September, 1991] © 1991 *The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn.*, ***64***, *2865—2867 (1991)* 2865

An Efficient Preparation of 3,3′-Methylenebisazulenes[1)]

Yoshiharu Matsubara, Masanori Morita,[†] Shin-ichi Takekuma,* Zhendong Zhao,
Hiroshi Yamamoto,*,[††] and Tetsuo Nozoe[†††]
Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University,
Kowakae, Higashi-Osaka 577
[†] Kinki University Co-Operative Laboratories Center, Kowakae, Higashi-Osaka 577
[††] Department of Chemistry, Okayama University, Okayama 700
[†††] Tokyo Research Laboratories, Takasago Corporation, Kamata,
Ohta-ku, Tokyo 144

(Received May 1, 1991)

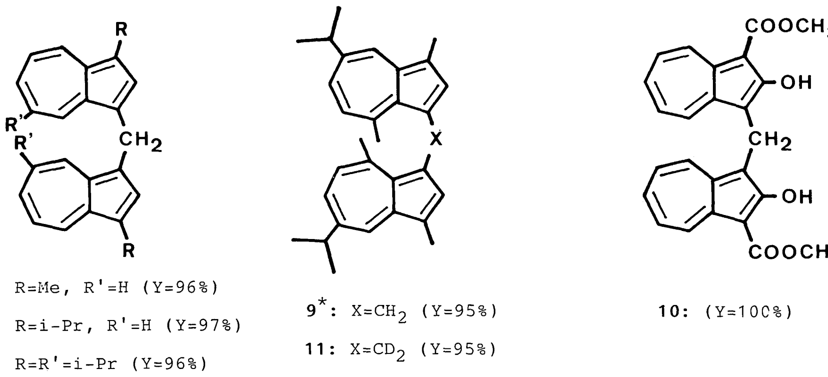
Synopsis. Various 3,3′-methylenebisazulenes were prepared in high yields upon treatment of 1-substituted azulenes with a solution of 0.1—0.2 wt% paraformaldehyde in glacial acetic acid at 25 °C for 1 h. Thus, 1-methyl-, 1-isopropyl-, 1,5-diisopropylazulene, guaiazulene, and methyl 2-hydroxy-1-azulenecarboxylate readily provided the corresponding 3,3′-methylenebisazulenes, respectively. Acetic acid which had been refluxed with 5 wt% $KMnO_4$ for 2 h and then distilled according to a purification method was found to contain 0.1—0.2 wt% formaldehyde and exert the same 3,3′-methylenebisazulene formation. 3,3′-Dideuteriomethylenebis(guaiazulene) was obtained by employing the similar distillate from acetic acid-d_4.

For the past several years, we have undertaken a systematic investigation on autoxidation of various azulenes in detail.[2)] We found that naturally originating 3,3′-methylenebis(guaiazulene) (**9**)[3)] and synthetic 3,3′-methylenebis(1,5-diisopropylazulene) (**8**), for example, gave various kinds of azulenylbenzofulvenes by autoxidation.[4,5)] Oxidation of **9** with peracetic acid has also been conducted recently, and a wide variety of azulenylbenzofulvenes and their precursors were isolated.[6)] Our interest in the physicochemical properties and biological activity of azulenylbenzofulvenes in general necessitated establishing an efficient preparative method of various 3,3′-methylenebisazulenes which in turn are expected to serve as effective intermediates for synthesis of the desired fulvenes. We wish to describe herein our results.

We employed the following 1-substituted azulenes as model substrates: 1-methylazulene (**1**), 1-isopropylazulene (**2**), 1,5-diisopropylazulene (**3**), guaiazulene (**4**), and methyl 2-hydroxy-1-azulenecarboxylate (**5**). When these compounds were treated, at 25 °C for 1 h, with a freshly prepared glacial acetic acid solution containing 0.1—0.2 wt% paraformaldehyde, we found that the corresponding 3,3′-methylenebisazulenes **6**,[7)] **7**,[8)] **8**,[5)] **9**,[9)] and **10** were best obtained (see Chart 1). Structure of the previously unknown product **10** was established on the basis of spectroscopic data (see the Experimental section). Compounds **6**—**9** had been obtained either during an attempted preparation of 3-hydroxymethylazulene derivatives or by autoxidation of the monomeric azulenes; in all cases the yields were moderate to low.

