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Synthesis of 2-(1-Azulenyl)ethanamine Derivatives by Aminoethylation of Azulenes with Aziridines

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Azulene analogs of biological active amines were synthesized. Reaction of azulene or guaiazulene with 1-butanoylaziridine or with 1-butanoyl-2-methylaziridine in the presence of Lewis acid catalyst formed the corresponding *N*-butanoyl-1-(1-azulenyl)-, *N*-butanoyl-2-(1-azulenyl)-, and *N*-butanoyl-2-(1-guaiazulenyl) derivatives of ethanamine, or 1-propanamine, or of 2-propanamine, respectively (**5**—**9**). Reaction of guaiazulene with 2-methyl-, or 1,1-dimethylaziridinium, or with 1,1,2,2-tetramethylaziridinium ions gave the corresponding 1-(1-guaiazulenyl)- and 2-(1-guaiazulenyl) derivatives of ethanamine, or 1-propanamine, or of 2-propanamine. 2-(1-Azulenyl)- and 2-(4,6,8-trimethyl-1-azulenyl) derivatives of ethanamine were also obtained by the action of 1,1-diethylaziridinium ion on azulene or on 4,6,8-trimethylazulene. Compounds **5**, **6**, and **9** were active *in vitro* in the inhibition of prostaglandin 15-hydroxydehydrogenase and of cyclic AMP-phosphodiesterase.

2-Arylethanamine derivatives constitute an important class of physiologically active compounds.[1] Natural compounds exhibit a variety of structural modifications and hundreds of additional derivatives have been synthesized in the search for therapeutic agents. A literature search did not reveal any examples having a nonbenzenoid aryl moiety. The low toxity of guaiazulene as an anti-inflammatory agent[2] led us to investigate the preparation of some 2-(1-azulenyl)ethanamine derivatives.

An earlier study had revealed that azulene reacted readily with tetracyanoethylene oxide to give concomitant epoxide ring opening and aromatic substitution.[3] An analogous behavior toward the aziridine ring would lead to the desired structure.

Results and Discussion

1-Butanoylaziridine (**1**) and 1-butanoyl-2-methylaziridine (**2**) were selected as reactants and were readily formed by the method of Brown and Tsukamoto,[4] with variation of the solvent as needed. From the treatment of **1** with azulene (**3**) in dichloromethane in the presence of aluminium chloride a 21% yield of *N*-butanoyl-2-(1-azulenyl)ethanamine (**5**) was obtained.

Similarly, from **2** and azulene (**3**) 20% of *N*-butanoyl-2-(1-azulenyl)-1-propanamine (**6**) was isolated. When the solvent was changed to benzene, the reaction of **3** with **2** formed **6** (21%) and a product (15%) having spectral and analytical data consistent with the isomeric structure **7**. Analogous reactions with guaiazulene (**4**) with **1** (in ether) and **2** (in dichloromethane) gave **8** (8%) and **9** (57%), respectively.

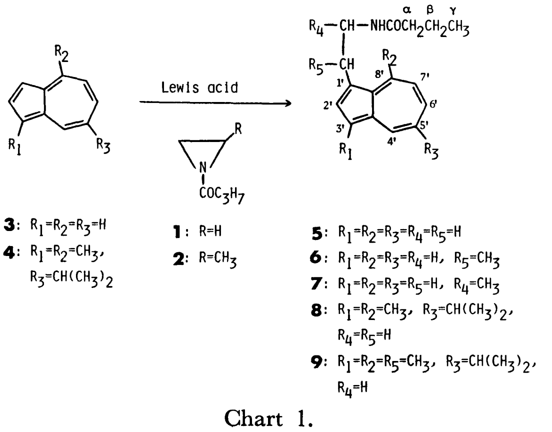
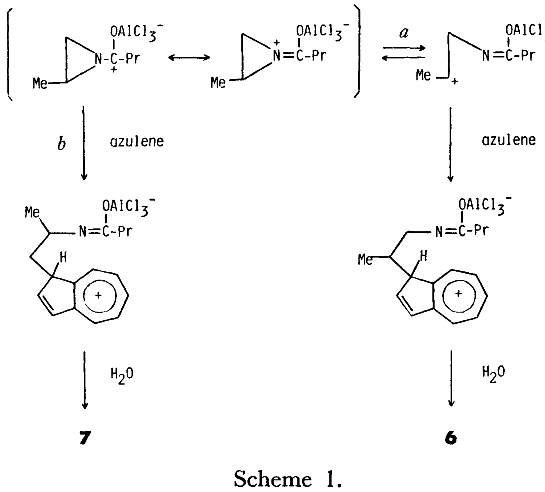


Chart 1.

The structural assignments for **5**—**9** were based on spectral analyses. These were consistent with substitution at the azulene 1-position and the presence of the amide function for all the products. ^{1}H NMR spin-decoupling was used for the characterization of the propyl side-chain moieties in **6** and **9**. In **6**, for example, irradiation at δ 3.68 (–CH) caused the doublet at δ 1.40 ($-CH_3$) to become a singlet, and irradiation at δ 3.42 and δ 3.92 ($-CH_2-$) did not affect the doublet at δ 1.40 ($-CH_3$). The $-CH_2-$ pattern exhibited coupling with the amide hydrogen (J=5 Hz) and with the methine hydrogen (J=5 and 7 Hz).

The isolation only of **6** in one experiment, and of **6** and **7** in another, suggests two reaction paths, one (*a*) dominant in dichloromethane and both (*a* and *b*) appreciably operative in benzene, as proposed by Milstein[5] and shown in Scheme 1. In *a* the more stable of the two possible carbocations is formed and leads to **6**. In *b* direct nucleophilic attack on the aziridinium ion occurs at the less hindered methylene and leads to **7**.

A second approach to this type of compound was by the reaction of guaiazulene with a simple (protonated) or quaternary aziridinium ion. 2-Methylaziri-



Scheme 1.

