Tetrahedron Letters,Vol.30,No.48,pp 6693-6696,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

1-Hydroxyazulene and 3-Hydroxyguaiazulene: Synthesis and Their Properties

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Summary: 1-Hydroxyazulene was obtained as an unstable green oil by the reduction of 1-acetoxyazulene with $LiAlH_4$. The compound did not show an equilibrium with its keto forms. 3-Hydroxyguaiazulene similarly obtained from 3-acetoxyguaiazulene was extremely unstable and easily changed to a mixture of its keto form and dimeric compound.

2-, 4-, and 6-hydroxyazulenes; isomers of naphthol, have been reported to exist in their tautomeric forms, respectively, depending on the solvent used.[1,2,3] Chiurdoglu and Fuks have reported that an inseparable mixture of two kinds of keto forms of 3-hydroxyguaiazulene were obtained as pale yellow crystals by Dakin reaction of 3-formylguaiazulene.[4] However, question has been raised regarding the structure of the keto forms of 3-hydroxyguaiazulene because of its light color and high melting point. We will report herein on the synthesis and some properties of 1-hydroxyazulene and 3-hydroxyguaiazulene (1-hydroxy-3,8-dimethyl-5-isopropylazulene).

Replogle[5] and McDonald et al.[6] have reported that alkaline hydrolysis of 1-benzoyloxyazulene (1) in the presence of methyl iodide afforded 1-methoxyazulene (2). However attempted synthesis of 1-hydroxyazulene by alkaline hydrolysis of 1 has resulted in the formation of a polymeric product.[5]

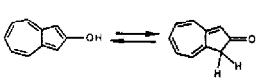
Reduction of 1-benzoyloxyazulene (1)[5,6] with $LiAlH_4$ in anhydrous THF afforded a green product together with benzylalcohol. Isolation of the colored product by chromatography was unsuccessful because of its instability. Acetylation of the reaction mixture with acetic anhydride and pyridine afforded 1-acetoxyazulene (3)[7] as blue crystals in 88% yield.

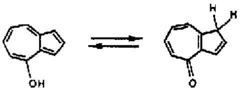
1-Acetoxyazulene (3) was reduced with $LiAlH_4$ in anhydrous THF. The reaction mixture was decomposed with 2N $HCl-CH_2Cl_2$ in the presence of ice, extracted with cold CH_2Cl_2 and dried with anhydrous $MgSO_4$. Removal of the solvent at -15°C under reduced pressure afforded 1-hydroxyazulene (4) as green oil in almost quantitative yield. The compound (4) is considerably stable at -30°C under a nitrogen atmosphere, but it changed to a dark-brown polymeric substance after prolonged standing at the same temperature. It rapidly changed at room temperature, and no clear compounds were isolated from the brown substance. The compound (4) also changed in solution, more rapidly in chloroform than in methanol, acetonitrile, or acetone. The compound (4) quite rapidly changed in alkaline condition to a brown polymeric substance.

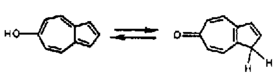
1-Hydroxy-2-deuteroazulene (4D) was also obtained starting from 2-deuteroazulene.[8]

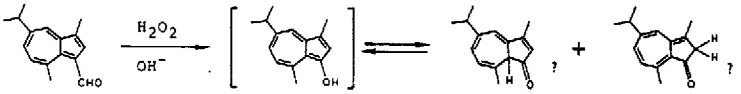
Acetylation of 4 by acetic anhydride and pyridine afforded the acetate (3) in good yield, but methylation with diazomethane yielded only polymeric substance, from which no clear products were obtained.

