Modified Preparation of Sodium Guaiazulenide and Reaction of the Reagent with 3-Formylguaiazulene

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(Received November 10, 1978)

As a modification for facilitating small-scale reactions, sodium *N*-methylanilinide was prepared from sodium hydride and *N*-methylaniline instead of by the usual method from sodium, *N*-methylaniline, and naphthalene (as assistant). Sodium *N*-methylanilinide, made by this procedure, was successively converted to sodium guaiazulenide, the formation of which was checked by tracing known reactions. The reaction of the reagent with 3-formylguaiazulene was also studied, and found to yield 4-substituted 2-formyl-1,4-dihydroguaiazulene and 6-substituted 2-formyl-3,6-dihydroguaiazulene. In this case, nucleophilic addition of guaiazulenide anion occured not at the carbonyl group but at the 6- and 8-positions of the seven-membered ring of formylguaiazulene, accompanied by formyl group and hydrogen migrations.

In the previous paper we reported that 1-[2-(4-azulenyl)vinyl]azulene and 1-[2-(1-azulenyl)vinyl]-azulene derivatives were formed by thermolysis of 3-formylguaiazulene (**9**).[1] One of the skeletal hydrocarbons, 1-[2-(1-azulenyl)vinyl]azulene, has already been synthesized from azulenylmethylphosphonium salt and formylazulene.[2]

As a means of access to hitherto unknown 1-[2-(4-azulenyl)vinyl]azulene, the reaction of sodium guaiazulenide (**1**) with **9** was studied, since the reaction was thought, if followed by dehydration of the resulting alcohol, to be a possible route to 1-[2-(7-isopropyl-1-methyl-4-azulenyl)vinyl]guaiazulene.[3,4]

Sodium *N*-methylanilinide, used for preparation of **1**,[3] is usually made from sodium wire and *N*-methylaniline, using naphthalene as an assistant.[5] However, the procedure was not satisfactory for our purpose of small-scale experiments, due to the technical problem of how to make such fine wires as would allow a fairly smooth reaction with a millimol-order quantity of *N*-methylaniline. For this reason, the sodium hydride available as fine powder (as oil mull) was used instead of sodium metal, without the aid of the assistant, for the preparation of **1** in this paper.

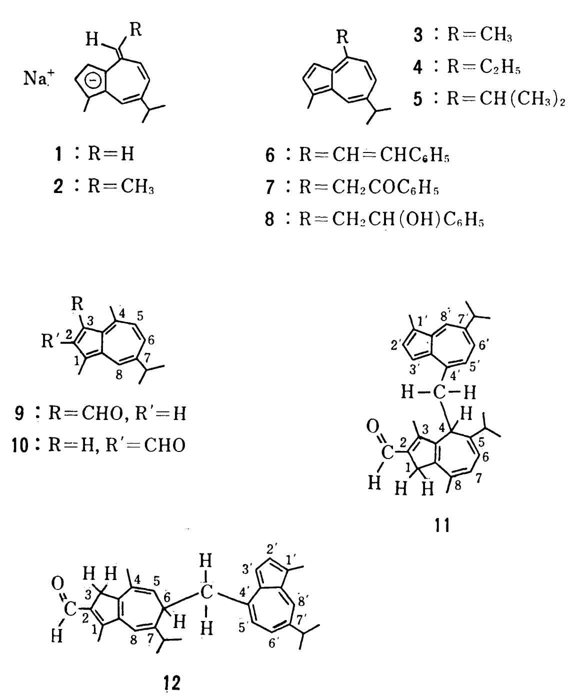

Fig. 1.

Results and Discussion

Sodium hydride and *N*-methylaniline reacted smoothly with evolution of hydrogen when a suspension in THF was heated, to form a pale yellow solution of sodium *N*-methylanilinide, which was subsequently changed into **1** by addition of **3**. The formation of **1** was apparent from the immediate color change of **3** from blue to brown, but was also proved by the reaction of **1** with methyl iodide to afford 4-ethyl-7-isopropyl-1-methylazulene (**4**),[3] though the yield (27.6%) was slightly lower than that (35%) in Ref. 3.

