponoid compounds, we have now studied the synthesis of 7-isopropyl-2,4-dimethylazulene (Se-guaiazulene) (I), obtained from the natural sesquiterpenoid precursors, from the troponoid compound, though this azulene had already been synthesized by Šorm *et al.*[4)] from an indanone derivative.

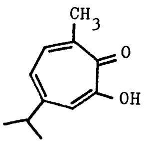
Results and Discussion

6-Isopropyl-3-methyltropolone(II)[5)] was used as the starting material for the synthesis of 7-isopropyl-2,4-dimethylazulene (**I**). This tropolone has the methyl and isopropyl substituents at the positions favorable for the synthesis of I, and was prepared from 4-isopropyltropolone in an 85% yield by means of morphorinomethylation and subsequent reductive demorphorination.[6)]

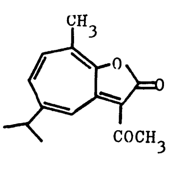
It is known that the reaction of 2-chloro- or 2-(*p*-tolylsulfonyloxy)tropones and ethyl sodioacetoacetate gives 3-acetyl-2*H*-cyclohepta[*b*]furan-2-one derivatives.[7,8)] Accordingly, the derivation of 2-(*p*-tolylsulfonyloxy)- or 2-chlorotropone derivatives from II was first examined. The treatment of II with *p*-toluenesulfonyl chloride gave a kind of *p*-tolylsulfonyloxy derivative(III).[6)] Because of the highly mobile tautomerism in tropolones,[2)] two isomeric *p*-tolylsulfonyloxy derivatives would be expected to be formed from unsymmetrical tropolone derivatives, but, in this case, only an isomer was obtained in a good yield. A similar result has been observed in the case of 3-methyltropolone, which gave only one of the isomers, 7-methyl-2-(*p*-tolylsulfonyloxy)tropone,[8)] this is thought to be due to the steric hindrance of the methyl group. Consequently, the (*p*-tolylsulfonyloxy)-tropone derivative, III, obtained here was assumed to have the structure of 4-isopropyl-7-methyl-2-(*p*-tolylsulfonyloxy)tropone. The 2-chlorotropone derivative (IV) was derived from III as follows. The treatment of III with hydrazine gave a hydrazinotropone derivative (V), which could be converted to IV by oxidative decomposition with copper sulfate in concentrated hydrochloric acid.[9)]



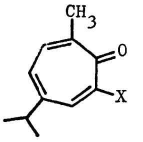
I



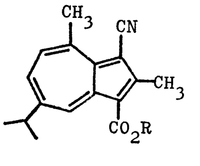
II



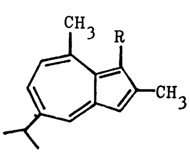
VI



III: X=OTs
IV: X=Cl
V: X=NHNH$_2$



VII: R=H
VIII: R=CH$_3$



IX: R=CN
X: R=CONH$_2$

In order to obtain the 3-acetyl-2*H*-cyclohepta[*b*]-furan-2-one derivative(VI), the reaction of III or IV with ethyl acetoacetate was examined. This reaction took place upon the heating of a mixture of III or IV and ethyl sodioacetoacetate in benzene. When ethanol was used as the solvent in place of benzene, only a resinous substance was formed, even when

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* Address correspondence to this author.

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

[2)] T. Nozoe, K. Takase, H. Matsumura, and T. Asao, *Dai-Yuki-Kagaku (Comprehensive Organic Chemistry)*, **Vol. 13**, Chapters 7, 16, 19, and 20, Asakura Publishing Co., Tokyo (1960).

[3)] T. Nozoe, K. Takase, T. Nakazawa, and S. Fukuda, *Tetrahedron*, to be published.

[4)] F. Šorm, J. Kučera, and J. Gut, *Collect. Czech. Chem. Communs.*, **16**, 184 (1951).

[5)] T. Nozoe, T. Mukai, and K. Takase, *Sci. Repts. Tohoku Univ., Ser. I*, **36**, 40 (1952).

[6)] Y. Kitahara and T. Kato, This Bulletin, **37**, 859 (1964).

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

[8)] T. Sato, *Nippon Kagaku Zasshi*, **80**, 1345 (1959).