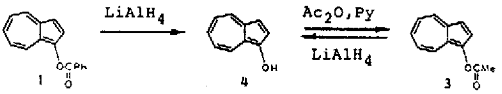
Mass spectrum of 4 indicated the molecular formula of $C_{10}H_8O$; HRMS, calcd 144.0575, found 144.0555. Visible absorption spectrum[9] of 4 in hexane exhibited a maximum at 673 nm; the











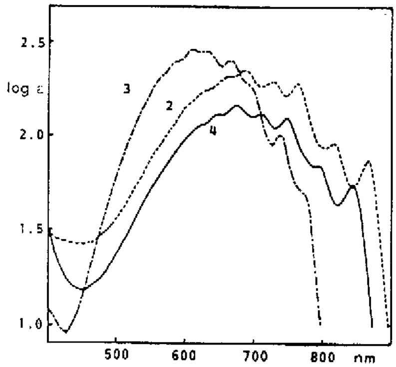
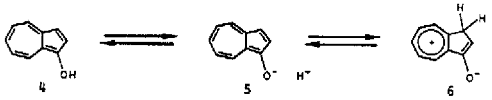


Fig. 1 Visible spectra of **2**, **3**, and **4** in hexane



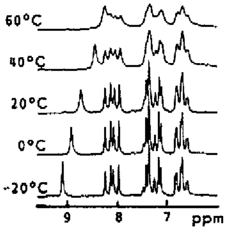
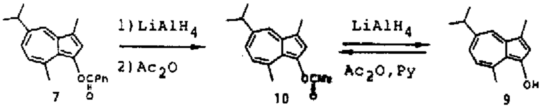
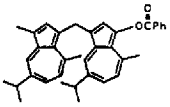


Fig. 2 ^{1}H-NMR of **4** in acetone-d_6 at various temperatures





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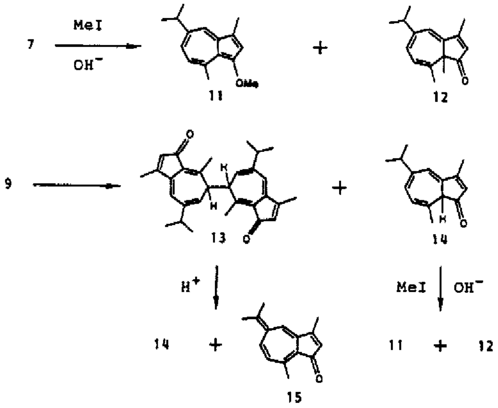


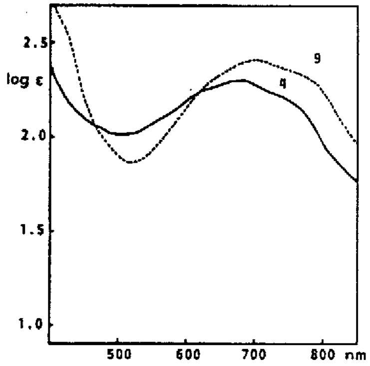
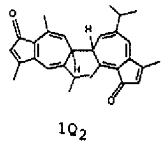
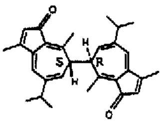


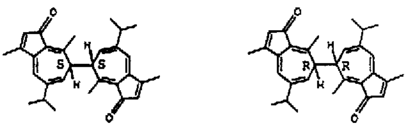
Fig. 3 Visible spectra of **4** and **9** in methanol



1Q$_2$



A (meso)



B (enantiomeric mixture)

bathochromic shift of 92 nm compared with that of azulene itself, showing a similar pattern with those of 1-methoxy- and 1-acetoxyazulenes as depicted in Fig. 1.

^{1}H-NMR spectra in acetone-d_6 are gradually broadened with rising temperature as shown in Fig. 2, which indicates that 4 exists in 1-hydroxyazulene at low temperature, but at higher temperature 4 must be in equilibrium with a certain isomeric compound. Almost the same temperature-dependent spectra were observed in $CDCl_3$, CD_2Cl_2 or CD_3CN. ^{1}H-NMR signals of 4 were assigned10) by ^{1}H-^{1}H and ^{1}H-^{13}C decoupling techniques at low temperature in acetone-d_6 and by comparison with that of 4D. Hydroxyl and H-3 signals disappeared in the ^{1}H-NMR spectrum of 4 in $CDCl_3$-D_2O or in CD_2Cl_2-D_2O system. In the acetone-d_6-D_2O system, however, only hydroxyl signal disappeared, and other signals did not change even heating at 70°C.