In this reaction, a by-product $C_{17}H_{22}$ (MS) was also found in a 3.4% yield. This compound is thought to be 4,7-diisopropyl-1-methylazulene (**5**) formed from **2**, because an alternative structure, 1,4-diethyl-7-isopropylazulene, is impossible owing to the lack of 1-ethyl-7-isopropyl-4-methylazulene in the reaction products.

For an additional proof of **1**, the reactivity toward formyl groups was examined by reaction of **1** with benzaldehyde.[4] The same products **6**, **7**, and **8** were isolated as in Ref. 4 and identified by UV, IR, NMR, and mass, but the yield of dehydration product **6** was prominent in our case (in THF) in contrast to the mere trace of **6** in Ref. 4 (in benzene).[7]

Reaction of **1** with **9** yielded two products: 1,4-dihydro-5-isopropyl-4-(7-isopropyl-1-methyl-4-azulenyl)-methyl-3,8-dimethyl-2-azulenecarbaldehyde (**11**) and 3,6-dihydro-7-isopropyl-6-(7-isopropyl-1-methyl-4-azulenyl)methyl-1,4-dimethyl-2-azulenecarbaldehyde (**12**), in 25.6 and 19.6% yields, respectively. Contrary to our expectation that addition of **1** would occur at carbonyl group, as in benzaldehyde, the nucleophilic addition of methylene carbanion of **1** took place at 6- and 8-positions of **9**, followed by migrations of the formyl group and hydrogen.

Rearrangement of the formyl group was shown by dehydrogenation of **11** and **12** with chloranil or *o*-chloranil, yielding 2-formylguaiazulene (**10**). The substitution mode of five-membered ring was also indicated by the NMR of **11** and **12**, in which the

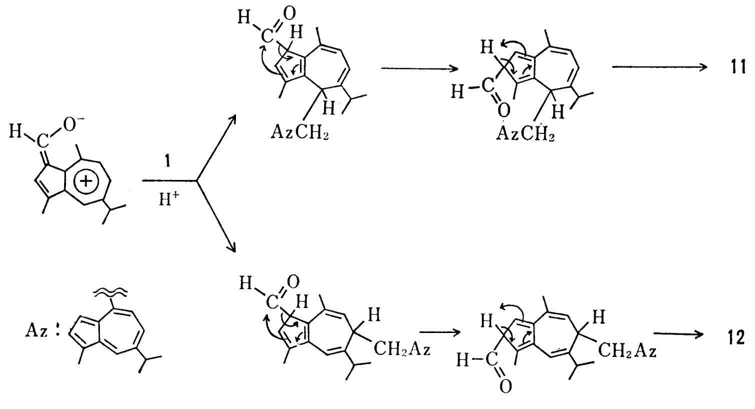

Fig. 2.

coupling constant 2.2 Hz (or 2.3 Hz) of 3-methyl and 1-methylene protons (or 1-methyl and 3-methylene protons) is in good agreement with 1.9 Hz of those of azulenium cations.[8,9)]

In the NMR of **11**, moreover, 6-, 7-, and 4-hydrogens appeared as doublet (6.06), double quartet (6.44) (quartet is due to allyl coupling with 8-methyl protons), and double doublet signals (3.96 ppm), respectively, in accordance with the 4-substituted 1,4-dihydroguaiazulene structure. Also, the 6-substituted 3,6-dihydroguaiazulene structure of **12** was supported by the appearance of singlet (6.33), double quartet (5.34), and doublet signals (2.84) for 8- and 5-hydrogens and for the 6-methylene group, though splitting of 6-hydrogen signals were not clear owing to the overlapping with 3-methylene signals. Furthermore, all of these assignments were ascertained by double resonance spectra.

