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Dioxopyrrolines. XXXV.[1] Synthesis of 2*H*-Azepin-2-ones (2-Azatropones)

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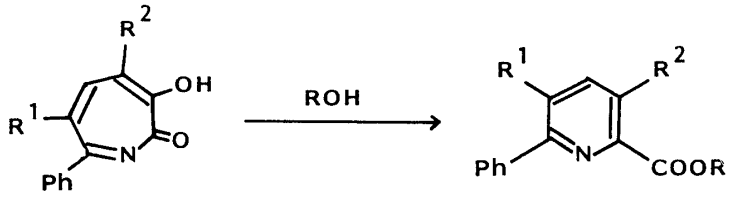
Eliminative ring expansion of 4-acetoxy (or mesyloxy)-2-azabicyclo[3.2.0]heptan-3-ones (**7**) yielded 1,5-dihydro-2*H*-azepin-2-ones (dihydro-2-azatropones) which, on DDQ oxidation, afforded the 2*H*-azepin-2-ones (2-azatropones, **9**). In contrast to azatropolones, the 2-azatropones were stable to protic solvents. However, irreversible solvolytic changes were observed in both acidic and basic media.

Keywords——dioxopyrroline; 2*H*-azepin-2-one; 2-azatropone; azatropolone; solvolytic change; eliminative ring expansion; 2*H*-azepin-2-one UV spectrum

We have previously reported the synthesis of a new heteroaromatic, 3-aza-α-tropolone (**1**), which, in contrary to our expectation, was unstable in protic solvents and readily rearranged into a pyridine-2-carboxylate (**2**).[2] In relation to the stability of a seven-membered heteroaromatic ring containing nitrogen, we accordingly became interested in the corresponding deoxycompound, 2*H*-azepin-2-one (2-azatropone).



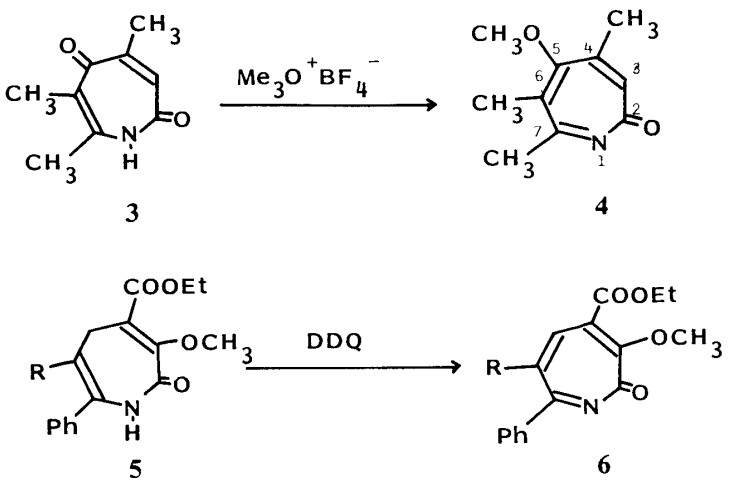
1 **2**

R^1 = Ph, OEt, H, COOEt
R^2 = COOEt, Ph, OEt

Chart 1

To our surprise, little work has been done on 2*H*-azepin-2-ones, although their dihydroderivatives, 1,3-dihydro-2*H*-azepin-2-ones[3] and 1,7-dihydro-2*H*-azepin-2-ones,[4] are well known. Only two methoxy derivatives of 2-azatropones are known; the 5-methoxy derivative **4** was reported by Moriconi and Maniscaclco[5] and the 3-methoxy derivative **6** by us,[2b] as shown in Chart 2. In this paper, we add two further examples, the 6-ethoxy-4-carbethoxy-7-phenyl and 4-carbethoxy-6,7-diphenyl derivatives, **9b** and **9a**.