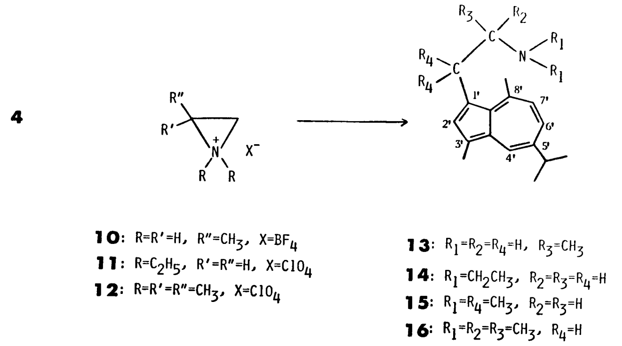


Chart 2.

dinium tetrafluoroborate (**10**)[6] was used for the former. A number of solvents, temperatures, and reaction times were tried (neat, 160—180 °C, 20 min; dichloromethane, *ca.* 20 °C, 1 h; 1,2-dimethoxyethane, 93 °C, 48 h; 1,2-diethoxyethane, 124 °C, 16 h; bis(2-methoxyethyl) ether, 160 °C, 4 h; bis(2-ethoxyethyl) ether, 190 °C, 1 h) but the yields of **13** were uniformly low (0.08—8%) and appreciably unchanged guaiazulene was recovered. The aziridinium salt was only slightly soluble in the solvents.

Treatment of guaiazulene with 1,1-diethylaziridinium perchlorate (**11**) in 1,2-dichloroethane gave a 35% yield of **14**. Under the same conditions but with a thirteen times longer reaction time, however, reaction with 1,1,2,2-tetramethylaziridinium perchlorate (**12**) afforded only 0.07% of **15** and 0.1% of **16** with 79% recovery of unchanged guaiazulene.

Similarly, reaction of azulene (**3**) with **11**, followed by treatment with hydrochloric acid, gave a 12% yield of the hydrochloride (**20**), from which **18** (78%) was regenerated by alkali treatment. Moreover, 4,6,8-trimethylazulene (**17**) reacted with **11** to afford 53% of **19**. The identities of **13**—**16**, **18**, and **19** were shown by ultraviolet-visible, infrared, ^{1}H nuclear magnetic resonance, and mass spectral characteristics, all of which were in agreement with the assigned structures.

However, some ambiguity was observed in ^{1}H NMR of **14**, **18**, and **19**. For instance, 1- and 2-methylene protons showed two multiplets, the pattern of which was exactly the same in three compounds. Thus, ^{13}C NMR was used for the characterization of **18** (in the form of **20**) and **19**. In this case, the methylene carbon signals appeared as clear triplets in good accordance with the structure. In the mass spectra of all 2-(1-azulenyl)ethanamine derivatives, allyl fission of aminoethyl side chain gave rise the most abundant ion, which was also used for structural assignments.

Compounds **5**, **6**, and **9** have been found to be active *in vitro* (20 μg in 1 cm^3) in the inhibition of prostaglandin 15-hydroxydehydrogenase (71, 69, and 50%, respectively), and of cyclic AMP-phosphodiesterase (24, 47, and 70%, respectively).[7] Details of the biological activities will be described elsewhere.

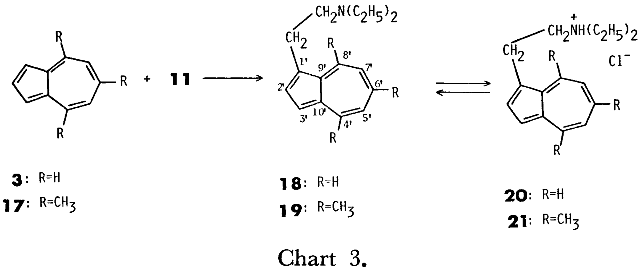


Chart 3.

Experimental

Spectral data were recorded on the following instruments: UV, Hitachi 624 digital spectrometer with a Hitachi 056 recorder; IR, Hitachi 260-10 spectrometer; ^{1}H NMR, JEOL MH-100 except for JNM-FX 100 for **13**; ^{13}C NMR, JNM-FX 100; MS, JEOL-D300 at 70 eV. GLC were done on a Shimadzu GC-3AH instrument and TLC were done on Merck precoated alumina sheet, silica gel 70 (Art. 5553), or neutral alumina 60F$_{254}$ type E (Art. 5550). A Schlenk apparatus[8] was used to exclude moisture for the preparation of **5**—**9**.

N-Butanoyl-2-(1-azulenyl)ethanamine (5). To an ice-cooled, stirred solution of 643 mg (5.02 mmol) of azulene in 50 cm^3 of dry dichloromethane was added 1.33 g (9.98 mmol) of aluminium chloride (washed in with 5 cm^3 of dichloromethane) (blue color changed to light yellow) and then, dropwise, a solution in 17 cm^3 of dry ether of *ca.* 10 mmol of 1-butanoylaziridine [prepared from 1.1 g (10.3 mmol) of butanoyl chloride, 430 mg (9.98 mmol) of aziridine, and 1.01 g (9.98 mmol) of triethylamine].[4] The light yellow color changed to blue. Stirring was continued at 0 °C for 1 h and the mixture was then added to 500 cm^3 of cold (0 °C) 10% sodium chloride-10% hydrochloric acid. The blue solution obtained by extraction (twice each) with 150, 100, and 50 cm^3 portions of chloroform was washed with 150 cm^3 of saturated sodium chloride, twice with 150 cm^3 of 10% sodium hydroxide and then dried (sodium sulfate). Removal of the solvent (reduced pressure) gave blue crystals (two major components by TLC on silica gel). Chromatography on a silica-gel column (elution with 3:1 hexane-THF) gave 549 mg of violet crystals, which on rechromatography (elution with hexane) afforded 429 mg (3.35 mmol) of unchanged azulene. Successive blue eluates (3:1 hexane-THF) yielded 545 mg of blue oil, which was rechromatographed to give 254 mg (1.05 mmol, 21%) of **5**. Further colored fractions removed by hexane-THF, acetone, and methanol were not characterized. In order to get analytical specimen, **5** was further purified by extraction of a benzene (30 cm^3) solution with 10 cm^3 of 85% phosphoric acid, washing the acid extract with 3×20 cm^3 of benzene, dilution with 300 cm^3 of 17% sodium chloride, and extraction with 3×100 cm^3 of benzene. Chromatography of the concentrate from the dried (potassium carbonate) benzene solution over silica gel (3:1 hexane-THF) gave 61.6 mg (11%) of **5** as a blue oil which formed tiny prisms, mp 48—50 °C, on refrigeration: UV (C_2H_5OH) 237 (log ε 4.12), 259 (sh, 4.13), 264 (sh, 4.30), 268 (sh, 4.44), 274 (sh, 4.57), 278 (4.64), 282 (sh, 4.39), 287 (sh, 4.44), 297 (sh, 3.64), 320 (sh, 3.22), 328 (sh, 3.39), 334 (sh, 3.42), 343 (3.58), 358 (3.27), 516 (ε sh, 104), 534 (sh, 144), 558 (sh, 199), 580 (sh, 232), 597 (226), 618 (sh, 234), 652 (223), 683 (sh, 111), and 722 nm (80); IR (CCl_4) 3460 (nonassoc N-H), 3350 (assoc N-H), and 1685 cm^{-1} (amide C=O); ^{1}H NMR ($CDCl_3$) $\delta=0.88$ (3H, t, $J=7.5$ Hz, γ-CH$_3$), 1.60 (2H, sext, $J=7.5$ Hz, β-CH$_2$), 2.06 (2H, t, $J=7.5$ Hz, α-CH$_2$), 3.30 (2H, t, $J=7.0$ Hz, 2-CH$_2$), 3.66 (2H, sext, $J=7.0$ and 5.0 Hz, 1-CH$_2$), 5.52 (1H, br m, NH), 7.16 (2H, t, $J=10.0$ Hz, 5'- and 7'-H), 7.40 (1H, d, $J=4.0$ Hz, 3'-H), 7.62 (1H, t, $J=10.0$ Hz, 6'-H), 7.82 (1H, d, $J=4.0$ Hz, 2'-H), 8.32 (1H, d,

