The Effect of Fused Rings on the Spectral and Electrochemical Properties of Bis-Fused 1,4-Diacetyl-1,4-dihydropyrazines

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A series of 1,4-diacetyl-1,4-dihydropyrazines fused with two bornene, cyclopentene, and cyclohexene rings were prepared by the reduction of the corresponding pyrazines with zinc powder in the presence of acetic anhydride. Cyclic voltammetry measurements revealed that the oxidation potentials of the dihydropyrazines decrease in the order of cyclohexene-, bornene-, and cyclopentene-fused derivatives. This trend is in harmony with that of the bathochromic shifts in their UV absorptions.

A number of recent studies on the aromatic compounds fused with bicyclic skeletons have demonstrated intriguing effects of the fused rings on the aromatic rings. For example, the fusion of strained bicycloalkenes such as bicyclo[2.1.1]hex-2-ene with some aromatic compounds has exhibited the bond-fixation of the aromatic rings.[1—3] Fusion of less strained bicyclo[2.2.2]oct-2-ene enhances the stabilities of a tropylium ion, a radical cation and a dication of cyclooctatetraene, and metallepines, probably due to the electron-donating and/or steric effect by the bicyclooctene skeleton.[4—8] Furthermore, the formation of stable radical cations of *p*-dialkoxybenzenes,[9] an increase in the electron affinities of naphthoquinones and benzo-TCNQ derivatives,[10] and a decrease of pK_a values of fused quinoxalines[11] have also been demonstrated upon the fusion of strained bicycloalkenes. We reported on the syntheses of a thiophene, pyrroles, and furans fused with norbornadiene[12,13] as well as an imidazole fused with a 2-azanorbornene skeleton,[14] and their unusual spectral properties and novel cycloaddition reactions which may be due to the angular strain effect.

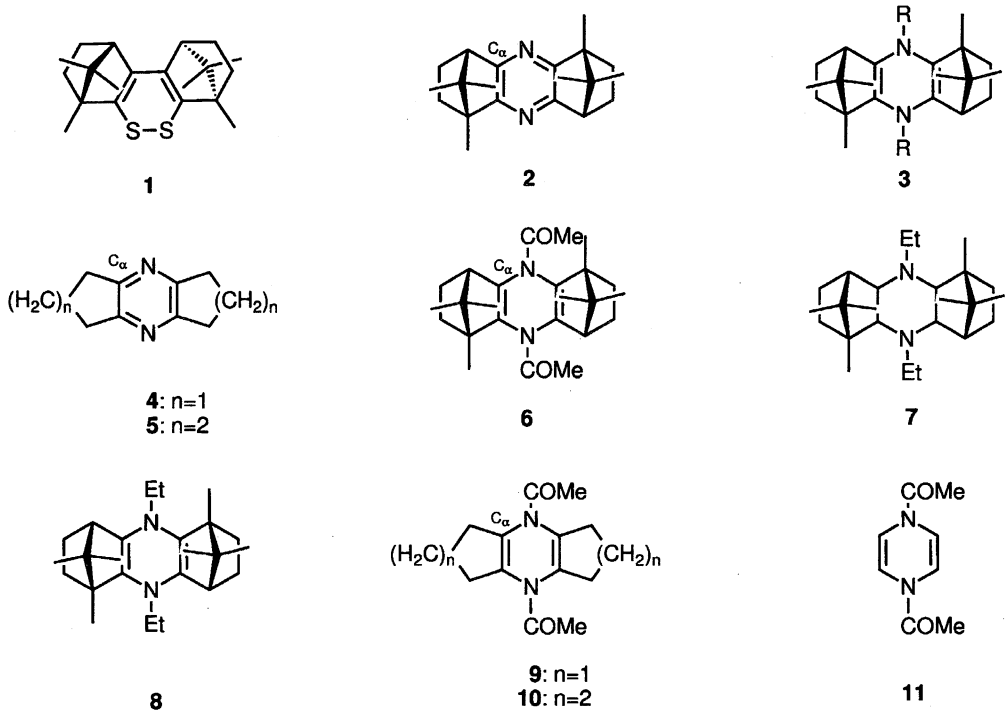
Unlike the rich chemistry of bicycloalkene-fused aromatic compounds, there are only a few studies concerning the effect of fusion for conjugated 4nπ heterocycles. Recently, the dibornene-fused 1,2-dithiin **1**, prepared by the oxidative dimerization of thiocamphor, was shown to have a great stability in spite of a conjugated heterocycle with 8π electrons; this stability is considered to be derived from the steric effect of the rigid and bulky bicyclic skeleton.[15,16] As part of our continuing efforts to understand the bicyclic effect, we considered it worthwhile to synthesize 1,4-dihydropyrazines fused with two bornene skeletons **3**, expecting to produce another kinetically stabilized 8π-electron system. We report here the synthesis and properties of a bornene-fused 1,4-dihydropyrazine, along with those of the cyclopentene- and cyclohexene-fused derivatives.

