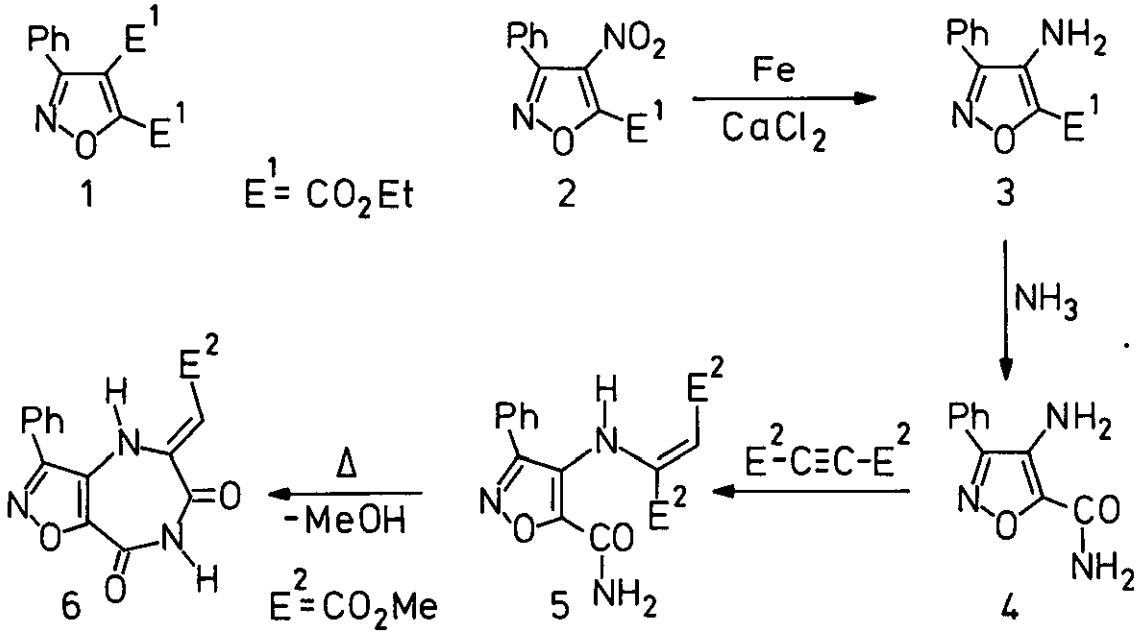
3-PHENYL-5-CARBOMETHOXYMETHYLENE-5H-ISOXAZOLO[4,5-e][1,4]DIAZEPINE-6,8(4H,7H)-DIONE : A NEW SEVEN MEMBERED BINUCLEAR SYSTEM

Rodolfo Nesi*, Donatella Giomi, Laura Quartara, Sandro Papaleo, and Piero Tedeschi

Centro di Studio del CNR sulla chimica e la struttura dei composti eterociclici e loro applicazioni, presso il Dipartimento di Chimica Organica 'Ugo Schiff', Via Gino Capponi 9, Firenze, Italy

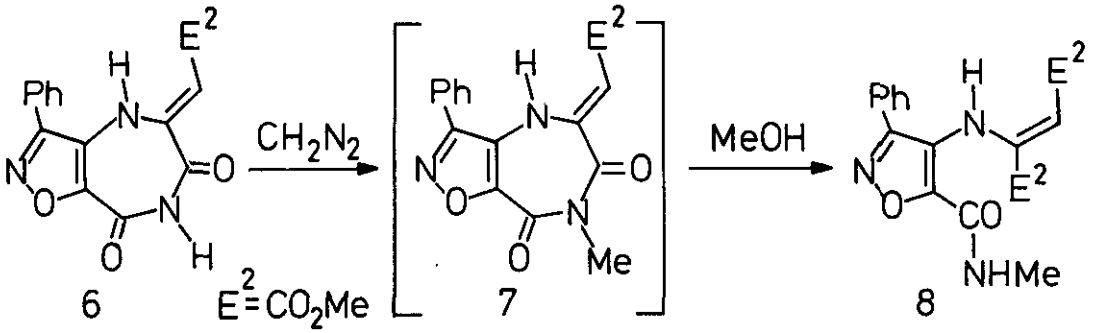
Abstract —— The ring closure of the Michael-type adduct (5), easily available from the nitro ester (2) through the corresponding amino derivatives (3) and (4), afforded the previously unreported heterocyclic system (6) in good yields; some spectral features of the new products were emphasized.

