1,2,3,4-TETRAHYDRO-1,2-DIAZEPINE DERIVATIVES FROM ISOXAZOLO[3,4-d] PYRIDAZIN-7(6*H*)-ONES

Vittorio Dal Piaz, Giovanna Ciciani, Annarella Costanzo, and Gabriella Auzzi

Dipartimento di Scienze Farmaceutiche dell'Università di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

Stefano Chimichi

Centro di Studio del CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, presso l'Istituto di Chimica Organica dell'Università, Via Gino Capponi 9, 50121 Firenze, Italy

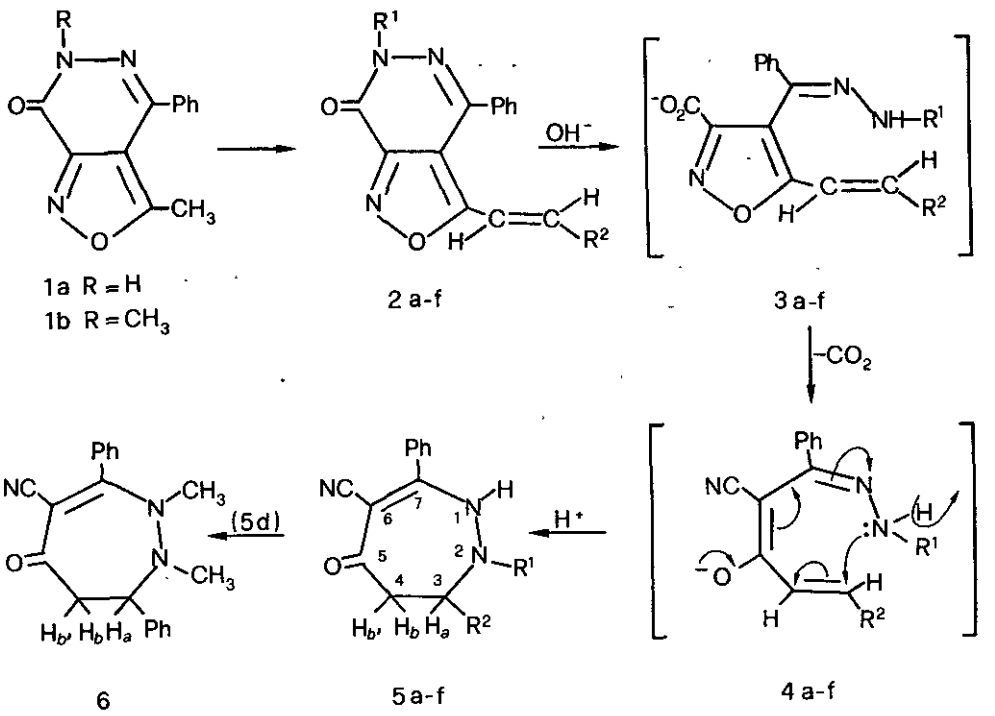
Abstract-Treatment of isoxazolo[3,4-d]pyridazin-7(6*H*)-ones (2a-f) with alkali give rise to the new 6-cyano-2,3-disubstituted 1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one derivatives (5a-f) through Michael type addition.

The reaction of 3-unsubstituted isoxazoles with bases, leading to ring opening with formation of an highly reactive *cis*-cyanoenolate ion, is well-known and has many applications.[1]

On these grounds the isoxazolo[3,4-d]pyridazin-7(6*H*)-ones (2a-f), easily available by condensation of the requisite aldehydes with the corresponding 5-methyl derivatives (1a-b), appeared to be very attractive and, in order to ascertain the potential of these compounds as sources of the new 6-cyano-2,3-disubstituted 1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-ones (5a-f), we investigated their behaviour in alkaline medium. Treatment of compounds 2a-f with dilute sodium hydroxide afforded, after acidification, a white solid which was formulated as 1,2,3,4-tetrahydro-1,2-diazepine on the basis of analytical and spectroscopic data (see later). The formation of compounds 5a-f can be accounted for through an initial nucleophilic attack of the hydroxide ion on the lactamic linkage of the pyridazinones 2a-f; the 4,5-disubstituted isoxazole-3-carboxylate anions 3a-f thus formed, can be easily decarboxylated to *cis*-cyanoenolates 4a-f which give rise to the 1,2-diazepines through Michael type addition (scheme).

The cyclization, similar to that reported for some $\alpha\beta,\gamma\delta$-unsaturated *p*-tolylsulfonylhydrazones,[2] provides an easy and direct route to the 1,2-diazepine system and does not show failures, probably by the effect of the conjugate CN group which is a strong electron-withdrawing group, in spite of the presence of an aromatic

SCHEME



a	R^1 = H	R^2 = C_6H_5
b	R^1 = H	R^2 = p-Cl C_6H_4
c	R^1 = H	R^2 = 2-thienyl
d	R^1 = CH_3	R^2 = C_6H_5
e	R^1 = CH_3	R^2 = p-Cl C_6H_4
f	R^1 = CH_3	R^2 = 2-thienyl

ring at the terminal of the dienic system.