Results and Discussion

The bornene-fused pyrazine **2**[17—19] was obtained by the oxidative dimerization of (1*R*,3*S*)-3-amino-2-bornanone.[20] The cyclopentene- and cyclohexene-fused pyrazines **4** and **5** were prepared from the corresponding α-amino ketones according to the procedures described in the literature.[21]

Our attempt to prepare the silylated 1,4-dihydropyrazines **3** (R = Me_3Si or *t*-$BuMe_2Si$) by the reactions of the bornene-fused pyrazine **2** with chlorosilanes in the presence of lithium[22,23] resulted in the recovery of **2** (Chart 1). Treatment of the pyrazine **2** with zinc powder in refluxing acetic anhydride provided the bornene-fused 1,4-diacetyl-1,4-dihydropyrazine **6** in 29% yield. The dihydropyrazine **6** was obtained as colorless needles and has a high melting point (272 °C) without decomposition. Since the stability of the dihydropyrazine **6** was considered to be derived from the electron-withdrawing acetyl groups,[24,25] the conversion of **6** to the di-*N*-ethyl-substituted derivative **8** was examined. The reduction of the dihydropyrazine **6** with lithium aluminum hydride or 1.6 molar equivalent of dimethyl sulfide–borane (1/1), however, gave the pyrazine **2** in 49 and 69% yields respectively. The unexpected formation of the pyrazine **2** under such reductive conditions is explained by the reductive elimination of acetyl groups[26] to give a dihydropyrazine **3** (R = metal or H), followed by air oxidation. On the other hand, the reduction of the diacetyldihydropyrazine **6** with a large excess of dimethyl sulfide–borane (1/1) gave the diethyl-substituted piperazine **7**, albeit in 18% yield. The observation of 12 signals in the ^{13}C NMR spectrum of **7** supports the presence of C_2 symmetry in this molecule, but the stereochemistry could not be deduced from the spectral data. Unfortunately, no evidence for the formation or intervention of the 1,4-diethyl-1,4-dihydropyrazine **8** in these reactions was obtained.

In order to compare the physical properties, the cyclopentene- and the cyclohexene-fused 1,4-diacetyl-1,4-dihy-



1 **2** **3**

4: n=1
5: n=2

6 **7**

8

9: n=1
10: n=2

11

Chart 1.