[9)] S. Seto, *Sci. Repts. Tohoku Univ., Ser. I*, **36**, 275 (1953).

the mixture was cooled with ice water. The structure of VI was confirmed from the following evidence. Its ultraviolet absorption spectrum is similar to those of 2*H*-cyclohepta[*b*]furan-2-ones,[7] and its infrared spectrum shows absorptions at 1736 and 1639 cm^{-1}, corresponding to those of the five-membered lactone and the conjugated carbonyl group respectively. Moreover, it is known[8] that 2-(*p*-tolylsulfonyloxy)-tropones or 2-chlorotropones bearing the alkyl substituent at the 7-position gave such 2*H*-cyclohepta-[*b*]furan-2-one derivatives as are formed in a normal substitution reaction; that is, the carbanion attacked the 2-position of the tropone nucleus to give substitution products.

The derivation of the azulene derivative(VII) from VI took place when VI was treated with ethyl cyanoacetate in a way similar to that described in the formation of 2-methylazulene derivatives from 3-acetyl-2*H*-cyclohepta[*b*]furan-2-one.[3] The reaction of VI with diethyl malonate, however, ended in the recovery of the original substance. The structure of VII was established as 3-cyano-7-isopropyl-2,4-dimethylazulene-1-carboxylic acid on the basis of the consideration that the reaction mechanism was analogous to that of the formation of 2-methylazulene derivatives from 3-acetyl-2*H*-cyclohepta[*b*]furan-2-one,[3] as well as on the basis of the following evidence. This compound, VII, is an acidic substance and gave a methyl ester (VIII) upon methylation with diazomethane. The ultraviolet and visible absorption spectra of VIII are consistent with those of azulene derivatives. The infrared spectrum of VII shows absorptions at 3200—2500, at 1647 and 940, and at 2212 cm^{-1}, corresponding to those of the carboxyl and cyano groups respectively, and that of VIII shows absorptions at 1684 and 2217 cm^{-1}, corresponding to those of the conjugated ester and cyano groups respectively.

The decarboxylation of VII proceeded effectively when it was heated in phosphoric acid at about 100°C; this gave 3-cyano-7-isopropyl-2,4-dimethylazulene(IX). The infrared spectrum of IX shows the absorption at 2208 cm^{-1} corresponding to the cyano group. Upon further heating in concentrated sulfuric acid or 100% phosphoric acid at about 130°C for a long period of time, IX gave 7-isopropyl-2,4-dimethylazulene(I), which was identified with an authentic specimen[10] on the basis of a comparison of the ultraviolet and visible absorption spectra and the infrared spectra, and by an admixture of the trinitrobenzolates. On the other hand, when IX was heated in concentrated sulfuric acid at about 100°C, the cyano group could not be eliminated; rather, it was partially hydrolyzed to give a carbamoylazulene derivative (X), which also gave I upon heating in 100% phosphoric acid at about 130°C.

Since 4-isopropyltropolone has already been synthesized,[11] the results described above indicate the total synthesis of 7-isopropyl-2,4-dimethylazulene (Se-guaiazulene). The yield of I from 4-isopropyltropolone was 20%. In this case, there is no such trouble as in the thermal isomerization[4] between S-guaiazulene and Se-guaiazulene at high temperatures, since the reaction took place under rather mild reaction conditions.

Experimental

All the melting points are uncorrected. The ultraviolet and visible absorption spectra were measured on a Hitachi EPS-3 spectrophotometer, and the infrared spectra were recorded on a Shimadzu IR-27 infracord apparatus.

*4-Isopropyl-7-methyl-2-(*p*-tolylsulfonyloxy)tropone (III).* To a stirred solution of 6-isopropyl-3-methyltropolone(II) (4.07 g) in pyridine (8 m*l*), *p*-toluenesulfonyl chloride was added (6.5 g) under cooling with ice water. After it had been stirred for an additional 3 hr, the mixture was allowed to stand overnight in a refrigerator. Water was added to this mixture, and the crystals thereby formed were collected. Yield, 6.80 g; mp 76—78°C. Recrystallization from ethanol gave III (5.41 g) as colorless prisms; mp 85—86°C. The melting point previously reported was 86—87°C.[6]

2-Hydrazino-4-isopropyl-7-methyltropone (V). A mixture of III (1.65 g) and a 50% ethanolic hydrazine solution (10 m*l*) was refluxed for 3 hr. The solvent was evaporated, the residue was triturated with water, and the crystals thereby formed were collected by filtration. Recrystallization from ether gave V (450 mg) as yellow needles; mp 80—81°C.