Addition of a nucleophilic strong base at 4- and 6-positions of the azulene nucleus was already observed by NMR spectroscopy.[10)] In the present reaction, 4- (or 8-) and 6-positions of **9** would become reactive toward nucleophiles owing to the contribution of the mesomeric form of a tropylium cation type, in which the formyl group plays an important role. This may cause an exclusive addition of the methylene carbanion of **1** to the seven-membered ring and thus would explain the difference between this reaction and that with benzaldehyde. This conclusion is supported by the fact that the seven-membered ring of diethyl 1,3-azulenedicarboxylate and its derivatives is activated enough to react with Grignard reagents.[11)]

On the other hand, conjugation of the formyl group with double bonds of dihydroguaiazulene is only attainable in **11** and **12** in a successive reaction course, and this might act as a driving-force of subsequent migrations of the formyl group and hydrogen.

Experimental

NMR spectra were taken in $CDCl_3$ with TMS as internal standard on a JEOL MH-100 spectrometer (100 MHz), or on a JEOL FX-90Q instrument (90 MHz) for spin-decoupling experiments. Mass spectra (MS) were obtained at 70 eV with a JEOL JMS-O1SG spectrometer, or at 24 eV with a JEOL-D300 instrument for GC-MS. UV spectra were recorded in cyclohexane on a Hitachi 624 digital spectrometer with a Hitachi 056 recorder, and IR spectra (liquids as films; solids as CCl_4 solutions) on a Hitachi 260-10 spectrometer. Mps are uncorrected. GLC was carried out on a Shimadzu GC-3AH instrument.

*Preparation of Sodium Guaiazulenide (**1**).* Under dry nitrogen 500 mg (10.4 mmol) of sodium hydride (50% dispersion in Bayol 85) was washed with hexane (10 cm^3), then with dry THF (10 cm^3×2), and suspended in a solution of 3.62 g (33.8 mmol) of *N*-methylaniline in 20 cm^3 of THF. This suspension was heated to refluxing for 30 min, and the resulting pale yellow solution was refluxed for 30 more min to complete the reaction. To this solution, at room temperature, was added another solution of 1.98 g (10.0 mmol) of **3** in 10 cm^3 of THF over a period of 20 min. The color of **3** changed from blue to brown at each moment of addition, and finally yielded a brown solution of **1** in THF, which was used for successive reactions without further purification.

*Reaction of **1** with Methyl Iodide.* To a stirred solution of **1** in THF was added dropwise 2.20 g (15.5 mmol) of methyl iodide over a period of 5 min; stirring was continued for an additional 1 h. The reaction mixture, after evaporation of THF (reduced pressure), was taken up into 200 cm^3 of hexane and the insoluble sodium iodide was filtered off. The filtrate was washed with 7% hydrochloric acid (100 cm^3×3), then with water, dried on sodium sulfate, and concentrated(reduced pressure) to give a blue oil. Successive hexane–silica gel elution chromatography afforded blue fractions containing **3**, **4**, **5**, and unknown minor components. From GLC analysis of these fractions, the yields of **3** (recovery), **4**, and **5** are calculated to be 47.4, 27.6, and 3.4%, respectively, based on **3**. Purification of each compound was not successful by means of elution chromatography, except that **4** was isolated as a mixture with **3** and **5**, and characterized by its NMR spectrum. **3**: GC-MS, *m/e* (rel intensity), 198 (66), 183 (100), 168 (17), 167 (18), 155 (17), 153 (26), and 128 (12). **4**: GC-MS, 212 (100), 197 (94), 169 (13), 167 (15), 154 (11), and 153 (12); NMR δ=1.26 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.34 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.64 (3H, s, 1-CH_3), 3.04 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 3.84 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 3.82 (1H, d, J=11.0 Hz, 5-H), 7.23 (1H, dd, J=11.0 and 2.0 Hz, 6-H), 7.24 (1H, d, J=3.8 Hz, 3-H), 7.58 (1H, d, J=3.8 Hz, 2-H), and 8.16 (1H, d, J=2.0 Hz, 8-H). **5**: GC-MS, 226 (100), 211 (76), 183 (39), 181 (17), 169 (17), and 155 (23).