dropyrazines **9** and **10** were similarly prepared by treatment of the fused pyrazines with acetic anhydride and zinc powder. In Table 1, the ^{13}C chemical shifts at the ring-juncture sp^2 carbon atoms (C_α), redox potentials measured by cyclic voltammetry, and absorption maxima in UV spectra of the fused pyrazines and dihydropyrazines along with those of 1,4-diacetyl-1,4-dihydropyrazine (**11**) are shown. In the ^{13}C NMR spectra of the fused pyrazines **2**, **4**, and **5**, a downfield shift of the ring-juncture carbons (C_α) with increasing strain was observed. A similar deshielding of the ring-juncture carbons has been reported for benzocycloalkenes and their pyridine analogues, as well as for the norbornadiene-fused five-membered heteroaromatics[12,14,27] On the contrary, such a systematic downfield shift for the ring-juncture carbons was not observed for the fused 1,4-diacetyl-1,4-dihydropyrazines **6**, **9**, and **10**. Such a result implies release of angular strain by conformational changes. The cyclic voltammetry measurements of the fused pyrazines **2**, **4**, and **5** show that their reversible reduction potentials are not affected by the fused rings. This result is in contrast with the observation that the reduction potentials of fused naphtoquinones decrease with increasing strain.[10,28] The fused 1,4-diacetyl-1,4-dihydropyrazines **6**, **9**, and **10** exhibited irreversible oxidation peaks, in contrast to the report that 1,4-diacetyl-1,4-dihydropyrazine (**11**) exhibits a reversible oxidation peak.[25] The oxidation potentials of the fused dihydropyrazines dramatically decreased in the order of cyclohexene-, bornene-, and cyclopentene-fused derivatives (**10** > **6** > **9**). The dramatic and unpredictable changes of the oxidation potentials could not be explained by the angular strain effect of the fused rings. The trend of these changes agrees with the order of bathochromic shifts in the UV spectra (Table 1). Accordingly, these facts are suggestive of an increase in the planarity of 1,4-dihydropyrazine ring and/or an extension of conjugation including the acetyl groups, depending on the fused rings.

Table 1. Physical Properties of Bis-Fused Pyrazines and 1,4-Diacetyl-1,4-dihydroyrazines

Compd	^{13}C Chemical shift	Redox potential	UV (in EtOH)	HOMO[a]	LUMO[a]
	C_α (ppm)	V vs. SCE	λ_{max} (log ϵ)	eV	eV
2	158.2, 159.6	−1.04[b]	313 (4.0)	−9.41	−0.26
4	155.6	−1.04[b]	318 (3.8)	−9.36	−0.29
5	149.1	−1.03[b]	308 (3.7)	−9.39	−0.21
6	135.8, 139.8	+0.72[c]	278 (4.1)	−7.57	+0.39
9	132.3	+0.50[c]	290 (4.2)	−7.57	+0.18
10	132.8	+0.91[c]	265 (4.1)	−7.40	+0.45
11	—	+0.74[d]	298 (4.4)	—	—

a) Calculation by AM1 method. b) Half wave potential in DMF. c) Irreversible wave potential in CH_3CN. d) Half wave potential in CH_3CN.

According to molecular orbital calculations and X-ray structural analyses, the conformations of 1,4-dihydropyrazine derivatives have been reported to vary from very shallow chair to boat depending on the substituents.[29] An ab-inito calculation with 6-21G level for 1,4-dihydropyrazine gives a value of 7.8° for the folding angle of the boat conformation with a minimun energy.[30] When we calculated on 1,4-dihydropyrazine with AM1, PM3, and MNDO methods,[31] AM1 method gave the closest value of the folding angle (8.5°) to that of the ab-initio calculation. Therefore, we adopted the AM1 method for the calculations to gain some geometrical information on the fused 1,4-dihydropyrazines.[31] Calculations with various input-geometries (chair, plane, and boat; and combinations of axial–equatorial and syn–anti of acetyl groups) provided the most stable conformations of the fused 1,4-dihydropyrazines, as shown in Fig. 1. The results indicate that the cyclopentene-fused derivative **9** takes a relatively planar conformation and the cyclohexene-fused one **10** has the most folded conformation. Only in the case of the cyclopentene-fused derivative **9**, both the two acetyl groups take axial positions with relatively large N–CO bond orders, while the other two dihydropyrazines **10** and **6** hold an equatorial and an axial acetyl group. The outcome of the geometry optimized by these calculations seems to match the trend observed in the oxidation potentials and the UV absorptions. However, we can find no correlation between the energy levels of HOMO calculated by AM1 (Table 1) and the trend of the oxidation potentials, or between the optimized geometries and the carbonyl absorptions in the IR spectra.

In conclusion, we have demonstrated that the fused rings exert a profound influence on the electrochemical and the UV spectral properties of the 1,4-diacetyl-1,4-dihydropyrazines rather than those for aromatic pyrazines. The effect on the dihydropyrazines could not be explained by the angular strain. Although the source of the unpredictable changes in the oxidation potentials and the UV absorptions is presently unknown, the conformational changes would be one of the most important factors in the case of the fused 1,4-dihydropyrazines.