Although different isoxazoloazepines[1] and isoxazolodiazepines[2] have been reported in the literature, the title ring system remained, to our knowledge, still unknown. On this ground, after ethyl 3-phenyl-4-nitroisoxazole-5-carboxylate (2), recently obtained from α-nitroacetophenone oxime in excellent yields,[3] was shown to represent a suitable synthon both for cycloaddition reactions[4] and spirocyclization processes[5], we decided to investigate the possibility of employing the same compound for the preparation of the above bicyclic isoxazole ring.



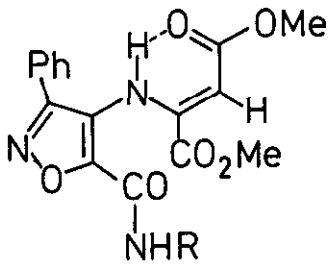
The chemoselective reduction of the NO_2 group at position 4 offered us a convenient direct entry to the amino ester (3) which has been previously obtained from the ester (1) by a four-steps sequence in 22% overall yield;[6] thus, the nitro derivative (2) reacted smoothly with Fe-$CaCl_2$ in ethanol at room temperature to give (3) as a pure product in 78% yield.

Treatment of the corresponding amide (4) with dimethyl acethylenedicarboxylate in boiling methanol afforded the Michael-type adduct (5), whose structure followed from analytical and spectral evidence (see below). Finally, the ring closure of the latter compound was accomplished by the method advantageously employed by Heindel for the preparation of 1,4-benzodiazepine-3,5-diones;[7] when (5) was refluxed for several hours in anhydrous xylene in the presence of a catalytic amount of sodium methoxide, the bicyclic derivative (6) was isolated in good yields.



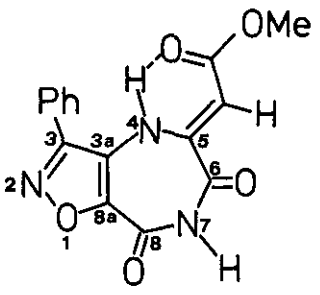
6 $E^2 = CO_2Me$ 7 8

Treatment of (6) with diazomethane in ether-methanol afforded the amide (8) through the unstable N-methyl derivative (7), which gave rise to ring cleavage by nucleophilic attack of the protic solvent at position 6.



5a R = H

8a R = Me



6a

The spectral data of the new products (see EXPERIMENTAL) agreed well with the assigned structures. In particular, whereas the 'normal' α-CO_2Me group of compounds (5) and (8) showed in the ir spectra a band at 1730-1735 cm^{-1}, the absorption of

the second ester group displayed a notable frequency shift overlapping the amidic CO band at 1690 cm^{-1}; this finding could be easily accounted for on the basis of the structures (5a) and (8a) involving a strong six membered intramolecular hydrogen bond. On going from the amides (5) and (8) to the bicyclic derivative (6), the first band disappeared and the ir spectrum was characterized by a strong absorption with maxima at 1682 and 1692 cm^{-1} due to the amidic CO groups and the conjugated ester of the chelated structure (6a).

The ^{1}H nmr spectra of compounds (5) and (8) clearly showed a singlet at δ 5.43 for the enamine CH proton; this signal exhibited a sensible downfield shift (δ = 6.02) in the spectrum of (6), probably due to a paramagnetic deshielding of the CO group at position 6. The presence of the enamine moiety in the above structures was confirmed by the off-resonance ^{13}C nmr spectra of the amides (5) and (8) and the dione (6) which characteristically displayed a doublet at δ 93.3 and 96.7, respectively, for the CH carbon; on the other hand, these spectra showed a singlet at δ 151.7 and 144.0, respectively, which was tentatively assigned to the quaternary carbon of the same moiety.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Ir spectra were measured for potassium bromide discs with a Perkin-Elmer 283 spectrometer. Unless otherwise stated, ^{1}H- and ^{13}C nmr spectra were recorded in $DMSOd_6$ on a Perkin-Elmer R32 instrument and a Varian FT-80A spectrometer, respectively; chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants in Hz. Silica-gel plates (Merck F_{254}) and silica-gel 60 (Merck; 230-400 mesh) were used for analytical tlc and flash-chromatography, respectively. Light petroleum refers to the fraction boiling at 40-70°C; xylene was dried by distillation over sodium wire.