These facts indicate that 4 may be in equilibrium with charge-separated species (5 and/or 6) depending on the solvent and the temperature. However, the spectra did not show any evidence of the existence of keto forms. Therefore, the structure of keto forms of 3-hydroxyguaiazulene obtained by Chiurdoglu and Fuks4) is doubtful.

Guaiazulene was reacted with benzoylperoxide in a simialr manner for azulene itself,5,6) and 3-benzoyloxyguaiazulene (7)11) and benzoyloxydiazulenylmethane derivative (8)12) were obtained in 35 and 5% yields, respectively.

The compound (7) was reduced with $LiAlH_4$ in anhydrous THF, and the reaction mixture was treated with acetic anhydride to give 3-acetoxyguaiazulene (10)13) in 85% yield. Similar acetylation of a green-colored product obtained by working up the above reduction of 7 afforded 10 in only 36% yield. These facts indicated that the reduction of 7 gave unstable, green-colored 3-hydroxyguaiazulene (9).

The acetoxy compound (10) was reduced with $LiAlH_4$, and working up at low temperature similarly as in the case of 3 yielded 9 as a very unstable green oil. Visible absorption spectrum9) of 9 in methanol is shown in Fig. 3, together with that of 4 in methanol, and mass spectrum and ^{1}H-NMR of 9 supported a structure of 3-hydroxyguaiazulene.14)

Reaction of 7 with methyl iodide in an alkaline solution afforded two products: 3-methoxyguaiazulene (11)15) and C-methylated product, 1,8a-dihydro-3,8,8a-trimethyl-5-isopropylazulene-1-one (12)16) as pale yellow oil, in 39 and 45% yields, respectively.

After the reduction product of 10 was allowed to stand at room temperature for 12 hr in ether solution, the green-colored 9 gradually changed to a brown solution, which was separated by chromatography to give almost colorless, pale yellow micro needles (13), mp 145-147°C (from hexane) in 59% yield and 1,8a-dihydro-3,8-dimethyl-5-isopropylazulene-1-one (14),17) a keto form of 9, as pale yellow crystals in 20% yield.

The spectroscopic data (IR and ^{1}H-NMR) of the compound (13) were found to be almost superimposable with those of the product obtained by Dakin reaction of 3-formylguaiazulene,4) and also with those of dimeric compound ($1Q_2$) obtained by oxidation of guaiazulene by Matsubara et al.18) From the detailed spectroscopic analysis of 13, we propose here that 13 is a diastereomeric mixture of A (meso) and B (enantiomeric mixture), presumably formed by oxidative coupling of 9. Details of the structural determination will be reported elsewhere in the near future.

When the compound (13) was dissolved in $CHCl_3$ or treated with HCl for short time, the color rapidly changed to dark red, from which dimethylheptafulvene derivative (15)19) as orange crystals and 14 were obtained in 92 and 72% yields, respectively. The compound (14) was also reacted with methyl iodide in alkaline condition to give a mixture of 11 and 12, in 37 and 38%

yields, respectively.

Acknowledgement: We thank Professor Y. Matsubara for the donation of the sample and the copies of the spectra of the compound $(1Q_2)$.

References and Notes

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7) 3; Blue needles, mp 47.5-50.2°C, ^{1}H-NMR ($CDCl_3$) δ = 2.41 (s, CH_3), 7.05 (dd, J=9.9, 9.2, H-7), 7.05 (dd, J=9.9, 9.5, H-5), 7.26 (d, J=4.0, H-3), 7.56 (dd, J=9.9, 9.9, H-6), 7.80 (d, J=4.0, H-2), 8.19 (d, J=9.5, H-4), 8.22 (d, J=9.2, H-8).

8) R. W. Alder and C. Wilchire, J. Chem. Soc., Perkin Trans. II, 1975, 1464.

9) Intensities of the absorption spectra were estimated on the assumption that the compounds (4 and 9) were obtained in quantitative yields, respectively.