J=10.0 Hz, 4′-H), and 8.36 (1H, d, J=10.0 Hz, 8′-H); MS *m/e* (rel intensity) 241 (M^+, 18), 154 ($M^+-C_4H_9NO$, 90), and 141 ($M^+-C_3H_7CONHCH_2$, 100).

Found: C, 79.60; H, 7.92; N, 5.72%. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80%.

N-*Butanoyl-2-(1-azulenyl)-1-propanamine* (*6*). *A*: The reaction of 640 mg (4.99 mmol) of azulene in 50 cm^3 of dichloromethane, 1.33 g (9.98 mmol) of aluminum chloride and *ca.* 9.9 mmol of 1-butanoyl-2-methylaziridine [from 1.10 g (10.3 mmol) of butanoyl chloride, 570 mg (9.98 mmol) of 2-methylaziridine, and 1.01 g (9.98 mmol) of triethylamine in 17 cm^3 of ether]$^{4)}$ was carried out as described for **5** except that the crude reaction mixture was added to 500 cm^3 of cold (0 °C) 10% hydrochloric acid prior to extraction successively with 150, 50 (thrice), and 60 cm^3 of dichloromethane. The organic extracts were washed with 100 cm^3 (thrice) of water before drying (sodium sulfate) and removal of the solvent. Chromatography of the residue over alumina (9:1 benzene-chloroform) gave 586 mg of violet crystals and 667 mg of blue oil. Rechromatography of the violet crystals (silica gel; hexane) gave 440 mg (69%) of unchanged azulene. From the blue oil after chromatography over silica gel twice (elution with chloroform and then 5:1 hexane–THF) was obtained 254 mg (20%) of **6** as a blue oil. This compound was further purified by washing a benzene (150 cm^3) solution with 150 cm^3 (thrice) of 10% sodium hydroxide and 100 cm^3 (thrice) of water, drying (sodium sulfate), removal of the solvent, resolution into 120 cm^3 of 5:1 hexane–benzene, and extraction into 85% phosphoric acid (50 cm^3, then 30 cm^3 twice). Dilution of the acid extract with 500 cm^3 of water and basification with solid potassium carbonate was followed by extraction into benzene (200 cm^3 then 100 cm^3 twice). Chromatography on silica gel (3:1 hexane–THF) of the residue from the washed (3×105 cm^3 of water), dried (sodium sulfate) benzene solution gave 68.2 mg (6%) of analytical specimen of **6** as a blue oil: UV (C_2H_5OH) 238 (log ε 4.03), 258 (sh, 4.00), 263 (sh, 4.18), 268 (sh, 4.35), 274 (sh, 4.49), 278 (4.55), 282 (sh, 4.51), 288 (sh, 4.34), 296 (sh, 3.55), 320 (sh, 3.12), 333 (sh, 3.33), 343 (3.51), 359 (3.23), 517 (ε sh, 82), 534 (sh, 116), 557 (sh, 162), 579 (sh, 192), 597 (221), 621 (sh, 190), 686 (sh, 81), and 722 nm (60); IR (CCl_4) 3450 (nonassoc N-H), 3350 (assoc N-H), and 1680 cm^{-1} (amide C=O); ^{1}H NMR ($CDCl_3$) δ=0.81 (3H, t, J=7.0 Hz, γ-CH_3), 1.40 (3H, d, J=7.0 Hz, 3-CH_3), 1.50 (2H, sext, J=7.0 Hz, β-CH_2), 1.94 2H, t, J=7.0 Hz, α-CH_2), 3.42 (1H, sext, J=13.0, 5.0, and 5.0 Hz, one H of 1-CH_2), 3.68 (1H, decet, J=7.0, 7.0, and 5.0 Hz, 2-CH), 3.92 (1H, octet, J=13.0, 7.0, and 5.0 Hz, one H of 1-CH_2), 5.60 (1H, br t, J=5.0 Hz, NH), 7.09 (2H, t, J=10.0 Hz, 5′- and 7′-H), 7.36 (1H, d, J=4.0 Hz, 3′-H), 7.54 (1H, t, J=10.0 Hz, 6′-H), 7.82 (1H, d, J=4.0 Hz, 2′-H), 8.25 (1H, d, J=10.0 Hz, 4′-H), and 8.35 (1H, d, J=10.0 Hz, 8′-H); MS *m/e* (rel intensity) 255 (M^+, 9), 168 ($M^+-C_3H_7CONH_2$, 24), and 155 ($M^+-C_3H_7CONHCH_2$, 100).

Found: C, 79.68; H, 8.37; N, 5.43%. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%.