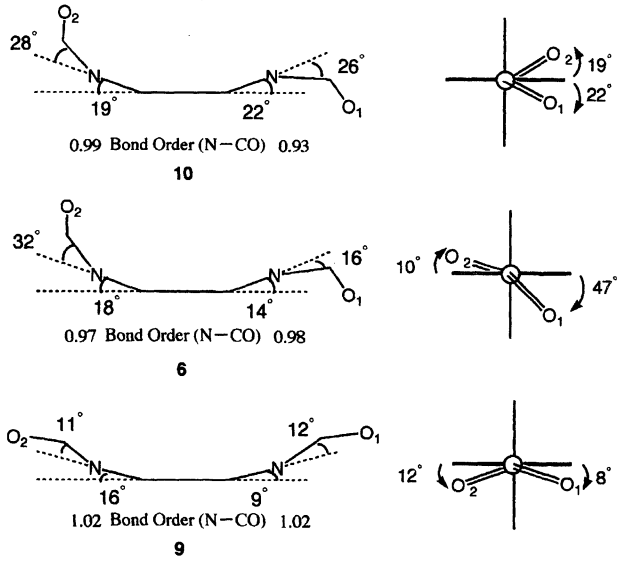


Fig. 1. Side views of the most stable conformers and tortional angles of carbonyl bonds from the ring-plane calculated by AM1 method for the fused 1,4-diacetyl-1,4-dihydropyrazines. Fused rings and methyl groups are omitted for making the figure legible. Two nitrogen atoms of **6** are lifted up toward the methano bridges.

Experimental

General. All the melting points were recorded with a Yanagimoto hot-stage aparatus and are uncorrected. IR spectra were obtained with a Hitachi 345 spectrometer. ^{1}H (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded with a JEOL JNM-FX-90Q spectrometer with tetramethylsilane as an internal standard. UV spectra were recorded with a Shimadzu UV-260 spectrophotometer. Mass spectra were taken with a Shimadzu GCMS-QP1000EX spectrometer operating in the electron impact mode with an ionizing energy of 70 eV. Elemental analyses were performed with a Perkin–Elmer Model 240 apparatus. Cyclic voltammograms were recorded with a Toho Giken PS-07 electrochemical analyzer with Et_4NClO_4 (0.1 mol dm^{-3}) as supporting electrolyte, Pt working electrode, Pt-wire counter electrode, and SCE reference electrode. The sweep rate was 200 mV s^{-1}.

The pyrazines **2**,[17–19] **4**[21], and **5**[21] were prepared from the corresponding α-amino ketones, as described in the literature.

2: Light tan needles (from ethanol–water); mp 159—160 °C, (lit,[17] mp 159.5—160.0 °C); IR (KBr) 1475, 1450, 1350, 1260, 1220, 1120, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.59 (6H, s, Me), 0.99 (6H, s, Me), 1.21 (4H, m), 1.33 (6H, S, Me), 1.79—2.24 (4H, m), 2.91 (2H, d, J = 3.8 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ = 10.2 (q, Me), 19.0 (q, Me), 19.8 (q, Me), 24.9 (t, C-5 or C-6), 32.0 (t, C-6 or C-5), 53.2 (d, C-4), 53.4 (s, C-1 or C-7), 56.8 (s, C-7 or C-1), 158.2 (s), 159.6 (s); MS *m/z* (rel intensity) 296 (M^+; 96), 281 ($M-CH_3$; 24), 253 ($M-C_3H_7$; 100). UV (EtOH) λ (log ϵ) 227 (3.4), 293 (4.1), 313 nm (4.0). Found: C. 80.81; H, 9.36; N, 9.66%. Calcd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45%.