10) 4; Green oil, ^{1}H-NMR (acetone-d_6, -20°C) δ = 6.72 (dd, J=9.7, 9.5, H-5 or 7), 6.75 (dd, J=9.7, 9.5, H-7 or 5), 7.16 (d, J=4.0, H-3), 7.38 (dd, J=9.7, 9.7, H-6), 7.41 (d, J=4.0, H-2), 8.02 (d, J=9.5, H-4 or 8), 8.17 (d, J=9.5, H-8 or 4), 9.06 (s, OH); Attempted assignment of proton signals of 4 using shift reagents such as Eu(DPM), was unsuccessful because 4 rapidly decomposed with the addition of the reagents.

11) 7; Blue prisms, mp 132.2-133.4°C, ^{1}H-NMR ($CDCl_3$) δ = 1.14 (d, J=7.0, 6H, isoPro), 2.64 (s, CH_3-1), 2.85 (s, CH_3-4), 3.00 (sept, J=7.0, 1H, isoPro), 6.75 (d, J=10.5, H-5), 7.27 (dd, J=10.5, 2.0, H-6), 7.41-7.67 (m, 4H, H-2,3',4',5'), 8.11 (d, J=2.0, H-8), 8.25 (dd, J=7.5, 1.8, H-2',6').

12) 8; Blue prisms, mp 146.9-148.9°C.

13) 10; Blue needles, mp 40.7-41.9°C, ^{1}H-NMR ($CDCl_3$) δ = 1.32 (d, J=6.8, 6H, isoPro), 2.35 (s, $COCH_3$), 2.61 (s, CH_3-1), 2.83 (s, CH_3-4), 2.99 (sept, J=6.8, 1H, isoPro), 6.74 (d, J=10.7, H-5), 7.26 (dd, J=10.7, 2.0, H-6), 7.37 (s, H-2), 8.07 (d, J=2.0, H-8).

14) 9; Green oil, HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1360, ^{1}H-NMR (acetone-d_6, -50°C) δ = 1.23 (d, J=7.0, 6H, isoPro), 2.52 (s, CH_3-1), 2.81 (sept, J=7.0, 1H, isoPro), 2.82 (s, CH_3-4), 6.22 (d, J=10.3, H-5), 6.96 (dd, J=10.3, 1.6, H-6), 7.19 (s, H-2), 7.73 (d, J=1.6, H-8), 9.81 (s, OH).

15) 11; Greenish blue oil, HRMS calcd for $C_{16}H_{20}O$ 228.1514, found 228.1514.

16) 12; Pale yellow oil, HRMS calcd for $C_{16}H_{20}O$ 228.1514, found 228.1513, ^{1}H-NMR ($CDCl_3$) δ = 0.81 (s, CH_3-8a), 1.15 (d, J=6.8, 3H, isoPro), 1.18 (d, J=6.8, 3H, isoPro), 1.77 (s, CH_3-8), 2.23 (d, J=1.1, CH_3-3), 2.62 (sept, J=6.8, 1H, isoPro), 5.94 (d, J=6.2, H-7), 5.99 (d, J=1.1, H-2), 6.33 (s, H-4), 6.34 (d, J=6.2, H-6).

17) 14; Pale yellow needles, mp 36.8-39.2°C, HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1355, ^{1}H-NMR (C_6D_6) δ = 1.03 (d, J=6.8, 3H, isoPro), 1.06 (d, J=6.8, 3H, isoPro), 1.61 (br s, J=0.9, CH_3-3), 1.90 (s, CH_3-8), 2.87 (s, H-8a), 5.84 (d, J=6.4, H-7), 5.86 (br s, J=0.9, H-2), 6.03 (s, H-4), 6.15 (d, J=6.4, H-6).

18) a) Y. Matsubara, S. Matsui, S. Takekuma, H. Yamamoto, and T. Nozoe, Nippon Kagaku Kaishi, 1988, 1704; b) Y. Matsubara, S. Matsui, S. Takekuma, Y. P. Quo, H. Yamamoto, and T. Nozoe, Bull. Chem. Soc. Jpn., 62, 2040 (1989).

19) 15; Orange needles, mp 79.1-81.2°C. [lit, Yellow orange oil, Y. Matsubara, S. Takekuma, H. Yamamoto, and T. Nozoe, Chem. Letters, 1987, 455; Orange needles, mp ca. 135°C (darkened), 18b)].

(Received in Japan 31 July 1989)