B: The reaction of 128 mg (1.00 mmol) of azulene in 30 cm^3 of dry benzene, 400 mg (3.00 mmol) of aluminum chloride and *ca.* 3.00 mmol of 1-butanoyl-2-methylaziridine [from 321 mg (3.0 mmol) of butanoyl chloride, 171 mg (3.00 mmol) of 2-methylaziridine, 303 mg (3.00 mmol) of triethylamine in 7 cm^3 of benzene at 5 °C]$^{4)}$ was carried out as described for **5** except for the change in solvent and a reaction temperature of 5 °C. The hydrolyzed (10% hydrochloric acid) mixture was extracted with 100 cm^3 of ether (4 times) and the extracts washed successively with 150 cm^3 of water (twice), 150 cm^3 of sodium hydroxide (twice), and 175 cm^3 of water (thrice). Chromatography of the crude product (isolated as described for **5**) over silica gel (3:1 hexane–THF) gave 101 mg of violet crystals, 37 mg of blue oil, and 171 mg of blue oil. Rechromatography of the violet crystals (silica gel; hexane) gave 70.6 mg (55%) of unchanged azulene. The first blue fraction was characterized as *N*-butanoyl-1-(1-azulenyl)-2-propanamine (**7**) (15%): IR (CCl_4) 3460 (nonassoc N-H), 3350 (assoc N-H), and 1680 cm^{-1} (amide C=O); ^{1}H NMR ($CDCl_3$) δ=0.93 (3H, t, J=7.0 Hz, γ-CH_3), 1.47 (3H, d, J=7.0 Hz, 3-CH_3), 1.58 (2H, sext, J=7.0 Hz, β-CH_2), 2.17 (2H, t, J=7.0 Hz, α-CH_2), 3.59 (2H, m, 1-CH_2), 4.10 (1H, 12 lines, J=7.0 and 3.0 Hz, 2-CH), 6.74 (1H, br d, J=3.0 Hz, NH), 7.03 (1H, t, J=10.0 Hz, 5′-H), 7.07 (1H, t, J=10 Hz, 7′-H), 7.36 (1H, d, J=4.0 Hz, 3′-H), 7.57 (1H, t, J=10.0 Hz, 6′-H), 7.82 (1H, d, J=4.0 Hz, 2′-H), 8.25 (1H, d, J=10.0 Hz, 4′-H), and 8.37 (1H, d, J=10.0 Hz, 8′-H);$^{9)}$ MS *m/e* (rel intensity) 255 (M^+, 33), 226 ($M^+-C_2H_5$, 83) 156 ($M^+-C_5H_9NO$, 100), and 141 ($M^+-C_3H_7CONHCHCH_3$, 10).

Found: N, 5.39%. Calcd for $C_{17}H_{21}NO$: N, 5.49%.

Rechromatography of the last blue fraction afforded 53.6 mg (21%) of blue oil identical (TLC, IR, MS) with **6** obtained from *A*.

N-*Butanoyl-2-(1-guaiazulenyl)ethanamine* (*8*). To an ice-cooled, stirred solution of *ca.* 9.9 mmol of 1-butanoylaziridine [from 430 mg (9.98 mmol) of aziridine, 1.10 g (10.3 mmol) of butanoyl chloride, 1.01 g (9.98 mmol) of triethylamine]$^{4)}$ in 6 cm^3 of ether was added slowly (syringe) a solution of 990 mg (5.00 mmol) of guaiazulene in 3 cm^3 of ether and then 2.60 g (10.0 mmol) of tin(IV) chloride. The color changed from blue to green and the mixture solidified. After 1 h at room temperature, 50 cm^3 of water was added and the solution was made alkaline with aqueous ammonium hydroxide. The mixture was extracted with ether and the ether solution filtered. The green-blue filtrate, including ether washings of the precipitate, was extracted with 50 cm^3 of saturated sodium carbonate (twice), 50 cm^3 of water (four times) and dried (sodium sulfate). Removal of the solvent and chromatography of the residue (silica gel; 9:1 benzene-chloroform) gave 660 mg of blue oil and 129 mg (8%) of **8** as blue crystals. Rechromatography of the blue oil over silica gel (hexane) separated unchanged guaiazulene (494 mg, 50%) and a green oil which, after rechromatography (silica gel; 9:1 hexane-benzene) amounted to 12.5 mg of green crystalline product identical (mp, TLC, UV, IR, MS) with authentic specimen of 3,3′-biguaiazulene.$^{10)}$

Rechromatography (silica gel; chloroform) and recrystallization (from 80% ethanol) of the blue crystals gave the analytical sample of **8** as tiny blue prisms, mp 108—109 °C: UV (C_2H_5OH) 202 (log ε 4.13), 218 (4.06), 247 (4.26), 287 (4.54), 290 (sh, 4.54), 306 (4.08), 338 (sh, 3.47), 352 (3.66), 369 (3.63), 577 (ε sh, 275), 621 (344), 673 (sh, 278), and 744 nm (sh, 95); IR ($CHCl_3$) 3470 (nonassoc N-H), 3350 (assoc N-H), and 1685 cm^{-1} (amide C=O); ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, t, J=7.0 Hz, γ-CH_3), 1.32 (6H, d, J=7.0 Hz, 5′-$CH(C\underline{H}_3)_2$), 1.62 (2H, sext, J=7.0 Hz, β-CH_2), 2.08 (2H, t, J=7.0 Hz, α-CH_2), 2.59 (3H, s, 3′-CH_3), 2.94 (3H, s, 8′-CH_3), 3.08 (1H, sept, J=7.0 Hz, 5′-$C\underline{H}(CH_3)_2$), 3.51 (4H, quint, J=6.8 Hz, 1- and 2-CH_2), 5.82 (1H, br s, NH), 6.81 (1H, d, J=10.6 Hz, 7′-H), 7.24 (1H, q, J=10.6 and 2.0 Hz, 6′-H), 7.44 (1H, s, 2′-H), and 8.06 (1H, d, J=2.0 Hz, 4′-H); MS *m/e* (rel intensity), 311 (M^+, 23), 224 ($M^+-C_3H_7CONH_2$, 48), and 211 (M^+

$-C_3H_7CONHCH_2$, 100).

Found: C, 81.16; H, 9.38; N, 4.50%. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.38; N, 4.50%.

