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# SYNTHESIS OF 4-AZULENEETHANAMINE DERIVATIVES FROM SODIUM GUAIAZULENIDE AND METHYLENEIMINIUM SALT

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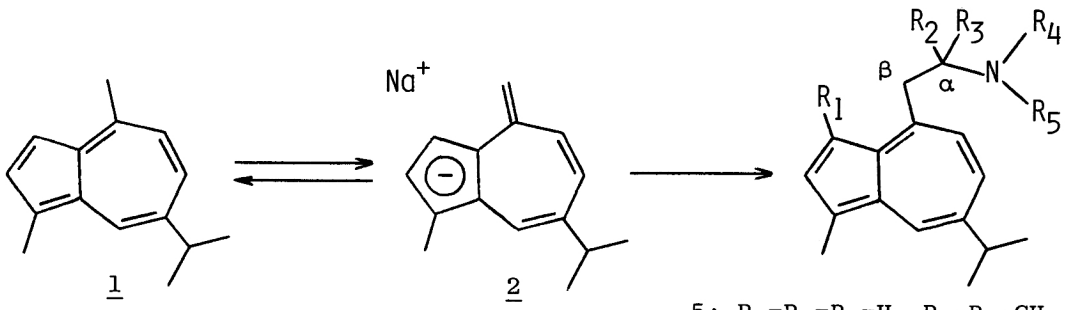
Alkyl- and aryl-substituted 4-azuleneethanamines, non-benzenoid analogs of biological active amines, were synthesized by the reaction of sodium guaiazulenide with methyleneiminium salt. These compounds were characterized by spectral data.

A group of compounds having β-phenylethylamine skeletone, e.g. amphetamine, ephedrine, adrenaline, dopamine, etc., belongs to biogenic amines or related biological active substances, as well as its indole analog, serotonin, melatonin, etc. In connection with these compounds, synthesis of azuleneethanamine derivatives has biochemical importance in increasing knowledges of structure and function relationship of biological active amines. As to azuleneethanamine derivatives, N,N-diethyl-β-methyl-1-azuleneethanamine is already known by Hafner azulene synthesis.[1] Moreover, we previously reported the electrophilic substitution of azulene and guaiazulene to yield amide or alkyl derivatives of 1-azuleneethanamine, by the use of N-acylaziridine or aziridinium salt as aminoethylation reagents.[2,3]

On the other hand, there is no report on azuleneethanamine derivatives having aminoethyl side chain on 7-membered ring of azulene nucleus. Therefore our effort was undertaken to synthesize 4-azuleneethanamine derivatives by the action of methyleneiminium salt on sodium guaiazulenide (2), which can be prepared by adding guaiazulene (1) into a solution of sodium N-methylanilinide in THF and used without further purification.[4,5] In addition, sodium N-methylanilinide is conveniently led from sodium hydride and N-methylaniline using THF as the solvent, according to our modification of usual procedure.[4]

To the stirred solution of 2 in THF, thus obtained, was added slowly twice molar equivalent of N-methylenedimethylammonium iodide[6] at ca. -80°C, and the mixture was gradually brought to room temperature. Proceeding of the reaction was checked by facile color change from brown to blue, observed at ca. -20°C. Successive separation of the reaction mixture by the use of alumina chromatography gave intended




1 2

5: $R_1=R_2=R_3=H$, $R_4=R_5=CH_3$

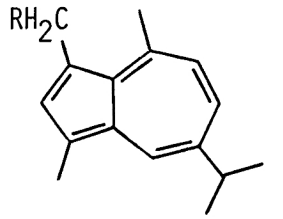
6: $R_1=CH_2N(CH_3)_2$, $R_2=R_3=H$, $R_4=R_5=CH_3$

7: $R_1=R_2=R_4=H$, $R_3=R_5=CH_3$

8: $R_1=H$, $R_2=R_3=R_4=R_5=CH_3$

9: $R_1=H$, $R_2=R_3=CH_3$; $R_4$, $R_5$= $-(CH_2)_4-$

10: $R_1=H$, $R_2=CH_3$, $R_3=C_6H_5$; $R_4$, $R_5$= $-(CH_2)_4-$

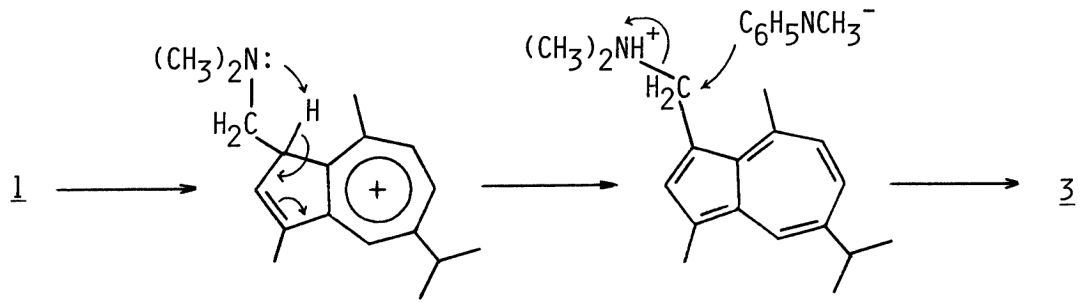



3: $R=C_6H_4NHCH_3(p)$

4: $R=N(CH_3)_2$

7-isopropyl-N,N,1-trimethyl-4-azuleneethanamine (5, 50%) as a major product, accompanied with unchanged 1 (2%), 3-(p-methylamino)benzylguaiazulene (3, 1%), 3-(N,N-dimethylamino)methylguaiazulene (4, 14%), and 3-(N,N-dimethylamino)methyl-7-isopropyl-N,N,1-trimethyl-4-azuleneethanamine (6, 7%).