*Reaction of **1** with Benzaldehyde.* To a stirred solution of **1** in THF (from 10 mmol of **3**) was added dropwise 2.5 g

(24 mmol) of benzaldehyde over a period of 20 min; stirring was continued for 4 h. The reaction mixture was worked up in the usual manner,[3,4] and **6**, **7**, and **8** were isolated in 64, 12, and 24% relative yields (**6**+**7**+**8**=100%).[7] **6**: NMR δ=1.32 (6H, d, J=7.0 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 2.64 (3H, s, 1-$\mathrm{CH_3}$), 3.04 (1H, m, J=7.0 Hz, $\mathrm{C\underline{H}(CH_3)_2}$), 7.08—7.60 (9H, m, 3-H, 5-H, 6-H, vinyl-H, and Ph), 7.60 (1H, d, J=4.0 Hz, 2-H), 7.94 (1H, d, J=17.0 Hz, vinyl-H (*trans*)), and 8.14 (1H, d, J=2.0 Hz, 8-H); MS, *m/e* (rel intensity), 286 (100), 285 (38), 284 (27), 271 (97), 243 (45), 241 (31), 239 (22), and 228 (26). **7**: NMR δ=1.32 (6H, d, J=7.0 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 2.64 (3H, s, 1-$\mathrm{CH_3}$), 3.04 (1H, m, J=7.0 Hz, $\mathrm{C\underline{H}(CH_3)_2}$), 4.76 (2H, s, $\mathrm{CH_2}$), 6.99 (1H, d, J=10.0 Hz, 5-H), 7.16—7.72 (6H, m, 2-H, 3-H, 6-H, and $\mathrm{B_2C}$ part of $\mathrm{A_2B_2C}$ system of Ph), 8.00—8.20 (2H, m, $\mathrm{A_2}$ part of $\mathrm{A_2B_2C}$ system of Ph), and 8.08 (1H, d, J=2.0 Hz, 8-H); MS, 302 (95), 105 (100), and 77 (28). **8**: NMR δ=1.38 (6H, d, J=7.0 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 2.70 (3H, s, 1-$\mathrm{CH_3}$), 3.12 (1H, m, J=7.0 Hz, $\mathrm{C\underline{H}(CH_3)_2}$), 3.56 (2H, d, J=8.0 Hz, $\mathrm{CH_2}$), 5.20 (1H, m, $\mathrm{C\underline{H}(OH)}$), 7.03 (1H, d, J=10.0 Hz, 5-H), 7.20—7.80 (8H, m, 2-H, 3-H, 6-H, and Ph), and 8.24 (1H, d, J=2.0 Hz, 8-H); MS, 304 (100), 198 (69), 185 (90), 184 (25), 183 (63), 167 (21), 165 (21), 155 (57), 149 (97), 143 (25), 107 (21), 105 (46), 84 (27), 79 (33), 78 (24), 77 (33), 43 (21), and 41 (26).

*Reaction of **1** with 3-Formylguaiazulene (**9**).* A solution of 1.13 g (5.00 mmol) of **9** in 15 cm³ of THF was added to a solution of **1** in THF (from 10.0 mmol of **3** and 25 cm³ of THF) drop by drop over a period of 40 min. The reaction mixture was stirred for an additional 4 h, diluted with water (20 cm³), and extracted with benzene (100 cm³ × 3); the extract was washed with 7% hydrochloric acid (100 cm³ × 3), then with water, dried, and concentrated (reduced pressure) to give a green oil. The oil was subsequently submitted to silica gel chromatography with hexane–AcOEt (4: 1) as the eluant, and separated into 331 mg (16.7%) of unchanged **3**, 543 mg (25.6 %) of **11**, 417 mg (19.6%) of **12**, 89.6 mg of unknown mixture, and 336 mg (29.7%) of recovery of **9**.