Reaction of Guaiazulene with 1-Butanoyl-2-methylaziridine. To an ice-cooled, stirred solution of 990 mg (5.00 mmol) of guaiazulene and *ca.* 15 mmol of 1-butanoyl-2-methylaziridine [from 860 mg (15.1 mmol) of 2-methylaziridine, 1.60 g (15.0 mmol) of butanoyl chloride, and 1.52 g (15.0 mmol) of triethylamine in 10 cm³ of dichloromethane at *ca.* −5 °C][4] in 50 cm³ of dichloromethane was added gaseous boron trifluoride below the surface until the solution was saturated. The mixture was then stirred for 1 h, added to 500 cm³ of ice water, and extracted with one 200 cm³ and three 150 cm³ portions of chloroform. The green-blue organic extracts were washed with 150 cm³ of 10% sodium hydroxide (twice), 150 cm³ of water (thrice) and dried (sodium sulfate). The solvent was removed and chromatography of the residue (silica gel; 3:1 hexane–THF) gave three fractions. From fraction 1 (blue oil) was recovered 46.9 mg (0.237 mmol) of unchanged guaiazulene. Fraction 2 (blue oil) was rechromatographed (silica gel; 3:1 hexane–THF) and the main blue fraction combined with fraction 3 (blue oil) to give 932 mg (57%) of blue oil. The spectral properties of this product were in good agreement with those expected for *N*-butanoyl-2-(1-guaiazulenyl)-1-propanamine (**9**): UV (C_2H_5OH) 202 (log ε 4.31), 218 (4.14), 247 (4.22), 287 (4.40), 305 (4.04), 353 (3.55), 369 (3.47), 574 (ε sh, 250), 617 (283), 670 (sh, 226), and 752 nm (sh, 76); IR (CCl_4) 3470 (nonassoc N–H), 3360 (assoc N–H), and 1690 cm⁻¹ (amide C=O); ¹H NMR ($CDCl_3$) δ=0.82 (3H, t, *J*=7.0 Hz, γ-CH_3), 1.36 (9H, t, *J*=7.0 Hz, 5′-$CH(C\underline{H}_3)_2$ and 3-CH_3), 1.46 (2H, sext, *J*=7.0 Hz, β-CH_2), 2.00 (2H, t, *J*=7.0 Hz, α-CH_2), 2.64 (3H, s, 3′-CH_3), 2.98 (3H, s, 8′-CH_3), 3.05 (1H, sept, *J*=7.0 Hz, 5′-$C\underline{H}(CH_3)_2$), 3.42 (1H, sext, *J*=13.0, 5.0, and 5.0 Hz, one H of 1-CH_2), 3.74 (1H, decet, *J*=7.0, 7.0, and 5.0 Hz, 2-CH), 4.10 (1H, octet, *J*=13.0, 7.0, and 5.0 Hz, one H of 1-CH_2), 5.64 (1H, br m, NH), 6.92 (1H d, *J*=10.0 Hz, 7′-H), 7.34 (1H, q, *J*=10.0 and 2.0 Hz, 6′-H), 7.68 (1H, s, 2′-H), and 8.18 (1H, d, *J*=2.0 Hz, 4′-H); MS *m/e* (rel intensity) 325 (M^+, 18), 238 ($M^+-C_3H_7CONH_2$, 20), and 225 ($M^+-C_3H_7CONHCH_2$, 100).

Found: N, 4.54%. Calcd for $C_{22}H_{31}NO$: N, 4.30%.

1-(1-Guaiazulenyl)-2-propanamine (***13***). A suspension of *ca.* 15 mmol of colorless 2-methylaziridinium tetrafluoroborate in dichloromethane was prepared from 860 mg (15.1 mmol) of 2-methylaziridine in 10 cm³ of dry dichloromethane and 2.46 g (15.1 mmol) of tetrafluoroboric acid in ether (54%, Merck) according to the method of Harder *et al.*[11] and was used without further purification.

To the salt suspension was added, under nitrogen with stirring, dropwise (10 min) a solution of 990 mg (5.00 mmol) of guaiazulene in 20 cm³ of 1,2-dimethoxyethane (monoglyme). After distillative removal of the ether and dichloromethane, the mixture was refluxed for 48 h and then cooled and poured onto 300 g of crushed ice. A 50% solution of potassium carbonate (200 g) was added and the mixture then extracted with 3×100 cm³ of chloroform. The combined extracts were washed twice with a 29% sodium chloride (100 g) solution and dried (sodium sulfate). Removal of the solvent (ambient temperature at 2700 Pa and then 30 °C at 133—266 Pa) left a blue oil which gave two major TLC spots (alumina, chloroform: R_f 0.12 for **13** and 0.86 for guaiazulene). Chromatography over alumina with chloroform separated 1072 mg of material which yielded 510 mg (52%) of pure, unchanged guaiazulene after rechromatography over silica gel (hexane). The blue oil fractions obtained by further elution with chloroform and, finally, with acetone amounted to 420 mg. Rechromatography (alumina, 95:5 benzene–methanol) gave 101 mg (8%) of **13** as a blue oil: UV (C_2H_5OH) 217 (log ε 4.07), 247 (4.22), 287 (4.47), 306 (4.05), 341 (sh, 3.48), 353 (3.62), 369 (3.55), 581 (ε sh, 290), 622 (334), 673 (sh, 288), and 751 nm (sh, 111); IR (CCl_4) 3380 and 3310 (nonassoc N–H), 3190 (assoc N–H), and, 1380 and 1370 cm⁻¹ (δ_s CH_3); ¹H NMR ($CDCl_3$) δ=1.16 (3H, d, *J*=6.0 Hz, propane-CH_3), 1.34 (6H, d, *J*=7.0 Hz, 5′-$CH(C\underline{H}_3)_2$, 1.36 (2H, s, NH_2), 2.63 (3H, s, 3′-CH_3), 2.98 (3H, s, 8′-CH_3), 3.02—3.72 (4H, m, CH-CH_2 and 5′-$C\underline{H}(CH_3)_2$, 6.90 (1H, d, *J*=11.0 Hz, 7′-H), 7.33 (1H, q, *J*=11.0 and 2.0 Hz, 6′-H), 7.54 (1H, s, 2′-H), and 8.14 (1H, d, *J*=2.0 Hz, 4′-H); MS *m/e* (rel intensity) 255 (M^+, 6%), 211 ($M^+-CH_3CHNH_2$, 100), and 44 (CH_3CHNH_2, 75%).

Found: C, 84.24; H, 9.88; N, 5.33%. Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48%.