The present synthesis of 2-azatropones is based on the base-catalyzed eliminative ring expansion of 4-acetoxy (or mesyloxy)-2-azabicyclo[3.2.0]heptan-3-ones (**7**)[6] to 1,5-dihydro-2*H*-azepin-2-ones (**8**). Compounds **7** are readily available by hydride reduction of the photocycloadduct of olefins with 4-ethoxycarbonyl-5-phenyl-1*H*-pyrrole-2,3-dione[7] followed



3 4

5 6

R = Ph, OEt, OAc, Et, SPh, H

Chart 2

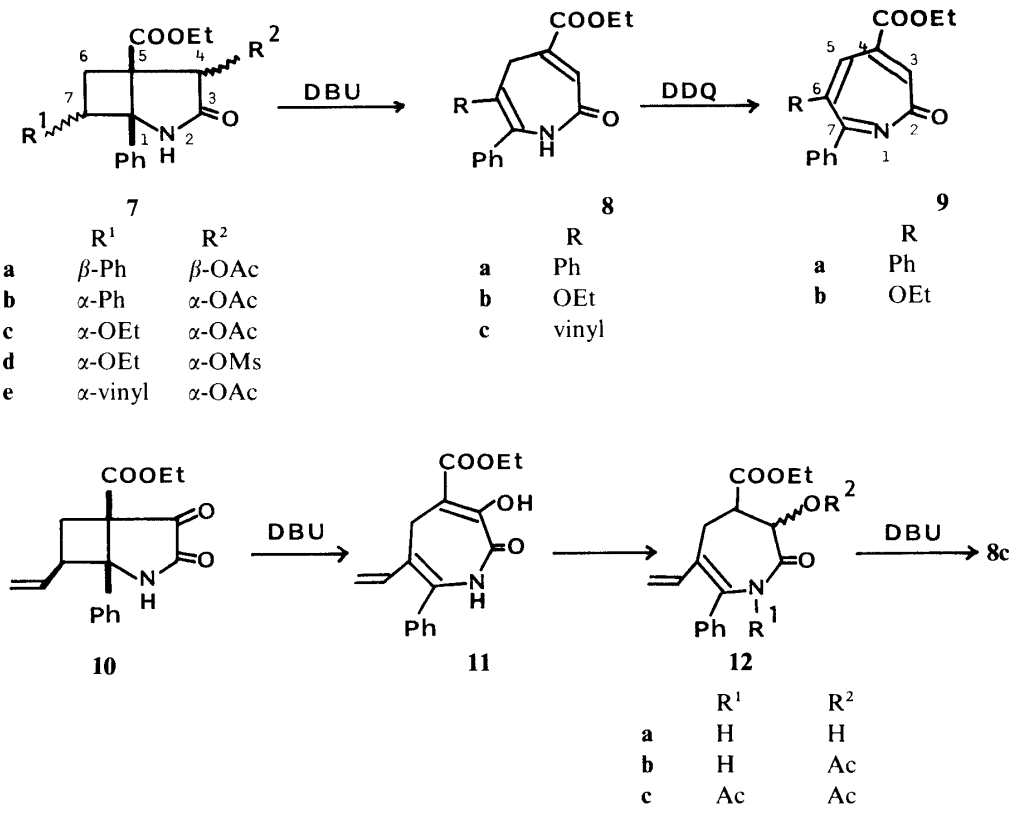
by acetylation (or methanesulfonylation). Heating of the acetoxyl derivatives **7** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene under reflux gave the expected ring-expanded product **8**, usually in good yield (70—80%), except in the case of the vinyl derivative **8c**, which was obtained in 27% yield. Moreover, similar treatment of the mesylate **7d** gave **8b** in quantitative yield. The reaction occurred smoothly regardless of the stereochemistry of the C_4 and C_7 substituents, as demonstrated in **7a** and **7b**, and this eliminative ring expansion reaction was facilitated by a good leaving group.

The structures of the products were confirmed by the following spectroscopic evidence and by an alternative synthesis of **8c**. For example, **8a**—**c** exhibited an absorption maximum at 330—340 nm in their ultraviolet (UV) spectra, and the proton nuclear magnetic resonance (^{1}H-NMR) spectra showed the presence of methylene protons at δ 3.3—3.5 as a singlet of 2H and an olefin proton at δ 7.3—7.7 (1H) in addition to the absorptions expected for the substituents.