Dimer **11** was obtained as a green oil, which solidified in a refrigerator to give green microprisms, mp 113—115 °C. TLC (hexane–AcOEt) R_f 0.30. $\mathrm{UV_{max}}$ 205 nm (log ε 4.50), 246 (4.44), 287 (4.61), 305 (sh 4.17), 341 (sh 4.09), 353 (4.17), 366 (sh 4.14), 543 (sh ε 269), 568 (sh 384), 592 (sh 469), 610 (543), 632 (493), 667 (485), 698 (sh 254), and 739 (192); IR 1650 (C=O), 2720 and 2825 $\mathrm{cm^{-1}}$ (formyl CH); NMR[12] δ=1.10 (6H, q, J=6.8 Hz, 5-$\mathrm{CH(C\underline{H}_3)_2}$), 1.30 (6H, d, J=6.8 Hz, 7′-$\mathrm{CH(C\underline{H}_3)_2}$), 1.55 (3H, t, J=2.2 Hz, 3-$\mathrm{CH_3}$), 2.26 (3H, broad s, 8-$\mathrm{CH_3}$) (broadening is due to couplings with 6-H and 7-H), 2.47 (1H, m, J=6.8 Hz, 5-$\mathrm{C\underline{H}(CH_3)_2}$), 2.62 (3H, s, 1′-$\mathrm{CH_3}$), 2.93 (1H, m, J=6.8 Hz, 7′-$\mathrm{C\underline{H}(CH_3)_2}$), 3.04 (2H, dd, J=8.8 and 6.6 Hz, 4-$\mathrm{CH_2}$), 3.27 (2H, q, J=2.2 Hz, 1-$\mathrm{H_2}$), 3.96 (1H, dd, J=8.8 and 6.6 Hz, 4-H) (double doublets look like a broad triplet due to allyl coupling with 6-H), 6.06 (1H, broad d, J=7.0 Hz, 6-H) (broadening is due to couplings with 4-H and 8-$\mathrm{CH_3}$), 6.44 (1H, dq, J=7.0 and 1.3 Hz, 7-H), 6.52 (1H, d, J=10.6 Hz, 5′-H), 7.15 (1H, d, J=4.0 Hz, 3′-H), 7.21 (1H, dd, J=10.6 and 1.8 Hz, 6′-H), 7.59 (1H, d, J=4.0 Hz, 2′-H), 8.08 (1H, d, J=1.8 Hz, 8′-H), and 9.62 (1H, s, 2-CHO); MS, *m/e* (rel intensity), 424 (4), 227 (100), 226 (11), 199 (13), 183 (14), 157 (21), and 142 (14).

Found: C, 87.79; H, 8.35%. Calcd for $\mathrm{C_{31}H_{36}O}$: C, 87.69; H, 8.55%.