N,N-*Diethyl-2-(1-guaiazulenyl)ethanamine* (***14***). From 17.1 g (0.100 mol) of *N*,*N*-diethyl-2-chloroethanamine hydrochloride was prepared a 44% solution of the corresponding amine in benzene as determined by GLC analysis (Silicone SE 30 on Chromosorb W, 1 m column, 50 °C, 20 cm³ min⁻¹ He, t_R=1.8 min), and a solution of 5.02 g (37.0 mmol) of this amine (obtained from an aliquot portion of the benzene solution) was converted to 1,1-diethylaziridinium perchlorate [7.00 g, 95%, IR (CCl_4) 3125 cm⁻¹, mp 188—192 °C decomp] (Ref. 12; 192 °C decomp) as described by Leonard and Paukstelis[12] except that the crude salt was purified twice by dissolving it in 10 cm³ of dichloromethane and then precipitation by the addition of 200 cm³ of ether.[13]

A mixture of 200 mg (1.01 mmol) of guaiazulene, 300 mg (1.50 mmol) of 1,1-diethylaziridinium perchlorate and 5 cm³ of 1,2-dichloroethane was refluxed for 6 h, then taken up in 100 cm³ of chloroform, washed with 2×50 cm³ of saturated aqueous potassium carbonate, 3×50 cm³ of water and dried (sodium sulfate). Solvent removal (reduced pressure) left a green oil which gave two TLC spots (alumina, chloroform; R_f 0.65 for **14** and 0.82 for guaiazulene). Chromatography (alumina, 9:1 benzene–chloroform then chloroform) gave 85.1 mg of blue oil, which yielded 67.8 mg (34%) of guaiazulene on rechromatography (silica gel, hexane), and 161 mg of green-blue oil. Rechromatography (alumina, chloroform) of the green-blue oil afforded 104 mg (35%) of **14** (green-blue oil, R_f=0.65 on alumina with chloroform): UV (C_2H_5OH) 218 (log ε 4.06), 246 (4.22), 287 (4.46), 304 (sh, 4.04), 339 (sh, 3.49), 352 (3.68), 369 (3.56), 582 (ε sh, 256), 622 (298), 675 (sh, 235), and 751 nm (sh, 78); IR (CCl_4) 2960 (ν_{as} CH), 2925 (ν_{as} CH_2), 2870 (ν_s CH), 1460 (δ_{as} CH_3), and, 1380 and 1370 cm⁻¹ (δ_s CH_3); ¹H NMR ($CDCl_3$) δ=1.08 (6H, t, *J*=7.0 Hz, $CH_2C\underline{H}_3$), 1.32 (6H, d, *J*=7.0 Hz, 5′-$CH(C\underline{H}_3)_2$), 2.61 (3H, s, 3′-CH_3), 2.66 (4H, q, *J*=7.0 Hz, $C\underline{H}_2CH_3$), 2.78 (2H, m, 1-CH_2), 3.37 (2H, m, 2-CH_2), 6.84 (1H, d, *J*=10.5 Hz, 7′-H), 7.28 (1H, q, *J*=10.5 and 2.0 Hz, 6′-H), 7.52 (1H, s, 2′-H), and 8.10 (1H, d, *J*=2.0 Hz, 4′-H); MS *m/e* (rel intensity) 297 (M^+, 2), 211 ($M^+-CH_2NEt_2$, 7), and 86 ($Et_2NCH_2^+$, 100).

Found: C, 84.13; H, 10.45; N, 4.88%. Calcd for $C_{21}H_{31}N$: C, 84.79; H, 10.50; N, 4.71%.

N,N-*Dimethyl-2-(1-guaiazulenyl)-2-methyl-1-propanamine* (***15***) *and* N,N-*Dimethyl-1-(1-guaiazulenyl)-2-methyl-2-propanamine* (***16***). From 13.0 g (70.0 mmol) of *N*-isopropylidenedimethylammonium perchlorate, mp 298—300 °C,[6] was prepared 5.57 g (40%) of 1,1,2,2-tetramethylaziridinium perchlorate [^{1}H NMR ($\mathrm{CH_2Cl_2}$) $\delta=1.74$ (6H, s, $\mathrm{C(C\underline{H}_3)_2}$), 3.08 (2H, s, $\mathrm{CH_2}$), and 3.18 (6H, s, $\mathrm{(CH_3)_2N^+}$] [Ref. 14; $\delta=1.72$ (6H, 3.02 (2H), and 3.16 (6H)] as described.[14]

A mixture of 990 mg (5.00 mmol) of guaiazulene and 2.00 g (10.0 mmol) of the above aziridinium salt in 25 cm^3 of 1,2-dichloroethane under nitrogen was stirred at reflux temperature for 80 h, then treated as described for the preparation of **14** (500 cm^3 of chloroform; 2×100 cm^3 of 25% potassium carbonate; 2×100 cm^3 of water). From the chromatography of the crude blue oil (alumina; 9:1 benzene-chloroform) were obtained 942 mg of blue oil and 24.4 mg of green-blue oil. Rechromatography of the blue oil (silica gel, hexane) gave 786 mg (79%) of unchanged guaiazulene. Preparative TLC on alumina (9:1 benzene-chloroform) of the green-blue oil afforded 1.04 mg (0.07%) of **15** as a green oil ($R_f=0.25$) and 1.69 mg (0.1%) of **16** as a blue oil ($R_f=0.15$).

15: UV ($\mathrm{C_2H_5OH}$) 247 ($\log\varepsilon$ 4.03), 289 (4.00), 305 (sh, 3.93), 590 (ε 146), and 665 nm (sh, 109); IR ($\mathrm{CHCl_3}$) 2970 (ν_{as} $\mathrm{CH_2}$), 2870 (ν_{s} CH), 1460 (δ_{as} $\mathrm{CH_3}$), and 1380 and 1370 cm^{-1} (δ_{s} $\mathrm{CH_3}$); MS m/e (rel intensity) 297 ($\mathrm{M^+}$, 10), 222 ($\mathrm{M^+-CH_2N(CH_3)_2-2H}$, 40), 58 ($\mathrm{CH_2\overset{+}{N}(CH_3)_2}$, 96), and 43 ($\mathrm{CH_2\overset{+}{N}CH_3}$, 100).