The alternative synthesis of **8c** is as follows. Compound **10**, the photoadduct of butadiene to the dioxopyrroline, was converted to the dihydroazatropolone **11** on treatment with DBU as reported already.[2b] Reduction of **11** with *n*-Bu_4NBH_4 and acetylation of the resulting alcohol **12a** gave the monoacetate **12b** and the *N*,*O*-diacetate **12c**. Treatment of **12b** with DBU in benzene gave **8c**, which was identical with the compound obtained above.

Dehydrogenation of 1,5-dihydro-1*H*-azepin-2-ones (**8**) to 2*H*-azepin-2-ones (**9**) was achieved by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation in benzene. However, the reactivity of the compound was found to be greatly influenced by the substituent at C_6. The 6-ethoxy derivative **8b** smoothly gave the 2-azatropone **9b** in 78% on reaction at 100 °C for 25 min, while the oxidation of the 6-phenyl derivative **8a** required a prolonged reaction and afforded **9a** in 24% yield. The vinyl derivative **8c** was extensively decomposed, no characterizable product being isolated from the reaction mixture.

The 2*H*-azepin-2-ones (**9a** and **9b**) are colorless compounds. Their UV spectra (Fig. 1) in both dioxane and methanol exhibited an absorption maximum at approximately 265 nm, and resembled those of 3-methoxy derivatives **6**[2b] except that the latter compounds have an additional weak absorption maximum at around 360 nm. The ^{1}H-NMR spectra of **9** exhibited aromatic proton signals on an azepinone ring at δ 7.40 and 7.95 for **9a** and at δ 6.92 and 7.15 for **9b**, both of which showed a long-range coupling (1 Hz) indicative of a *meta*-relationship. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra showed the lactam carbonyl signal at 164.6 ppm for **9a** and 169.1 ppm for **9b**.



	R^1	R^2
a	β-Ph	β-OAc
b	α-Ph	α-OAc
c	α-OEt	α-OAc
d	α-OEt	α-OMs
e	α-vinyl	α-OAc

	R
a	Ph
b	OEt
c	vinyl

	R
a	Ph
b	OEt

	R^1	R^2
a	H	H
b	H	Ac
c	Ac	Ac

Chart 3

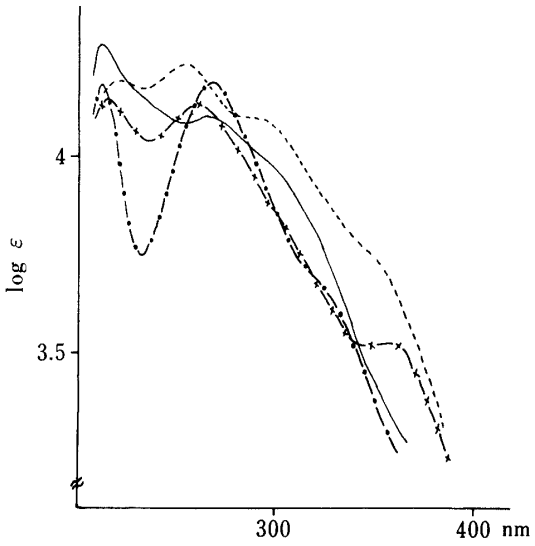


Fig. 1. UV Spectra of **6** and **9** in Dioxane

2*H*-Azepin-2-ones: —— **9a**; — · — **9b**. 3-Methoxy-2*H*-azepin-2-ones: ------ **6a**, — × — **6b**.