4: Colorless needles (from hexane); mp 90.5—91.0 °C, (lit,[21] mp 89—91 °C); IR (KBr) 2950, 1460, 1420, 1360, 1285, 1220, 1150, 1015, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.19 (4H, quint, J = 7.2 Hz), 3.00 (8H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 21.1 (t), 31.2 (t), 155.6 (s); MS *m/z* (rel intensity) 160 (M^+; 81), 159 ($M-1$; 100), 66 (16); UV (EtOH) λ (log ϵ) 214 (3.7), 297 (4.0), 318 nm (sh, 3.8). Found: C. 74.87; H, 7.24; N, 17.56%. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48%.

5: Colorless plates (from hexane); mp 109—110 °C, (lit,[21] mp 109.6—110.6 °C); IR (KBr) 2935, 2860, 1435, 1420, 1330, 1215, 1180, 1130, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.89 (8H, m), 2.88 (8H, m); ^{13}C NMR ($CDCl_3$) δ = 22.7 (t), 31.5 (t), 149.1 (s); MS *m/z* (rel intensity) 188 (M^+; 100), 160 ($M-C_2H_2$; 38), 132 ($M-2C_2H_2$; 12); UV (EtOH), λ_{max} (log ϵ) 213 (3.8), 290 (4.0), 308 nm (sh, 3.8). Found: C. 76.82; H, 8.69; N, 15.13%. Calcd for $C_{12}H_{10}N_2$: C, 76.55; H, 8.57; N, 14.88%.

5,10-Diacetyl-1,2,3,4,5,6,7,8,9,10-decahydro-1,6,11,11,12,12-hexamethyl-1,4 : 6,9-dimethanophenazine (6): Zinc powder (2.60 g, 40 mmol) was added portionwise to a solution of the bornene-fused pyrazine **2** (2.37 g, 8 mmol) in acetic anhydride (8.20 g, 80 mmol). Then the mixture was refluxed for 9 h. Insoluble materials were removed by filtration and washed with dichloromethane. The filtrate was concentrated and the residue was separated by column chromatography (silica gel, dichloromethane). The resulting solid was recrystallized from hexane to give the bornene-fused 1,4-

dihydropyrazine **6** (889 mg, 29%) as colorless needles: Mp 271—272 °C; IR (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.79 (6H, s, 1-Me), 1.13 (12H, s, Me), 1.30—2.01 (8H, m), 2.20 (6H, s, COMe), 2.65 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 13.7 (q, Me), 18.8 (q, Me), 18.9 (q, Me), 23.9 (q, COMe), 25.9 (t), 35.0 (t), 53.6 (s), 54.6 (d), 57.5 (s), 135.8 (s), 139.8 (s), 170.6 (CO); MS *m/z* (rel intensity) 382 (M^+; 3), 339 (M − COMe; 14), 298 (M − 2COMe; 25), 297 (M − 2COMe − H; 100); UV (EtOH) λ_{max} (log ϵ) 278 nm (4.1). Found: C. 75.24; H, 9.03; N, 7.35%. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32%.

Attempted Reduction of the Dihydropyrazine 6 with Lithium Aluminum Hydride. To a suspension of lithium aluminum hydride (57 mg, 1.5 mmol) in anhydrous THF (1 cm^3) was added a solution of the dihydropyrazine **6** (191 mg, 0.5 mmol) in THF (3 cm^3) over 5 min at room temperature. The mixture was stirred at room temperature for 20 h. Ethyl acetate (1 cm^3) was carefully introduced to quench the excess lithium aluminum hydride; then aqueous NaOH (5%) was successively added. The mixture was extracted with dichloromethane and the extracts were washed with sat. aqueous NaCl solution and dried over Na_2SO_4. After removal of the solvent, the residue was separated by column chromatography (silica gel, chloroform) to give the bornene-fused pyrazine **2** (72 mg, 49%, mp and mixed mp 157—159 °C).