By-product 4 is thought to be produced from 1, which coexists in the THF solution of 2 at equilibrium, via the same electrophilic aromatic substitution as is observed in the formation of 6 from 5. On the other hand, 3 may be formed from conjugate acid of 4 via nucleophilic attack of anilinide anion at 3-methylene position in the course of formation of 4 (Scheme 1).




1 3

Scheme 1

By virtually the same procedure as described above, treatments of 2 with N-isopropylidenedimethylammonium perchlorate, N-isopropylidenepyrrolidinium perchlorate, or N-1-methylbenzylidenepyrrolidinium perchlorate,[7] at -20°C or at ambient temperature, yielded corresponding 4-azuleneethanamine derivatives 8 - 10, no appreciable by-products being detected in these cases. Furthermore, the reaction of 2 with N-ethylidenemethylamine[8] also afforded 4-azuleneetanamine derivative 7. However, it is apparent from low yield of the product that electrophilicity of azomethine carbon atom is rather insufficient to bring a smooth reaction of it with methylene carbanion of 2, different from the cases of methyleneiminium salt.

Yields (based on 1) and physical data of 4-azuleneethanamine derivatives are

Table 1. Yields and selected physical data of 4-azuleneethanamine derivatives

| Compd. | Yield (%) | UV (EtOH) nm (ε) nm (log ε) | MS (70 eV) m/e (%) | $^1$H-NMR ($CDCl_3$) δ (ppm), J (Hz) [$^{13}$C-NMR ($CDCl_3$) δ (ppm)] |
|---|---|---|---|---|
| 5 | 50 | 602 (443)<br>284 (4.57) | 255 (100) | 2.28 (s, 6H, $N(CH_3)_2$), 2.76 (m, 2H, α-$CH_2$), 3.30 (m, 2H, β-$CH_2$)<br>[36.3 (α-C), 45.2 ($N(\underline{C}H_3)_2$), 60.7 (β-C)] |
| 6 | 7 | 609 (436)<br>289 (4.56) | 312 (3.4)<br>58 (100) | 2.23 (s, 6H, $N(CH_3)_2$), 2.36 (s, 6H, $N(CH_3)_2$), 2.72 (m, 2H, α-$CH_2$), 3.68 (m, 2H, β-$CH_2$) |
| 7 | 8 | 607 (461)<br>285 (4.58) | 255 (7.1)<br>58 (100) | 1.12 (d, 3H, J=6.3, α-CH($C\underline{H}_3$)), 1.71 (s, 1H, NH), 2.39 (s, 3H, $NCH_3$), 2.88 - 3.40 (m, 4H; α-$C\underline{H}(CH_3)_2$, β-$CH_2$, and 7-$C\underline{H}(CH_3)_2$) |
| 8 | 64 | 609 (454)<br>285 (4.54) | 283 (0.7)<br>86 (100) | 1.01 (s, 6H, α-$C(CH_3)_2$), 2.44 (s, 6H, $N(CH_3)_2$), 3.30 (s, 2H, β-$CH_2$) |
| 9 | 62 | 611 (412)<br>285 (4.50) | 310 (1.2)<br>112 (100) | 1.06 (s, 6H, α-$C(CH_3)_2$), 1.75 (m, 4H, 3'- and 4'-$CH_2$), 2.79 (t, 4H, J=6.0, 2'- and 5'-$CH_2$), 3.32 (s, 2H, β-$CH_2$) |
| 10 | 54 | 612 (413)<br>286 (4.51) | 371 (1.7)<br>174 (100) | 1.24 (s, 3H, α-$C(CH_3)$), 1.74 (m, 4H, 3'- and 4'-$CH_2$), 2.70 (t, 4H, J=6.0, 2'- and 5'-$CH_2$), 3.31 and 4.01 (each d, 2H, J=12.5, β-$CH_2$), 7.10 - 7.38 (m, 5H, $C_6H_5$)<br>[14.3 (α-$C\underline{H}_3$), 24.1 (3'- and 4'-C), 46.1 (2'- and 5'-C), 49.7 (α-C), 63.3 (β-C); 126.7, 127.5, and 144.9 ($\underline{C}_6H_5$)] |

listed in Table 1.[9] Multiplet pattern of α- and β-methylene protons in $^{1}$H-NMR of 5 suggests the existence of some preferred conformation in this compound, but the possibility seems to be denied since the pattern remains unchanged even at 100°C (pyridine-$d_5$ as the solvent). Thus resulted ambiguity of the methylene portion was clarified by off resonance, partial decoupling experiments of $^{13}$C-NMR of 5, in which two clear triplets of both methylene carbons were observed. On the other hand, non-equivalence of β-methylene protons in $^{1}$H-NMR of 10 is attributable to the effect of adjacent asymmetric center and the spectrum, together with $^{13}$C-NMR of 10, well supports the structure of aminoethyl side chain. Of interest is the occurrence of the reverse reaction of above synthetic work observed in mass spectra of 7 - 10, where allyl fission of α,β-bond to form methyleneiminium ion (or isomeric ion) gave the base peak.

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9) Primed numbering is used for pyrrolidine ring to avoid confusion of it with azulene ring ($\overset{1'}{\text{N}}\text{-}\overset{2'}{\text{C}}\text{-}\overset{3'}{\text{C}}\text{-}\overset{4'}{\text{C}}\text{-}\overset{5'}{\text{C}}$).

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