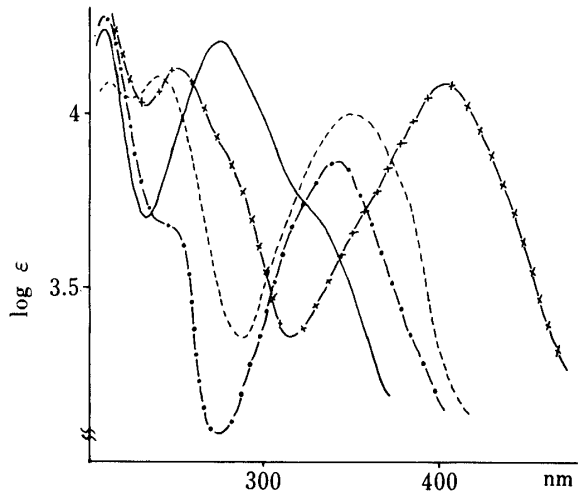


Fig. 2. UV Spectra of **9b** in MeOH, MeOH–HCl, and MeOH–KOH

—— in MeOH; — · — in MeOH–HCl (0.15%) after 3 h; — × — in MeOH–KOH (0.5%) after 30 min; ------ re-acidification of the basic solution with HCl.

In contrast to 3-aza-α-tropolones (**1**), 2-azatropones were stable to protic solvents. For example, the UV spectrum of **9b** in methanol did not change with time, and **9b** was recovered unchanged after heating in methanol for 40 h. However, it was susceptible to both acidic and basic media. On addition of hydrochloric acid, the spectrum of **9b** in methanol gradually changed to a new spectrum having a maximum at 340 nm after 3 h (Fig. 2), and did not return

to the original spectrum on careful neutralization or basification with potassium hydroxide.

On addition of potassium hydroxide, the UV spectrum of **9b** in methanol rapidly changed to a spectrum having a maximum at 405 nm (Fig. 2), which on acidification with hydrochloric acid immediately shifted to 350 nm. The resulting spectrum, however, was not identical with that in the acidic solution described above. Re-basification did not cause any change of this spectrum.

The above irreversible changes can not be explained by an azatropinium ion formation or by a rearrangement to a pyridine derivative as observed in 3-aza-α-tropolones,[2] and instead we suggest that solvolytic changes of the azatropone nucleus occur in both acidic and basic media. We feel that this phenomenon implies a weak or none aromatic character of the azatropone ring. This will be discussed in detail in a future publication.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus and are uncorrected. Infrared (IR) spectra were taken in Nujol mulls with a Hitachi 260-10 spectrometer and are given in cm^{-1}. UV spectra were recorded in dioxane with a Hitachi 200-10 spectrophotometer. ^{1}H-NMR (100 MHz) and ^{13}C-NMR (25 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL FX-100 spectrometer. High-resolution mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. For column chromatography, Wakogel C-200 (silica gel) was used.

1,5-Dihydro-2*H*-azepin-2-one (8)——Compound **7** (100 mg) in benzene (10 ml) containing DBU (2 g for **7a**, 0.2 g for **7b** and 1 g for **7c**—**d**) was heated under reflux for an appropriate time (16 h for **7a**, 6 h for **7c**, **7e**, and 1 h for **7d**) or stirred at room temp. for 16 h (in the case of **7b**). The mixture was diluted with CH_2Cl_2 and washed with 5% HCl, water, dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed in benzene to give **8** as colorless prisms from CH_2Cl_2–Et_2O.

8a: mp 163.5—165 °C (58 mg, 69% from **7a** and 65 mg, 77% from **7b**). IR: 3270, 1695, 1680. UV λ_{max} nm (ε): 238 (22700), 330 (10400). ^{1}H-NMR δ: 1.33 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.47 (2H, s, C_5-H), 4.27 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 7.0—7.62 (10H, m, Ar-H), 7.48 (1H, br s, NH), 7.62 (1H, s, olefinic-H). MS m/z: Calcd for $C_{21}H_{19}NO_3$ (M^+): 333.1375. Found: 333.1381. *Anal.* Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.41; H, 5.61; N, 4.26.

8b: mp 100—102 °C (67 mg, 80% from **7c** and 85 mg, 100% from **7d**). IR: 3180, 1720, 1695, 1690. UV λ_{max} nm (ε): 340 (11500). ^{1}H-NMR δ: 1.08 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 1.35 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.35 (2H, s, C_5-H), 3.69 (2H, q, J=7 Hz, OCH_2CH_3), 4.29 (2H, q, J=7 Hz, $COOCH_2CH_3$), 7.20 (1H, s, NH), 7.27 (1H, s, olefinic-H), 7.3—7.7 (5H, m, Ar-H). MS m/z: Calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1350. Found: 301.1315. *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.75; H, 6.35; N, 4.62.