Reduction of the Dihydropyrazine 6 with Dimethyl Sulfide–Borane (1/1). To a solution of the dihydropyrazine **6** (382 mg, 1 mmol) in THF (5 cm^3) was added dimethyl sulfide–borane (1/1) (400 mg, 5.3 mmol) under nitrogen atmosphere. Then the solution was refluxed for 30 min. The solvent was removed by distillation and 2 M hydrochloric acid (1 cm^3) was added to the residue. After the mixture was stirred for 1 h, 0.5 M NaOH solution (10 cm^3) was added. The mixture was extracted with dichloromethane, washed with water, and dried over K_2CO_3. After removal of the solvent, the residue was separated by column chromatography (silica gel, dichloromethane) to give the piperazine **7** (65 mg, 18%): Mp 119.5—120 °C; colorless needles (from ethanol); IR (KBr) 1455, 1365, 1320, 1175, 1100, 1070, 1020, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.73 (6H, t, J = 7.0 Hz, CH_3CH_2), 0.87 (6H, s, Me), 0.94 (6H, s, Me), 0.96 (6H, s, Me), 1.33—1.40 (4H, m), 1.65 (2H, m), 2.05 (4H, q, J = 7.0 Hz, CH_2), 2.50—2.85 (8H, m); ^{13}C NMR ($CDCl_3$) δ = 4.3 (q), 17.1 (q), 18.9 (q), 20.6 (q), 20.8 (t), 27.9 (t), 42.3 (t, NCH_2), 47.3 (s), 47.8 (d), 49.6 (s), 59.8 (s), 62.8 (d); MS *m/z* (rel intensity) 358 (M^+; 100), 329 (M − Et; 33). Found: C. 80.41; H, 11.97; N, 7.80%. Calcd for $C_{24}H_{42}N_2$: C, 80.38; H, 11.80; N, 7.81%.

A similar reaction of **6** (382 mg, 1 mmol) with dimethyl sulfide–borane (1/1) (0.15 cm^3, 1.6 mmol) in refluxing THF (5 cm^3) gave **2** (204 mg, 69%, mp and mixed mp 157—158 °C).

4,8-Diacetyl-1,2,3,4,5,6,7,8-octahydrodicylopentapyrazine 9: A mixture of the cyclopentene-fused pyrazine **4** (930 mg, 5.8 mmol) and zinc powder (3.9 g, 60 mmol) in acetic anhydride (12 cm^3) was refluxed for 20 h. Insoluble materials were removed by filtration and water (20 cm^3) was added to the filtrate. The mixture was extracted with dichloromethane. The extracts were washed with aq sodium hydrogencarbonate and dried over Na_2SO_4. After removal of the solvent, the residue was separated by column chromatography (silica gel, ethyl acetate) to provide the cyclopentene-fused 1,4-dihydropyrazine **9** (277 mg, 19%) as colorless needles (from cyclohexane): Mp 119—120 °C; IR (KBr) 1665, 1630, 1375, 1350, 1320, 1195, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.01—2.32 (4H, m), 2.14 (6H, s, COMe), 2.71 (8H, br t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 23.7 (t), 24.4 (q), 30.9 (q), 132.3 (s),168.9 (s); UV (EtOH) λ_{max} (log ϵ) 290 nm (4.2). Found: C. 68.16; H, 7.34; N, 11.13%. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%.

5,10-Diacetyl-1,2,3,4,5,6,7,8,9,10-decahydrophenazine 10: A mixture of the cyclohexene-fused pyrazine **5** (1.13 g, 6 mmol) and zinc powder (3.9 g, 60 mmol) in acetic anhydride (10 cm^3) was refluxed for 8 h. A similar work-up as described for **9** gave the cyclohexene-fused 1,4-dihydropyrazine **10** (1.02 g, 62%) as colorless plates (from cyclohexane): Mp 115—116 °C; IR (KBr) 1680, 1670, 1650, 1440, 1380, 1360, 1320, 250, 1200, 1140, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.38—2.24 (12H, m), 2.12 (6H, s, COMe), 2.65—3.07 (4H, m); ^{13}C NMR ($CDCl_3$) δ = 22.5 (t), 24.0 (q), 28.5 (t), 132.8 (s),168.9 (s); MS *m/z* (rel intensity) 274 (M^+; 2), 231 (M − $COCH_3$; 11), 189 (M − 2$COCH_3$ + H; 100); UV (EtOH) λ_{max} (log ϵ) 221 (3.7). 265 nm (4.1). Found: C. 70.02; H, 8.11; N, 10.16%. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21%.

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