During this investigation we attempted to purify acetic acid by refluxing with 5 wt% potassium permanganate for 2 h, followed by distillation according to a standard procedure.[10)] On dissolving azulenes **1**—**5** in the above acetic acid distillate and allowing to stand at 25 °C for 1 h, we obtained 3,3′-methylenebisazulenes **6**—**10** in almost the same yields as in the case of using the paraformaldehyde solution. The analysis of the acetic acid distillate by the use of GLC and GC-MS spectrometry as well as chemical reaction with *p*-toluenesulfonohydrazide[11)] revealed that it contained 0.1—0.2 wt% formaldehyde.[12)] Commercially unavailable formaldehyde-d_2 (0.1—0.2 wt%) can therefore be prepared by the above distillation procedure with acetic acid-d_4. 3,3′-Dideuteriomethylenebis(guaiazulene) (**11**) was thus efficiently prepared in 95% yield by the present method.

The most plausible reaction pathways for the formation of formaldehyde liberated from acetic acid by the purification method[10)] and of 3,3′-methylenebisazulenes

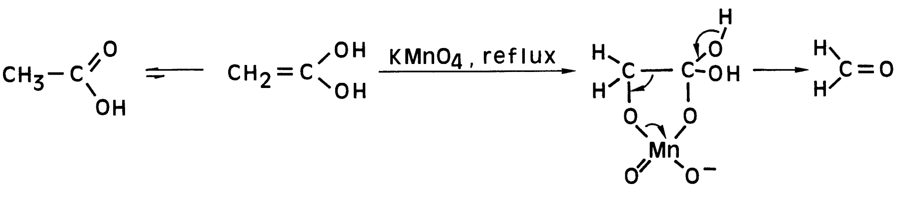


6*: R=Me, R'=H (Y=96%)
7*: R=i-Pr, R'=H (Y=97%)
8*: R=R'=i-Pr (Y=96%)

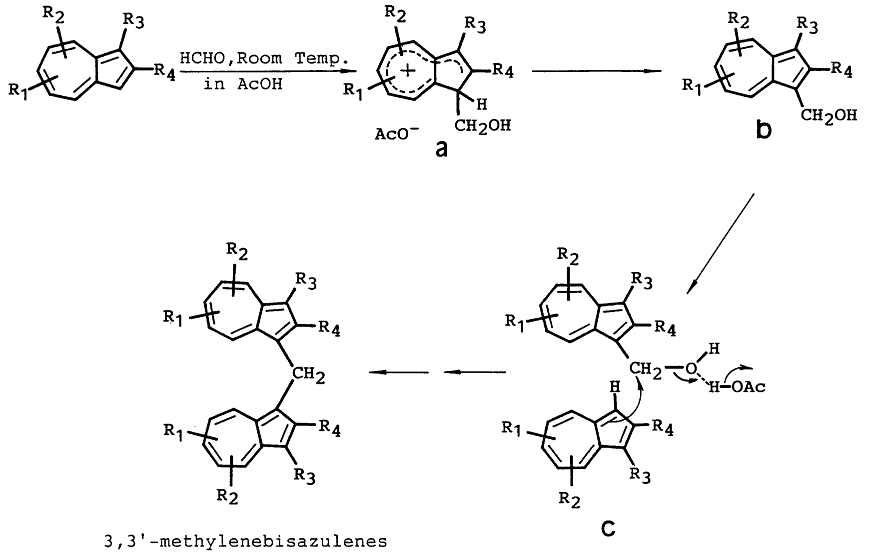
9*: X=CH$_2$ (Y=95%)
11: X=CD$_2$ (Y=95%)

10: (Y=100%)

Chart 1. Structures and yields/% of 3,3′-methylenebisazulenes **6**—**11**.
* Previously known compound.



Scheme 1. A possible reaction pathway for the formation of formaldehyde present in the acetic acid distillate.



Scheme 2. A possible reaction pathway for the formation of 3,3′-methylenebisazulenes **6**—**10** from azulenes **1-5** and formaldehyde in acetic acid.