Found: C, 68.57; H, 8.39; N, 14.40%. Calcd for $C_{11}H_{16}ON_2$: C, 68.72; H, 8.39; N, 14.57%.

2-Chloro-4-isopropyl-7-methyltropone (IV). To a solution of V (420 mg) in concentrated hydrochloric acid (10 m*l*) being heated at about 100°C, a 30% aqueous copper sulfate solution (10 m*l*) was added in one lot. After being heated for 5 min, the mixture was cooled to room temperature, diluted with water, and extracted with chloroform. The subsequent evaporation of the solvent left a brown, oily material which was then dissolved in benzene and passed through a short column of alumina. The evaporation of the solvent from the effluent gave IV (315 mg) as a pale yellow oil.

Found: C, 67.15; H, 6.62%. Calcd for $C_{11}H_{13}OCl$: C, 67.17; H, 6.66%.

*3-Acetyl-5-isopropyl-8-methyl-2*H*-cyclohepta[*b*]furan-2-one (VI).* *a) From III:* Ethyl acetoacetate (4.20 g) was dissolved in a 1 M ethanolic sodium ethoxide solution (32 m*l*), and the solvent was evaporated to dryness, giving ethyl sodioacetoacetate. To this dry benzene (30 m*l*) and III (5.23 g) were added, and then the mixture was refluxed for 3 hr. The reaction mixture was shaken with water, and the organic layer was dried over anhydrous sodium sulfate. The evaporation of the solvent left a mixture of crystals and an oily material, from which VI (990 mg) was isolated, mp 141—143°C, by the addition of ether, followed by filtration. The ether-soluble part was chromatographed on an alumina column and eluted with ether to give further crops of VI (100 mg), mp 140—143°C. Recrystallization from ethanol afforded yellow needles; mp 144—145°C.

Found: C, 74.04; H, 6.63%. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%. UV (MeOH): λ_{max} nm (log ε); 227 (4.42), 254 (4.12), 285 (4.41), 420 (4.40).

The aqueous layer was acidified with 6 N hydrochloric acid and extracted with benzene. The benzene extract

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[10] Se-Guaiazulene prepared from guiene was supplied by Dr. Yoshiharu Matsubara of the Nippon Terpene Co., Ltd., for which we thank him.

[11] T. Nozoe, S. Seto, K. Kikuchi, T. Mukai, S. Matsumoto, and M. Murase, *Proc. Japan Acad.*, **26** (7), 43 (1950); T. Nozoe, S. Seto, K. Kikuchi, and H. Takeda, *ibid.*, **27**, 146 (1951); J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, **1951**, 695.

was shaken with a 2 N sodium hydroxide solution (5 m*l*), to give the sodium salt of II (860 mg) as pale yellow scales.

b) From IV: To dried ethyl sodioacetoacetate prepared from ethyl acetoacetate (340 mg) and 1 M sodium ethoxide (2.6 m*l*), dry benzene (8 m*l*) and IV (350 mg) was added; the mixture was then treated as has been described above. The crude crystals (120 mg); mp 137—139°C, were recrystallized from ethanol to give VI as yellow needles (mp 144—145°C).

3-Cyano-7-isopropyl-2,4-dimethylazulene-1-carboxylic Acid (VII). To a solution of VI (450 mg) and ethyl cyanoacetate (450 mg) in anhydrous ethanol (5 m*l*), a 1 M sodium ethoxide solution (8 m*l*) was added; the mixture was stirred for 3 hr and then allowed to stand overnight at room temperature. The reaction mixture was dissolved in water and shaken with chloroform. The aqueous layer was acidified with 6 N hydrochloric acid, the product was extracted with chloroform, and the chloroform extract was shaken with a sodium hydrogen carbonate solution. The carbonate layer was acidified with 6 N hydrochloric acid to give VII (410 mg) as pale red crystals; mp 155°C (decomp.). Recrystallization from dioxane afforded pale red micro-needles; mp 157°C (decomp.).

Found: C, 76.71; H, 6.35; N, 5.38%. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24%.