Dimer **12** was obtainde as a blue oil, which also solidified in a refrigerator to give blue crystals, dec at *ca.* 70 °C. TLC (hexane–AcOEt) R_f 0.26. $\mathrm{UV_{max}}$ 202 nm (log ε 4.44), 249 (sh 4.51), 285 (4.62), 289 (sh 4.61), 303 (sh 4.18), 346 (sh 4.10), 352 (4.14), 368 (sh 4.03), 543 (sh ε 298), 565 (sh 402), 591 (sh 489), 609 (557), 632 (500), 666 (482), 699 (sh 238), and 738 (182); IR 1655 (C=O), 2720 and 2825 $\mathrm{cm^{-1}}$ (formyl CH); NMR[12] δ=1.02 (6H, d, J=6.8 Hz, 7-$\mathrm{CH(C\underline{H}_3)_2}$), 1.35 (6H, d, J=7.0 Hz, 7′-$\mathrm{CH(C\underline{H}_3)_2}$), 1.96 (3H, d, J=1.3 Hz, 4-$\mathrm{CH_3}$), 2.40 (1H, m, J=6.8 Hz, 7-$\mathrm{C\underline{H}(CH_3)_2}$), 2.48 (3H, t, J=2.3 Hz, 1-$\mathrm{CH_3}$), 2.65 (3H, s, 1′-$\mathrm{CH_3}$), 2.84 (2H, d, J=7.9 Hz, 6-$\mathrm{CH_2}$), 3.06 (1H, m, J=7.0 Hz, 7-$\mathrm{C\underline{H}(CH_3)_2}$), 3.50 (1H, broad m, J=9.0 and 7.9 Hz, 6-H) (broadening is due to allyl coupling with 8-H), 3.61 (2H, m, J=2.3 Hz, 3-$\mathrm{H_2}$), 5.34 (1H, dq, J=9.0 and 1.3 Hz, 5-H), 6.33 (1H, broad s, 8-H) (broadening is due to allyl coupling with 6-H), 6.62 (1H, d, J=10.8 Hz, 5′-H), 7.06 (1H, d, J=3.7 Hz, 3′-H), 7.32 (1H, dd, J=10.8 and 2.0 Hz, 6′-H), 7.60 (1H, d, J=3.7 Hz, 2′-H), 8.13 (1H, d, J=1.7 Hz, 8′-H), and 10.08 (1H, s, 2-CHO); MS, 424 (7), 227 (100), 157 (15), 149 (19), 142 (11), and 43 (11).

Found: C, 87.80; H, 8.35 %. Calcd for $\mathrm{C_{31}H_{33}O}$: C, 87.69; H, 8.55 %.

*2-Formylguaiazulene (**10**). A. From **11**.* A solution of 10 mg (0.024 mmol) of **11** and 15 mg (0.061 mmol) of chloranil in 2 cm³ of benzene was stirred for 12 h at room temperature. The reaction mixture was diluted with petroleum ether (20 cm³), shaken with a 4% aqueous solution of potassium hydroxide (25 cm³), washed with water, dried, and the resultng green precipitates, insoluble in most organic solvents, were filtered off. Evaporation of the solvent and subsequent benzene–silica gel elution chromatography yielded 0.33 mg (6.2%) of **10**, identical with the authentic specimen in TLC, IR, and MS.

*B. From **12**.* The procedure given in *A* afforded 0.71 mg (4.7%) of **10**, identical (TLC and IR) with that from *A*, from 28 mg (0.067 mmol) of **12** and 60 mg (0.24 mmol) of *o*-chloranil.

As a control experiment, **9** was treated with a mixture of chloranil and *o*-chloranil in the same manner as described in *A*. In this case, however, only unchanged **9** was observed and formation of **10** was not detected in TLC of the reaction mixture.

The author wishes to thank Miss Naoko Kitahara of Saga University for her assistance in the experimental work as a part of her graduation thesis of Saga University. Thanks are also due to Dr. Hajime Koga of Hisamitsu Pharmaceutical Co., Ltd., and Dr. Toru Hinomoto of JEOL, Ltd., for their kind measurements of mass spectra and double resonance spectra.

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6) Ref. 3 reported a 52% yield of **4** from **1**, and a 68% yield of **1** from **3**. From these data, an overall yield of **4** was calculated to be 35% based on **3**.

7) Ref. 4 reported that the relative yields of **6**, **7**, and **8** were trace, 98, and 2% when a 1: 1 ratio of **1** and benzaldehyde was used in a benzene solution, while the yield of **8**

increased to 28—73% for the reagent ratio of 1 : 2.

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9) An alternative structure having 1-methyl (or 3-methyl) and 2-methylene groups was also possible if the migration of formyl group could occur by dehydrogenation of **11** and **12**. This possibility was excluded, because the coupling constant expected for that structure was less than 1 Hz according to Ref. 8.

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