The ^{1}H-nmr spectra of compounds 5 in DMSO-d_6 were consistent with the proposed structures; in particular compounds 5d-f showed the presence of an AYZ spin system for the CH and CH_2 groups, beside a broad singlet at δ 10.4-10.5 due to the 1-NH. The A part of the spectra always appears as a "triplet" at about δ 5 for the H_a, whereas the YZ part is degenerated showing fewer than the expected eight lines for the 4-CH_2 (H_b and $H_{b'}$) near δ 2.8-2.9. In the spectrum of compound 5f ($\nu_y - \nu_z$) is zero, making this an AYY' system; the spacing in the "triplet" is 8 Hz [$\frac{1}{2}(J_{YA} + J_{ZA})$]

The same considerations can be made for the spectra of compounds 5a-c, the "virtual coupling" of H_a to the YZ (or YY') nuclei being always observed, but now the A part of the spectra appears as a doublet of triplets due to coupling to 2-NH (J = 4 Hz); this coupling disappears by treatment with D_2O or by an irradiation at δ 6.5.

The 5-oxo structure of all the new diazepines in dimethylsulfoxide solution is confirmed also by the presence, in the ^{13}C-nmr spectra in the same solvent, of a singlet at δ 193 for the conjugated C=O group. This attribution is supported by the resonance at δ 193.5 for the 5-CO group in the spectrum of the N,N'-dimethyl derivative 6 obtained as the sole product by treatment of compound 5d with dimethyl sulfate in alkaline medium. The presence of the cyano group is supported by the ir absorption at 2200 cm^{-1} (strong) and by the singlet at δ 119 in the ^{13}C-nmr spectra.

According to the behaviour of phenylcyclohexane and phenylcyclopentane under electron impact,[3] the mass spectra of compounds 5a-f exhibited, beside peaks for M^+ and $M-H_2O^{\neg+}$, signals at m/e 104,138, and 110 for the C_6H_5-CH=CH_2, *p*-ClC_6H_4-CH=CH_2, and 2-thienyl-CH=CH_2 ions, respectively.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Ir spectra were measured for nujol mulls with a Perkin-Elmer 337 spectrometer. ^{1}H-nmr spectra were recorded with either a Varian EM-360 or Perkin-Elmer R32 spectrometers and ^{13}C-nmr spectra with a Varian FT-80A instrument; chemical shifts are reported in ppm from tetramethylsilane, coupling constants in Hz. Mass spectra were obtained with a Perkin-Elmer 270 spectrometer using a direct insertion probe. Silica-gel plates (Merck F_{254}) were used for analytical t.l.c..

Compounds 2a and 2d were prepared as reported in reference 4.

All the new compounds gave satisfactory microanalytical data (± 0.3%).

Reaction of Compounds 1a-b with Aldehydes

i) To a mixture of 1a (5 mmoles) and *p*-chlorobenzaldehyde (10 mmoles) in dry methanol (10 ml) was added sodium methoxide (10 mmoles) in the same solvent (6 ml) and the suspension was refluxed for 35 min. After evaporation of the solvent, the residue was treated with water (100 ml), extracted with diethyl ether (1 x 50 ml) and rapidly filtered to give 3-[2-(4-chlorophenyl)ethenyl]-4-phenylisoxazolo-[3,4-d]pyridazin-7(6*H*)-one (2b): (y 61.7%); yellow crystals, mp 298 °C(decomp.) (from acetone); ir 3150-3050br (NH), 1685 (CO), and 980 cm^{-1} (*trans*-CH=CH-); ^{1}H-nmr (DMSO-d_6): δ=6.67 and 7.62 (AB,2H,J_{AB}16), 7.39-7.62 (m,9H,ArH_5 and ArH_4), and 12.72 (exch. br s,1H,NH).

ii) Operating as above, reaction of 1a with 2-thienylaldehyde gave 3-[2-(2-thienyl)

ethenyl]-4-phenylisoxazolo[3,4-d]pyridazin-7(6*H*)-one (2c): (y 90%); yellow crystals, mp 256 °C (decomp.) (from ethanol); ir 3200br (NH), 1690 (CO), and 970 cm^{-1} (*trans*-CH=CH-); ^{1}H-nmr (DMSO-d_6): δ=6.52 and 7.74 (AB,2H,J_{AB}16), 6.90-7.74 (m,8H,ArH_5 and thienyl protons), and 12.48 (exch. br s,1H,NH).