Methyl 3-Cyano-7-isopropyl-2,4-dimethylazulene-1-carboxylate (VIII). To a suspension of VII (130 mg) in ethyl acetate (5 m*l*), an ethereal solution of diazomethane (2 m*l*) was added; the mixture was then stirred for 5 hr under cooling with ice water. The solvent was evaporated, the residue was dissolved in benzene, and the benzene solution was passed through a short column of alumina. The evaporation of the solvent from the effluent left red crystals (130 mg), mp 102—106°C, which were subsequently recrystallized from methanol to give VIII as reddish-violet micro-needles; mp 108-109°C.

Found: C, 76.93; H, 6.66; N, 4.74%. Calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98%. UV (MeOH): λ_{max} nm (log ε); 243 (4.51), 270 (4.05), 296 (4.40), 308 (4.52), 344 (3.86), 373 (3.64), 500 (2.77).

3-Cyano-7-isopropyl-2,4-dimethylazulene (IX). A mixture of VII (270 mg) and 100% phosphoric acid (2 m*l*) was heated at about 100°C for 15 min, then diluted with water and extracted with chloroform. The solvent was evaporated, the residue was dissolved in benzene, and the benzene solution was passed through a short column of alumina. The subsequent evaporation of the solvent from the effluent gave crude IX (207 mg), mp 62—63°C. Recrystallization from ethanol afforded reddish-violet needles; mp 65—66°C.

Found: C, 86.07; H, 7.94; N, 6.06%. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27%. UV (MeOH): λ_{max} nm (log ε); 223 (4.20), 241 (4.30), 295 (4.66), 301 (4.73), 313 (4.40), 354 (4.03), 371 (3.98), 530 (2.75).

3-Carbamoyl-7-isopropyl-2,4-dimethylazulene (X). A mixture of IX (65 mg) and concentrated sulfuric acid (1 m*l*) was heated at 100°C for an hour, then diluted with water and extracted with chloroform. The chloroform solution was chromatographed on an alumina column and eluted with the same solvent. The subsequent evaporation of the solvent from the effluent left pale violet crystals (60 mg); mp 184—185°C. Recrystallization from chloroform gave X as violet plates; mp 186—187°C.

Found: C, 79.49; H, 7.87; N, 5.74%. Calcd for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80%. UV (MeOH): λ_{max} nm (log ε); 244 (4.37), 291 (4.70), 335 (3.64), 348 (3.77), 555 (2.66). IR (KBr); 3425, 3289, 3165, 1642 cm^{-1}.

7-Isopropyl-2,4-dimethylazulene (I). *a) From IX*: A mixture of IX (100 mg) and 100% phosphoric acid (1 m*l*) was heated at 120—130°C for 6 hr, then diluted with water and extracted with benzene. The benzene solution was passed through a short column of alumina; the subsequent evaporation of the solvent from the effluent left a blue-violet oil (80 mg).

Found: C, 90.62; H, 9.17%. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15%. UV (MeOH): λ_{max} nm (log ε); 245 (4.43), 280 (4.76), 290 (4.82), 308 (4.00), 334 (3.51), 348 (3.77), 362 (2.96), 565 (2.58), 580 (2.53), 606 sh (2.52), 665 sh (2.12).

The infrared spectrum and the ultraviolet and visible absorption spectra of this oil are identical with those of 7-isopropyl-2,4-dimethylazulene (I).9)

Trinitrobenzolate: Violet micro-needles (from ethanol); mp 154—154.5°C. The melting point previously reported4) was 152°C.

Found: C, 61.37; H, 5.36; N, 10.02%. Calcd for $C_{21}H_{21}O_6N_3$: C, 61.31; H, 5.15; N, 10.21%.

Picrate: Reddish violet micro-needles (from ethanol); mp 116—117°C. The melting point previously reported4) was 110°C.

Found: C, 59.32; H, 4.95; N, 9.69%. Calcd for $C_{21}H_{21}O_7O_3$: C, 59.01; H, 4.95; N, 9.83%.

A similar treatment of IX (100 mg) in 75% sulfuric acid also gave I (70 mg).

b) From X. A mixture of X (50 mg) and 100% phosphoric acid (1 m*l*) was heated at 130—140°C for 2 hr and then treated in a manner similar to that described in a) to give I (37 mg).

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