6—**10** from azulenes **1**—**5** are illustrated in Schemes 1 and 2, respectively. Extension of the present method to azulene itself and some other substrates is under intensive investigation.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and are uncorrected. GLC analysis of the acetic acid distillate was conducted with a YANACO G2800 gas liquid chromatograph system equipped with a HFID (hydrogen flame ionization detector) and a PEG 20M glass-capillary column (ϕ 0.28 mm×20 m, column temp 40—180 °C/2 °C-min^{-1}).

The UV and IR spectra were taken on a Hitachi 323 spectrophotometer and a JASCO IR-A-202 Grating spectrometer, respectively. Mass spectra were taken on a JEOL JMS-HX100 (with a JEOL JMA-DA5000 mass data system) high-resolution instrument and are given in terms of m/z (rel intensity) compared with the base peak. The ^{1}H NMR spectra were recorded in CDCl$_3$ with a JEOL FX-200 (200 MHz) cryospectrometer at 27 °C. The assignments of all singals were made by employing a first-order analysis with the aid of decoupling technique and were confirmed by a computer-assisted simulation analysis.

Preparation of 3,3′-Methylenebisazulenes (6—11). To a solution of paraformaldehyde (0.1—0.2 wt%) in acetic acid (12 ml) was added 100 mg each of 1-methylazulene (**1**), 1-isopropylazulene (**2**), 1,5-diisopropylazulene (**3**), guaiazulene (**4**), and methyl 2-hydroxy-1-azulenecarboxylate (**5**).[13] The mixture was stirred at 25 °C for 1 h under nitrogen. The precipitated 3,3′-methylenebisazulenes **6**—**10** were filtered off, washed carefully with water, and dried in a vacuum desiccator, affording pure products **6**—**10** (70—80% yields). Each of the filtrates was carefully neutralized with aq Na$_2$CO$_3$ and extracted with ether (3×30 ml). The extract was washed with water, dried (Na$_2$SO$_4$), and evaporated in vacuo, giving additional pure 3,3′-methylenebisazulenes **6**—**10** (20—25% yields). Compounds **6**—**10** were also obtained from **1**—**5** in almost the same yields by the treatment with acetic acid distillate (see later).

Previously Known Compounds: Compounds **6** (96% yield),[7] **7** (97%),[8] **8** (96%),[5] and **9** (95%)[9] were identified either by comparison of their melting points, UV-vis, ^{1}H NMR, and EI MS spectral data with those of authentic 3,3′-methylenebisazulenes.

Dimethyl 3,3′-Methylenebis(2-hydroxy-1-azulenecarboxylate) (10): Reddish orange prisms; 103 mg (100%); mp>300 °C; IR (KBr) 3650—3250 (OH) and 1640 cm^{-1} (C=O); ^{1}H NMR δ=4.03 (6H, s, COOCH$_3$-1,1′), 4.53 (2H, s, CH$_2$-3), 7.37 (2H, dddd, J=11.0, 10.0, 2.0, 0.3 Hz, H-5,5′), 7.37 (2H, dddd, J=11.0, 9.0, 2.0, 0.5 Hz, H-7,7′), 7.46 (2H, dddd, J=10.0, 9.0, 2.0, 1.5 Hz, H-6,6′), 8.64 (2H, ddd, J=11.0, 1.5, 0.5 Hz, H-4,4′), 8.84 (2H, ddd, J=11.0, 2.0, 0.3 Hz, H-8,8′), and 11.10

(2H, s, OH-2,2′); EI MS *m*/*z* 416 (M$^+$; 47%), 384 (5), 352 (100), 323 (23), 307 (6), 296 (7), 268 (7), 239 (22), 215 (34), 202 (7), 183 (52), 176 (34), 170 (30), 156 (5), 142 (5), 127 (5), 119 (18), 114 (7), and 106 (4). Found: *m*/*z* 416.1243. Calcd for $C_{25}H_{20}O_6$: M, 416.1260.