Ethyl 3-Phenyl-4-aminoisoxazole-5-carboxylate (3)

Iron powder (2.4 g) and $CaCl_2.2H_2O$ (0.3 g) were added to the nitro ester (2) (1 g) in ethanol (95%, 20 ml) and the mixture was vigorously stirred at room temperature until the starting material disappeared (tlc, 15 h). The inorganic products were separated by centrifugation and washed with the same solvent (20 ml); evaporation to dryness of the combined solutions left a residue which was dissolved in ether and filtered in order to remove colloidal impurities. Removal of the solvent under reduced pressure gave a pale yellow solid (0.77 g) mainly containing compound (3) (tlc and ^{1}H nmr); a second crop of the same product (0.06 g) was recovered from the inorganic material by extraction with ether (3 x 50 ml). Sublimation of the combined solids at 45-50°C and 0.02 mm Hg afforded the amino ester (3) (0.69 g, yield 78%), mp 61-62°C (from n-hexane) (lit.[6], 58.5-59.5°C); ir ν_{max} : 3475, 3435,

3380, 3350, 1695, 1640, 1590, 1465, 1330, 1270, 1135, 775, and 700 cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.39 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.42 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 4.65 (2H, br s, NH_2), 7.45-7.60 (3H, m, ArH_3), 7.65-7.80 (2H, m, ArH_2); ^{13}C nmr ($CDCl_3$) δ : 14.0 ($OCH_2\underline{CH_3}$), 60.9 ($O\underline{CH_2}CH_3$), 127.1-129.8 (Ph), 133.55 (C-4), 139.8 (C-5), 155.2 (C-3), 158.5 (CO). Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.88; H, 5.02; N, 12.09.

3-Phenyl-4-amino-5-carbamoylisoxazole (4)

According to the literature,[6] compound (4) was prepared in 89% yield from (3) and aqueous ammonium hydroxide (30%), as a white solid, mp 175-176°C (from methanol); ir ν_{max}: 3470, 3420, 3345, 3290, 3150, 1690, 1570, 1440, 1375, 1210, 775, 730, and 690 cm^{-1}; ^1H nmr δ : 5.30 (2H, br s, NH_2), 7.50-7.70 (3H, m, ArH_3), 7.70-8.0 (4H, m, ArH_2+ $CONH_2$); ^{13}C nmr δ : 127.4-130.0 (Ph), 132.1 (C-4), 142.5 (C-5), 155.5 (C-3), 160.4 (CO).

Dimethyl [N-(3-Phenyl-5-carbamoylisoxazol-4-yl)amino]fumarate (5)

Dimethyl acethylenedicarboxylate (7.93 g, 6.86 ml) was added to a solution of the amide (4) (9.46 g) in hot methanol (140 ml) and the mixture was gently refluxed for 24 h. The adduct (5) which separated on cooling was filtered off and dried under vacuum (KOH) (12.84 g); a further amount of the same product (1.85 g, overall yield 91.4%) was recovered by concentration of the filtrate (ca. 30 ml). An analytical sample, obtained by crystallization from ethyl acetate, wrinkled above 160°C and melted at 173-174°C; ir ν_{max}: 3405, 3370, 3300, 3170, 1730, 1690, 1610, 1440, 1360, 1285, 1230, 770, 690, and 600 cm^{-1}; ^1H nmr δ: 3.40 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 5.43 (1H, s, CH), 7.50-7.70 (5H, m, Ph), 8.0 (1H, br s, NH of $CONH_2$), 8.30 (1H, br s, NH of $CONH_2$), 9.63 (1H, sbr s, NH); ^{13}C nmr δ : 51.2 ($CO_2\underline{CH_3}$), 52.6 ($CO_2\underline{CH_3}$), 93.3 (CH), 122.8 (C-4), 127.0-130.2 (Ph), 146.4 (C-5), 151.7 (HN-$\underline{C}$=CH), 157.8 ($CONH_2$), 158.9 (C-3), 162.4 ($\underline{CO_2}CH_3$), 168.5 ($\underline{CO_2}CH_3$). Anal. Calcd. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.77; H, 4.46; N, 12.24.