8c: mp 154—155.5 °C (23 mg, 27.3%). IR: 1705, 1670. UV λ_{max} nm (ε): 238 (20900), 279 (8300), 324 (9600). ^{1}H-NMR δ: 1.36 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.38 (2H, s, C_5-H), 4.31 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 5.08 (1H, dd, J=1, 11 Hz), 5.28 (1H, dd, J=1, 18 Hz), 6.40 (1H, dd, J=11, 18 Hz) olefinic-H, 7.3—7.5 (5H, m, Ar-H), 7.70 (1H, s, olefinic-H). MS m/z: Calcd for $C_{17}H_{17}NO_3$ (M^+): 283.1211. Found: 283.1236.

1,5-Dihydro-4-ethoxycarbonyl-3-hydroxy-7-phenyl-6-vinyl-2*H*-azepin-2-one (11)——Compound **11** was prepared by the reported method.[2b] A solution of **10** (1 g) and DBU (200 mg) in benzene (10 ml) was stirred at room temp. for 16 h. The mixture was diluted with CH_2Cl_2, washed with 5% HCl and water, then dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed in CH_2Cl_2 to give **11** (800 mg, 80%) as pale yellow needles from CH_2Cl_2–Et_2O, mp 162—167 °C. IR: 3200, 1680, 1660, 1610. UV λ_{max} nm (ε): 233 (19900), 263 (19600). ^{1}H-NMR δ: 1.38 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.28 (2H, s, C_4-H), 4.35 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 5.13 (1H, dd, J=1, 10 Hz), 5.56 (1H, dd, J=1, 17 Hz), 6.17 (1H, dd, J=10, 17 Hz) olefinic-H, 7.38 (5H, s, Ar-H), 7.65 (1H, br s, NH). MS m/z: Calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1158. Found: 299.1178. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.98; H, 5.65; N, 4.65.

Reduction of the Dihydroazatropolone 11——A solution of **11** (100 mg) and $(n\text{-}Bu)_4NBH_4$ (87 mg) in dry CH_2Cl_2 (10 ml) was stirred at −40 °C for 3 h. After dilution with CH_2Cl_2, the mixture was washed with water, dried over Na_2SO_4 and concentrated to give **12a** (58 mg, 57.6%) as a colorless amorphous solid. IR: 3400, 3200, 1730, 1690, 1680. UV λ_{max} nm (ε): 230 (10000), 294 (11000). ^{1}H-NMR δ: 0.73 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.88 (1H, d, J=12 Hz, C_4-H), 2.90 (1H, d, J=12 Hz, C_4-H), 3.69 (1H, ddd, J=7, 8, 12 Hz, C_3-H), 4.22 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.43 (1H, d, J=8 Hz, C_2-H), 8.16 (1H, d, J=11 Hz), 5.40 (1H, d, J=17 Hz), 6.59 (1H, dd, J=11, 17 Hz) olefinic-H, 7.26 (1H, s, NH), 7.37 (5H, s, Ar-H). MS m/z: Calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1315. Found: 301.1315.

Acetylation of 12a——Compound **12a** (50 mg) was acetylated with pyridine (2 ml) and Ac_2O (1 ml) with stirring overnight at room temperature. The mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated to dryness. Chromotography of the residue in benzene gave the monoacetate **12b** (32 mg, 56%) and diacetate **12c** (13 mg, 20%).

Monoacetate **12b**: Colorless prisms from CH_2Cl_2–Et_2O, mp 145—150 °C. IR: 3340, 3260, 1750, 1735, 1695. UV λ_{max} nm (ε): 224 (11800), 286 (11200). ^{1}H-NMR δ: 1.33 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.15 (3H, s, OAc), 2.97 (1H, d, J=9 Hz, C_5-H), 2.98 (1H, d, J=10 Hz, C_5-H), 3.55 (1H, m, C_4-H), 4.28 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 5.15 (1H, d, J=11 Hz), 5.37 (1H, d, J=17 Hz) olefinic-H, 5.40 (1H, d, J=8 Hz, C_3-H), 6.60 (1H, dd, J=11, 17 Hz, olefinic-H), 6.84 (1H, br s, NH), 7.39 (5H, s, Ar-H). MS *m/z*: Calcd for $C_{19}H_{21}NO_5$ (M^+): 343.1419. Found: 343.1454.