3,3-Dideuteriomethylenebis(guaiazulene) (11). This was prepared from **4** upon treatment, at 25 °C for 1 h, with the distillate obtained from acetic acid-d_4 (see below): Dark blue prisms; 98 mg (95%); mp 186 °C; ^{1}H NMR δ=1.34 (12H, d, J=7.0 Hz, *i*-Pr-7,7′), 2.52 (6H, s, Me-1,1′), 2.92 (6H, s, Me-4,4′), 3.00 (2H, sept, J=7.0 Hz, Me_2CH-7,7′), 6.77 (2H, d, J=11.0 Hz, H-5,5′), 7.08 (2H, s, H-2,2′), 7.22 (2H, dd, J=11.0, 2.0 Hz, H-6,6′), and 8.03 (2H, d, J=2.0 Hz, H-8,8′); EI MS *m*/*z* 410 (M$^+$; 52%), 395 (11), 367 (3), 212 (38), 205 (10), 198 (100), 183 (27), and 167 (5). Found: *m*/*z* 410.2940. Calcd for $C_{31}H_{34}D_2$: M, 410.2943.

Preparation of Acetic Acid Distillate. The acetic acid distillate was obtained according to the general distillation procedures of acetic acid.[10] Namely, acetic acid (1.0 kg) was refluxed with 5 wt% potassium permanganate (50 g) for 2 h and then fractionally distilled (bp 117—118 °C). Similarly, acetic acid-d_4 (100 g) was refluxed with 5 wt% potassium permanganate (5 g) for 2 h and distilled (bp 114—115 °C).

We are grateful to Professor Masafumi Yasunami (Tohoku University) for a generous gift of 1-methyl-, 1-isopropyl-, and 1,5-diisopropylazulene and to Konan Kako Co. (Osaka) for guaiazulene.

References

1) A part of the results were presented at Japan Kokai Tokkyo Koho, Y. Matsubara and S. Takekuma, JP 8860946 A2, JP 6360946 (1988); *Chem. Abstr.*, **109**, 92354p (1988).

2) S. Takekuma, Y. Matsubara, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **61**, 475 (1988), and references cited therein.

3) M. K. W. Li and P. J. Scheuer, *Tetrahedron Lett.*, **25**, 587 (1984).

4) Y. Matsubara, S. Takekuma, K. Ibata, H. Yamamoto, and T. Nozoe, *Nippon Kagaku Kaishi,* **1987**, 1555.

5) S. Takekuma, Y. Matsubara, S. Matsui, H. Yamamoto, and T. Nozoe, *Nippon Kagaku Kaishi,* **1988**, 923.

6) S. Matsui, Y. Matsubara, S. Takekuma, H. Yamamoto, and T. Nozoe, *Nippon Kagaku Kaishi,* **1989**, 838.

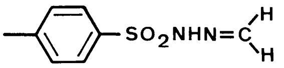
7) K. Hafner and W. Senf, *Justus Liebigs Ann. Chem.*, **656**, 34 (1962); S. Takekuma, Y. Matsubara, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **60**, 3721 (1987).

8) Y. Matsubara, S. Matsui, S. Takekuma, H. Yamamoto, and T. Nozoe, *Yukagaku,* **38**, 471 (1989).

9) W. Treibs, *Chem. Ber.*, **90**, 761 (1957); Y. Matsubara, S. Takekuma, K. Yokoi, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **60**, 1415 (1987).

10) J. A. Riddick and E. E. Toops, Jr., "Organic Solvents," 2nd ed, Interscience, New York (1955), pp. 390—392.

11) Hydrazone **A** was obtained by the reaction of the acetic acid distillate with *p*-toluenesulfonohydrazide according to the procedures of Blankley et al. for preparation of glyoxylic acid *p*-toluenesulfonohydrazone: C. J. Blankley, F. J. Sauter, and H. O. House, *Org. Synth.*, Coll. Vol. V, 258 (1973). Hydrazone **A**: EI MS *m*/*z* 198 (M$^+$, 100%). Found: *m*/*z* 198.0444. Calcd for $C_8H_{10}O_2N_2S$: M, 198.0462.



A

12) To our knowledge, this is the first report to find out the presence and concentration of formaldehyde in the distillate. Therefore care must be taken in the use of this purification method, particularly when the acetic acid distillate is employed for a formaldehyde-sensitive substrate.

13) T. Nozoe, S. Seto, K. Takase, S. Matsumura, and T. Nakazawa, *Nippon Kagaku Kaishi,* **1965**, 346.