3-Phenyl-5-carbomethoxymethylene-5H-isoxazolo[4,5-e][1,4]diazepine-6,8(4H,7H)-dione (6)

Freshly prepared sodium methoxide (0.12 g) was added to a solution of the adduct (5) (5 g) in hot anhydrous xylene (150 ml) and the mixture was refluxed under vigorous stirring for 9 h, removing by distillation the methanol evolved in the cyclocondensation . The yellow brown residue obtained by evaporation to dryness under reduced pressure, was washed with n-pentane (2 x 30 ml), stirred with chloroform (100 ml) for 2 h at room temperature, and filtered to give compound (6) [2.77 g, yield 71% based on the recovered starting material (see below)]; an analytical sample, obtained as a pale yellow solid by crystallization from acetone, gradually

darkened above 220°C and melted with decomposition at 238-239°C; ir ν_{max}: 3200, 3100, 3070, 2960, 2900, 1692, 1682, 1645, 1620, 1445, 1360, 1300, 1245, and 1200 cm^{-1}; ^1H nmr δ : 3.69 (3H, s, CO_2CH_3), 6.02 (1H, s, CH), 7.55-7.85 (5H, m, Ph), 11.12 (1H, sbr s, NH), 11.95 (1H, br s, NH of CONHCO); ^{13}C nmr δ : 51.8 ($CO_2\underline{CH_3}$), 96.7 (CH), 123.6 (C-3a), 125.2-131.1 (Ph), 144.0 (C-5), 145.5 (C-8a), 153.1 (CONH), 155.5 (C-3), 159.0 (CONH), 169.45 ($\underline{CO_2}CH_3$). Anal. Calcd. for $C_{15}H_{11}N_3O_5$: C, 57.51; H, 3.54; N, 13.41. Found: C, 57.52; H, 3.54; N, 13.51.

Evaporation to dryness of the chloroform filtrate afforded a solid from which the starting amide (5) was recovered as a pure product (0.7 g) by flash-chromatography (ethyl acetate - light petroleum 3:2 v/v).

Dimethyl [N-(3-Phenyl-5-methylcarbamoylisoxazol-4-yl)amino]fumarate (8)

A suspension of compound (6) (1.65 g) in ether (100 ml) and methanol (20 ml) was treated with an excess of ethereal diazomethane (molar ratio 1:2.5) and set aside overnight at room temperature. After a small amount of tarry material was removed by filtration, the solution was evaporated to dryness to give a solid (1.75 g) largely consisting of the N-methylamide (8) (tlc and ^1H nmr), which was purified by flash-chromatography (light petroleum - ethyl acetate 3:2 v/v), mp 132-134°C (from ether); ir ν_{max}: 3400, 3200, 2955, 1735, 1685, 1620, 1540, 1435, 1275, 1220, 1140, 1030, 805, and 765 cm^{-1}; ^1H nmr δ: 2.79 (3H, d, J=4.3 Hz, HN-$\underline{CH_3}$), 3.41 (3H, s, CO_2CH_3), 3.69 (3H, s, CO_2CH_3), 5.43 (1H, s, CH), 7.45-7.75 (5H, m, Ph), 8.87 (1H, br q, J=4.3 Hz, $\underline{HN}$-CH_3), 9.66 (1H, sbr s, NH); ^{13}C nmr δ: 25.5 (HN-CH_3), 51.25 ($CO_2\underline{CH_3}$), 52.65 ($CO_2\underline{CH_3}$), 122.4 (C-4), 127.1-130.3 (Ph), 146.6 (C-5), 151.7 (HN-$\underline{C}$=CH), 156.6 ($\underline{CO}$-NHCH$_3$), 159.0 (C-3), 162.5 ($\underline{CO_2}CH_3$), 168.7 ($\underline{CO_2}CH_3$). Anal. Calcd. for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.60; H, 4.66; N, 11.85.

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