16: UV ($\mathrm{C_2H_5OH}$) 218 ($\log\varepsilon$ 4.16), 247 (4.29), 289 (4.48), 306 (sh, 4.13), 342 (sh, 3.61), 353 (3.69), 371 (3.65), 575 (ε 258), 618 (300), 672 (sh, 237), and 755 nm (sh, 70); IR ($\mathrm{CCl_4}$) 2970 (ν_{as} CH), 2930 (ν_{as} $\mathrm{CH_2}$), 1460 (δ_{as} $\mathrm{CH_3}$), and, 1380 and 1360 cm^{-1} (δ_{s} $\mathrm{CH_3}$); ^{1}H NMR ($\mathrm{(CD_3)_2C{=}O}$) $\delta=1.36$ (6H, s, 1-$\mathrm{C(C\underline{H}_3)_2}$), 1.64 (6H, d, $J=6.0$ Hz, 5′-$\mathrm{CH(C\underline{H}_3)_2}$), 2.39 (6H, s, $\mathrm{N(CH_3)_2}$), 2.57 (3H, s, 3′-$\mathrm{CH_3}$), 2.86 (3H, s, 8′-$\mathrm{CH_3}$), 2.92 (1H, sept, $J=6.0$ Hz, 5′-$\mathrm{C\underline{H}(CH_3)_2}$), 3.19 (2H, s, 2-$\mathrm{CH_2}$), 5.74 (1H, d, $J=9.0$ Hz, 7′-H), 6.08 (1H, q, $J=9.0$ and 1.5 Hz, 6′-H), 6.37 (1H, s, 2′-H), and 6.66 (1H, d, $J=1.5$ Hz, 4′-H); MS m/e (rel intensity) 297 ($\mathrm{M^+}$, 8), 211 ($\mathrm{M^+-(CH_3)_2NC(CH_3)_2}$, 13), and 86 ($\mathrm{(CH_3)_2\overset{+}{N}C(CH_3)_2}$, 100).

N,N-*Diethyl-2-(1-azulenyl)ethanamine (**18**).* From 128 mg (1.00 mmol) of azulene and 300 mg (1.50 mmol) of 1,1-diethylaziridinium perchlorate was obtained, as described for **14**, a green-blue oil as the crude product. Chromatography (alumina, 98:2 benzene-methanol) separated 11.9 mg (9%) of unchanged azulene from 309 mg of blue oil. A benzene (70 cm^3) solution of the latter was extracted with 1 mol dm^{-3} hydrochloric acid (3×70 cm^3) and the combined acid solutions were extracted with chloroform (4×70 cm^3). Removal of the solvent from the dried (sodium sulfate) chloroform solution and chromatography of the residue (silica gel, 7:3 chloroform-methanol) gave 30.7 mg (12%) of hydrochloride (**20**) as tiny blue prisms, mp 150—151 °C: UV ($\mathrm{C_2H_5OH}$) 238 ($\log\varepsilon$ 4.36), 267 (sh, 4.57), 273 (sh, 4.69), 277 (4.74), 282 (sh, 4.71), 288 (sh, 4.55), 298 (sh, 4.03), 328 (sh, 3.90), 331 (3.90), 344 (3.97), 359 (3.84), 547 (s sh, 252), 563 (sh, 290), 589 (340), 610 (sh, 312), 636 (289), and 705 nm (111); IR ($\mathrm{CHCl_3}$) 2520, 2390, and 2330 ($\mathrm{NH^+}$), and 1186 cm^{-1} (C–N); ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta=1.42$ (6H, t, $J=7.5$ Hz, $\mathrm{CH_2C\underline{H}_3}$), 3.18 (4H, q, $J=7.5$ Hz, $\mathrm{C\underline{H}_2CH_3}$), 3.22 (2H, m, 1-$\mathrm{CH_2}$), 3.68 (2H, m, 2-$\mathrm{CH_2}$), 7.14 (2H, br t, $J=$*ca.* 10 Hz, 5′- and 7′-H), 7.31 (1H, d, $J=4.0$ Hz, 3′-H), 7.58 (1H, t, $J=10.0$ Hz, 6′-H), 7.74 (1H, d, $J=4.0$ Hz, 2′-H), 8.28 (1H, d, $J=9.5$ Hz, 4′-H), and 8.46 (1H, d, $J=9.5$ Hz, 8′-H); ^{13}C NMR ($\mathrm{CDCl_3}$) $\delta=8.8$ (q, $\mathrm{CH_2\underline{C}H_3}$), 22.5 (t, 2-C), 46.3 (t, $\mathrm{\underline{C}H_2CH_3}$), 52.9 (t, 1-C), 116.9 (d, 3′-C), 122.7 (d, 7′-C), 123.0 (d, 5′-C), 123.7 (s, 1′-C), 133.7 (d, 8′-C), 136.1 (s, 4′-C), 136.5 (s, 9′-C), 136.9 (d, 6′-C), 138.1 (d, 2′-C), and 140.7 (s, 10′-C).[15]

To a mixture of 28.7 mg (0.109 mmol) of **20** and 52 cm^3 of 50:2 benzene-methanol was added slowly 100 cm^3 of ice-cooled 50% aqueous potassium carbonate. The separated aqueous layer was extracted with benzene (3×40 cm^3). Removal of the solvent from the combined, dried (sodium sulfate) original benzene layer and extracts gave 19.4 mg (78%, 10% overall) of **18** (blue oil, $R_f=0.37$ on alumina with 7:3 benzene-ethyl acetate): UV ($\mathrm{C_2H_5OH}$) 238 ($\log\varepsilon$ 4.27), 263 (sh, 4.44), 268 (sh, 4.46), 273 (sh, 4.71), 277 (4.76), 281 (sh, 4.73), 287 (sh, 4.58), 297 (sh, 3.96), 315 (sh, 3.34), 322 (sh, 3.43), 334 (3.59), 344 (3.74), 359 (3.48), 537 (ε sh, 222), 560 (sh, 294), 581 (sh, 343), 601 (387), 622 (sh, 343), 655 (322), 687 (sh, 169), and 724 nm (123); IR ($\mathrm{CCl_4}$) 2980 and 2940 (ν_{as} CH), 2880 (ν_{s} CH), 1465, 1457, and 1439 (δ_{as} $\mathrm{CH_3}$), and, 1397, 1388 and 1378 cm^{-1} (δ_{s} $\mathrm{CH_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta=1.09$ (6H, t, $J=7.5$ Hz, $\mathrm{CH_2C\underline{H}_3}$), 2.69 (4H, q, $J=7.5$ Hz, $\mathrm{C\underline{H}_2CH_3}$), 2.84 (2H, m, 1-$\mathrm{CH_2}$), 3.26 (2H, m, 2-$\mathrm{CH_2}$), 7.08 (1H, t, $J=10.0$ Hz, 5′-H), 7.12 (1H, t, $J=10.0$ Hz, 7′-H), 7.37 (1H, d, $J=4.0$ Hz, 3′-H), 7.57 (1H, t, $J=10.0$ Hz, 6′-H), 7.85 (1H, d, $J=4.0$ Hz, 2′-H), 8.29 (1H, d, $J=10.0$ Hz, 4′-H), and 8.34 (1H, d, $J=10.0$ Hz, 8′-H); MS m/e (rel intensity) 227 ($\mathrm{M^+}$, 3), 141 ($\mathrm{M^+-CH_2N(C_2H_5)_2}$, 8), and 86 ($\mathrm{CH_2N(C_2H_5)_2{}^+}$, 100).