iii) Sodium methoxide (5 mmoles) in dry methanol (3 ml) was added to a suspension of 1b (5 mmoles) and 4-chlorobenzaldehyde (10 mmoles) in the same solvent (10 ml) and the mixture was refluxed for 3 min. After cooling, the solution was filtered to give 3-[2-(4-chlorophenyl)ethenyl]-4-phenyl-6-methylisoxazolo[3,4-d]pyridazin-7(6*H*)-one (2e): (y 76.6%); yellow crystals, mp 208 °C (from ethanol); ir 1680 (CO) and 980 cm^{-1} (*trans*-CH=CH-); ^{1}H-nmr ($CDCl_3$): δ=3.80 (s,3H,NCH_3),6.70 and 7.55 (AB,2H,J_{AB}16), and 7.20-7.60 (m,9H,ArH_4, and ArH_5).

iv) Reaction of 1b with 2-thienylaldehyde was carried out as in iii and gave 3-[2-(2-thienyl)ethenyl]-4-phenyl-6-methylisoxazolo[3,4-d]pyridazin-7(6*H*)-one (2f): (y 72.2%); yellow crystals, mp 209 °C (decomp.) (from ethanol); ir 1680 (CO) and 990 cm^{-1} (*trans*-CH=CH-); ^{1}H-nmr ($CDCl_3$): δ=3.82 (s,3H,NCH_3), 6.52 and 7.68 (AB,2H, J_{AB}16), 6.95-7.45 (m,3H,thienyl protons), and 7.6 (s,5H,ArH_5).

6-Cyano-7-phenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one derivatives (5a-f)

(General procedure)

Compounds 2a-f (3 mmoles) were refluxed with 1N NaOH (50 ml) or with a mixture of 1N NaOH (70 ml) and ethanol (40 ml) for 3-45 min, except for compound 5e (45 °C for 15h). After cooling, the solution was acidified with 6N HCl (pH 1-2) and filtered.

6-Cyano-3,7-diphenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5a): (y 72%); white crystals, mp 225 °C (from methanol); ir 3280br (NH), 2200 (C≡N), and 1620 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=2.96 (AYZ,2H,H_b and $H_{b'}$), 4.81 (AYZ,1H,H_a), 6.52 (exch. d, J4,1H,2-NH), 7.20-7.70 (m,10H,2xArH_5), and 10.75 (exch. br s, 1H,1-NH); ^{13}C-nmr (DMSO-d_6): δ=49.0 (t), 66.3 (d), 83.7 (s), 119.6 (s), 126.7, 127.5, 128.3, 128.6, 129.6, 132.0, 132.2 (s), 141.6 (s), 168.7 (s), and 193.9 (s); MS: m/e(%)=289 (34.2) M^+, 271(73.7) $M-H_2O^{\neg+}$, 104(100) $PhCH{=}CH_2^{\neg+}$, 103(65.8) $PhCN^+$, 185(40.1) $M-PhCH{=}CH_2^{\neg+}$, and 77(96.0) Ph^+.

3-*p*-Chlorophenyl-6-cyano-7-phenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5b): (y 50%), white crystals, mp 223 °C (decomp.) (from ethanol); ir 3280br (NH), 2200 (C≡N), and 1620 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=2.92 (AYZ,2H,H_b and $H_{b'}$), 4.82 (AYZ, 1H,H_a), 6.55 (exch. d,J4,1H,2-NH), 7.30-7.70 (m,9H,ArH_5 and ArH_4), and 10.70 (exch. br s,1H,1-NH); ^{13}C-nmr (DMSO-d_6): δ=48.75 (t), 65.6 (d), 83.7 (s), 119.4 (s), 128.15, 128.6, 129.6, 131.95, 132.0, 132.1, 140.6 (s), 169.1 (s), and 193.6 (s); MS: m/e(%)=325(8.0) $M^{+\ 37}Cl$, 323(24.5) $M^{+\ 35}Cl$, 307(30.6) $M-H_2O^{\neg+\ 37}Cl$, 305(61.2) $M-H_2O^{\neg+\ 35}Cl$, 140(24.5) $^{37}ClC_6H_4CH{=}CH_2^{\neg+}$, 138(38.8) $^{35}ClC_6H_4CH{=}CH_2^{\neg+}$, 103(24.5) $PhCN^+$, 185(28.6) $M-ClC_6H_4CH{=}CH_2^{\neg+}$, and 77(49) Ph^+.