Diacetate **12c**: Colorless prisms from CH_2Cl_2–Et_2O, mp 123—128 °C. IR (CH_2Cl_2): 1745, 1740, 1720 sh. UV λ_{max} nm (ε): 222 (13400), 268 (14300). ^{1}H-NMR δ: 1.33 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.19 (3H, s, OAc), 2.54 (3H, s, NAc), 2.89 (1H, d, J=12 Hz, C_5-H), 2.92 (1H, d, J=6 Hz, C_5-H), 3.32 (1H, m, C_4-H), 4.28 (2H, qd, J=7, 2 Hz, $COO\underline{CH_2}CH_3$), 5.31 (1H, d, J=11 Hz, olefinic-H), 5.45 (1H, d, J=8 Hz, C_3-H), 5.50 (1H, d, J=18 Hz), 6.65 (1H, dd, J=11, 18 Hz) olefinic-H, 7.36 (5H, s, Ar-H). MS *m/z*: Calcd for $C_{21}H_{23}NO_6$ (M^+): 385.1525. Found: 385.1533.

Preparation of 8c from 12b——A solution of **12b** (50 mg) and DBU (3 g) in benzene (30 ml) was heated under reflux for 4 h. After dilution with CH_2Cl_2, the mixture was washed with 5% HCl and water, then dried over Na_2SO_4, and concentrated to dryness. The residue in CH_2Cl_2 was passed through a short column to give **8c** (31 mg, 76%).

***2H*-Azepin-2-one (9)**——A mixture of **8** (50 mg) and DDQ (50 mg) in dry benzene (5 ml) was heated at 100 °C (2.5 h for **8a** and 25 min for **8b**). The reaction mixture was directly chromatographed. Elution with benzene gave **9**.

9a: Colorless gum (12 mg, 24%). IR (CH_2Cl_2): 1725, 1690, 1685, 1610. UV λ_{max} nm (ε): 265 (12600). ^{1}H-NMR δ: 1.41 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 4.46 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 7.2—7.7 (10H, m, Ar-H), 7.40 (1H, d, J=1 Hz, C_3-H), 7.98 (1H, d, J=1 Hz, C_5-H). ^{13}C-NMR (ppm): 14.1 (q), 62.5 (t), 128.2 (d, 3C), 128.7 (d, 2C), 128.9 (d, 2C), 130.2 (d, 2C), 131.2 (d), 132.9 (d), 133.8 (s), 134.9 (d), 136.9 (s), 138.4 (s), 144.2 (s), 162.3 (s), 164.6 (s), 172.4 (s). MS *m/z*: Calcd for $C_{21}H_{17}NO_3$ (M^+): 331.1221. Found: 331.1208.

9b: Colorless needles from CH_2Cl_2–Et_2O, mp 109—110 °C, (39 mg, 78%). IR: 1725, 1675. UV λ_{max} nm (ε): 268 (15500). ^{1}H-NMR δ: 1.35 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 1.37 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 4.05 (2H, q, J=7 Hz, $OCH_2\underline{CH_3}$), 4.35 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 6.92 (1H, d, J=1 Hz, C_3-H), 7.15 (1H, d, J=1 Hz, C_5-H), 7.35—7.9 (5H, m, Ar-H). ^{13}C-NMR (ppm): 14.1 (q, 2C), 62.4 (t), 64.5 (t), 108.3 (d), 128.2 (d, 3C), 130.2 (d, 2C), 131.7 (d), 133.1 (s), 135.3 (s), 157.2 (s), 158.6 (s), 169.1 (s), 173.2 (s). MS *m/z*: Calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1159. Found: 299.1155. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.05; H, 5.69; N, 4.66.

References and Notes

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