Found: C, 84.50; H, 9.29; N, 6.08%. Calcd for $\mathrm{C_{16}H_{21}N}$: C, 84.53; H, 9.31; N, 6.16%.

N,N-*Diethyl-2-(4,6,8-trimethyl-1-azulenyl)ethanamine (**19**).* From 172 mg (1.01 mmol) of 4,6,8-trimethylazulene and 300 mg (1.50 mmol) of 1,1-diethylaziridinium perchlorate was obtained, as described for **14** except that the mixture was refluxed for 23 h; a violet oil was obtained as the crude product. Chromatography (alumina, 9:1 hexane-ethyl acetate) of a solution of the oil in a small volume of acetone separated 25.1 mg (15%) of unchanged trimethylazulene from 143 mg (53%) of **19** (blue oil, $R_f=0.30$ on alumina with 9:1 hexane-ethyl acetate): UV ($\mathrm{C_2H_5OH}$) 246 ($\log\varepsilon$ 4.42), 278 (sh, 4.40), 284 (sh, 4.57), 288 (4.66), 293 (4.65), 298 (sh, 4.61), 327 (sh, 3.46), 338 (3.58), 352 (3.68), 367 (sh, 3.18), 555 (ε sh, 368), 564 (428), 607 (sh, 340), and 667 nm (sh, 129); IR ($\mathrm{CCl_4}$) 2975 (ν_{as} CH), 2930 (ν_{as} $\mathrm{CH_2}$), 2880 (ν_{s} CH), 1470, 1462, 1445 and 1426 (δ_{as} $\mathrm{CH_3}$), and, 1382 and 1372 cm^{-1} (δ_{s} $\mathrm{CH_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta=1.06$ (6H, t, $J=7.0$ Hz, $\mathrm{CH_2C\underline{H}_3}$), 2.48 (3H, s, 6′-$\mathrm{CH_3}$), 2.63 (4H, q, $J=7.0$ Hz, $\mathrm{C\underline{H}_2CH_3}$), 2.75 (3H, s, 4′-$\mathrm{CH_3}$), 2.76 (2H, m, 1-$\mathrm{CH_2}$), 2.96 (3H, s, 8′-$\mathrm{CH_3}$), 3.34 (2H, m, 2-$\mathrm{CH_2}$), 6.81 (2H, s, 5′- and 7′-H), 7.22 (1H, d, $J=4.0$ Hz, 3′-H), and 7.44 (1H, d, $J=4.0$ Hz, 2′-H); ^{13}C NMR ($\mathrm{CDCl_3}$) $\delta=11.5$ (q, $\mathrm{CH_2\underline{C}H_3}$), 25.4 (q, 4′-$\mathrm{CH_3}$), 27.4 (q, 8′-$\mathrm{CH_3}$), 28.3 (q, 6′-$\mathrm{CH_3}$), 29.6 (t, 2-C), 46.8 (t, $\mathrm{\underline{C}H_2CH_3}$), 56.0 (t, 1-C), 115.2 (d, 3′-C), 126.0 (d, 5′-C), 128.2 (d, 7′-C), 129.0 (s, 1′-C), 132.2 (s, 9′-C), 135.8 (d, 2′-C), 137.0 (s, 10′-C), 144.7 (s, 4′-C), 145.5 (s, 6′-C), and 146.1 (s, 8′-C); MS m/e (rel intensity) 269 ($\mathrm{M^+}$, 4), 183 ($\mathrm{M^+-CH_2N(C_2H_5)_2}$, 4), and 86 ($\mathrm{(C_2H_5)_2NCH_2{}^+}$, 100).

A solution of 111 mg (0.412 mmol) of **19** in 60 cm^3 of benzene was extracted with 1 mol dm^{-3} hydrochloric acid (3×35 cm^3), and the hydrochloric acid layer was extracted with chloroform (6×35 cm^3). The chloroform solution was dried (sodium sulfate), concentrated (reduced pressure), and chromatographed on a silica gel column (elution with 8:2 chloroform-methanol) to give 84.4 mg (67%) of **21** as a purple oil: UV ($\mathrm{C_2H_5OH}$) 247 ($\log\varepsilon$ 4.44), 277 (sh, 4.38), 283 (sh, 4.55), 288 (4.63), 293 (4.63), 297 (sh, 4.60), 336 (3.56), 345 (sh, 3.57), 351 (3.61), 552 (ε 334), 592 (sh, 276), and 647 nm (sh, 108); IR ($\mathrm{CHCl_3}$) 2470, 2440, 2400, 2355, and 2330 ($\mathrm{NH^+}$), and 1195 cm^{-1} (C–N);

^{1}H NMR ($CDCl_3$) δ=1.43 (6H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.16 (1H, s, NH^+), 2.60 (3H, s, 6′-CH_3), 2.84 (3H, s, 4′-CH_3), 3.07 (3H, s, 8′-CH_3), 3.25 (q, 4H, J=7.0 Hz, $C\underline{H}_2CH_3$), 3.27 (2H, m, 1-CH_2), 3.85 (2H, m, 2-CH_2). 7.08 (2H, s, 5′- and 7′-H), 7.39 (1H, d, J=4.0 Hz, 3′-H), and 7.60 (1H, d, J=4.0 Hz, 2′-H).

Found: C, 74.99; H, 9.88; N, 4.71; Cl, 11.23%. Calcd for $C_{19}H_{28}NCl$: C, 74.60; H, 9.23; N, 4.58; Cl, 11.59%.

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