6-Cyano-7-phenyl-3-(2-thienyl)-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5c): (y 51%) white crystals, mp 193°C(decomp.) (from ethanol); ir 3270 (NH), 2200 (C≡N), and 1620 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=3.02 (AYZ,2H,H_b and $H_{b'}$), 5.06 (AYZ,1H,H_a), 6.57 (exch. d,J4,1H,2-NH), 6.95-7.58 (m,3H,thienyl protons),7.60 (s,5H,ArH_5), and 10.68 (exch. br s,1H,1-NH); ^{13}C-nmr (DMSO-d_6): δ=49.25 (t), 62.0 (d), 84.0 (s), 119.4 (s), 124.6, 125.1, 126.7, 128.5, 129.6, 132.0, 144.8 (s), 169.3 (s), and 193.0 (s); MS:m/e(%)=295(9.1) M^+, 294(16.6) M-$H^{\neg+}$, 277(100) M-$H_2O^{\neg+}$, 110(15.8) 2-thienylCH=$CH_2^{\neg+}$, 185(6.6) M-2-thienylCH=$CH_2^{\neg+}$, and 77(23.3) Ph^+.

6-Cyano-2-methyl-3,7-diphenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5d): (y 60%) white crystals, mp 223°C(decomp.) (from methanol); ir 3140 (NH), 2200 (C≡N), and 1610 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=2.58 (s,3H,NCH_3), 2.88 (AYZ,2H,H_b and $H_{b'}$), 4.70 (AYZ,1H,H_a), 7.25-7.85 (m,10H,2xArH_5), and 10.56 (exch. br s,1H, 1-NH); MS: m/e(%)=303(12.0) M^+, 285(40.8) M-$H_2O^{\neg+}$, 104(100) PhCH=$CH_2^{\neg+}$, 103 (68.4) $PhCN^+$, 199(82.8) M-PhCH=$CH_2^{\neg+}$, and 77(67.1) Ph^+.

3-*p*-Chlorophenyl-6-cyano-2-methyl-7-phenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5e): (y 65%), white crystals, mp 217°C(decomp.) (from ethanol); ir 3160 (NH), 2200 (C≡N), and 1610 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=2.58 (s,3H,NCH_3), 2.82 (AYZ,2H,H_b and $H_{b'}$), 4.78 (AYZ,1H,H_a), 7.27-7.80 (m,9H,ArH_5 and ArH_4), and 10.55 (exch. br s,1H,1-NH); MS: m/e(%)=337(14.8) M^+, 319(33.3) M-$H_2O^{\neg+}$, 140(24.1) $^{37}ClC_6H_4CH{=}CH_2^{\neg+}$, 138(77.7) $^{35}ClC_6H_4CH{=}CH_2^{\neg+}$, 103(94.4) $PhCN^+$, 199(75.9) M-$ClC_6H_4CH{=}CH_2^{\neg+}$, and 77(100) Ph^+.

6-Cyano-2-methyl-7-phenyl-3-(2-thienyl)-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (5f): (y 70.6%), white crystals, mp 222°C(decomp.) (from ethanol); ir 3160 (NH), 2200 (C≡N), and 1610 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ=2.63 (s,3H,NCH_3), 2.90 (YY',J4,2H,H_b and $H_{b'}$), 5.10 (AYY',1H,H_a), 6.90-7.56 (m,3H,thienyl protons), 7.65 (s,5H,ArH_5), and 10.45 (exch. br s,1H,1-NH); MS: m/e(%)=309(11.1) M^+, 291(19.7) M-$H_2O^{\neg+}$, 110(100) 2-thienylCH=$CH_2^{\neg+}$, 103(13.6) $PhCN^+$, 199(70.4) M-2-thienyl-CH=$CH_2^{\neg+}$, and 77(34.6) Ph^+.

6-Cyano-1,2-dimethyl-3,7-diphenyl-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-one (6): reaction of 5d with $(CH_3)_2SO_4$ gave a yellow product, (y 64%), mp 203°C(decomp.) (from ethanol); ir 2200 (C≡N) and 1630 cm^{-1} (CO); ^{1}H-nmr ($CDCl_3$): δ=2.62 (s,3H, 2-NCH_3), 3.06 (s, and AYZ,5H,1-NCH_3,H_b and $H_{b'}$), 4.66 (AYZ,1H,H_a), and 7.30-7.65 (m,10H,2xArH_5); ^{13}C-nmr ($CDCl_3$): δ=38.6 (NCH_3), 39.0 (NCH_3), and 193.5 (CO).

ACKNOWLEDGEMENT

We are grateful for the excellent technical assistance of Miss Sandra Gallori

REFERENCES

1. N.K. Kochetkov and S.D. Sokolov, Adv. Heterocycl. Chem., 1963, 2, 365.

2. C.D. Anderson, P.N. Anderson, and J.T. Sharp, J. Chem. Soc., Perkin Trans. 1, 1979, 1640.
3. E. Stenhagen, S. Abrahamsson, and F.W. McLafferty, Registry of Mass Spectral Data, J. Wiley 1974, pp 353 and 472.
4. V. Dal Piaz, S. Pinzauti, and P. Lacrimini, J. Heterocyclic Chem., 1976, 13, 409.

Received, 23rd March, 1984