Polycondensed Nitrogen Heterocycles. Part 17 [1]. Isoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]triazepine. A New Ring System

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Received January 12, 1987

The title compounds were prepared by nitration of compounds **2**, reduction of the dinitro derivatives **4** and diazotization of the diamino derivatives **6** followed by an intramolecular coupling reaction. Compound **4a** showed good activity against *Salmonella cholerasuis* and *Clostridium perfringens* bacteria.

J. Heterocyclic Chem., **24**, 1309 (1987).

Several 1,3,5- and 1,2,4-triazepine derivatives have shown antibacterial and antiinflammatorial activity [2-4] but the 1,2,3-triazepine nucleus is unknown.

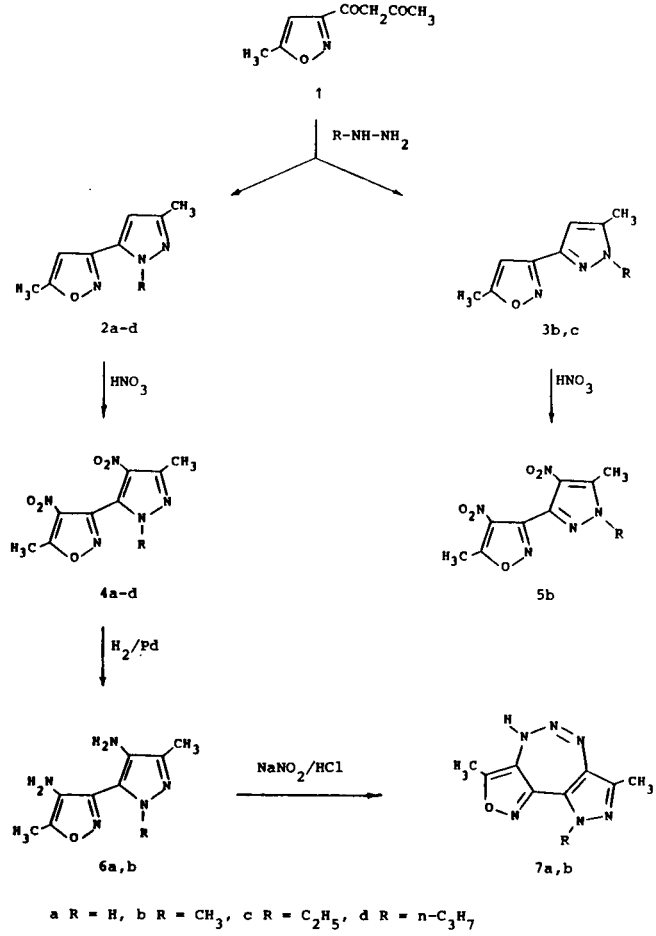
In connection with our studies on polycondensed nitrogen heterocycles [5,6], we became interested in the synthesis of some derivatives of the new ring system isoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]triazepine considering also that the isoxazole and pyrazole nuclei are present in several biologically interesting molecules.

For this purpose the 3-(3-methyl-1-R-pyrazole-5-yl)-5-methylisoxazoles **2a-d** were prepared by condensation of the β-diketone **1** [7] with suitable hydrazino derivatives. In these reactions the other isomers 3-(5-methyl-1-R-pyrazole-3-yl)-5-methylisoxazoles **3** were isolated in yields which decreased with the increase in the length of the alkyl chain and in the case where R = *n*-propyl only compound **2d** was isolated.

When R = methyl the two isomers, which were obtained in comparable yields, were identified on the basis of the ^{1}H nmr spectra. In fact considering that in the case of **2c** and **2d** the signals due to the methyl protons in the 3-position on the pyrazole ring appear at δ 2.30-2.33 the structure **2b** was assigned to the isomer which showed a singlet for 3 protons at δ 2.30, whilst to the isomer which showed the signal at δ 2.19 was assigned the structure **3b**.

Compounds **2a-d** were nitrated with nitric acid in sulphuric acid to give the dinitro derivatives **4a-d** in 90-95% yield. The compounds **4** allowed us to have further support for the structure of the starting materials on the basis of their ^{1}H nmr spectra. In particular, due to the proximity influence of the nitro group on the isoxazole ring, the protons of the *N*-methyl and *N*-methylenic groups experience, in comparison with the corresponding derivatives **2**, a small downfield shift, while in the case of 3-(1,5-dimethyl-4-nitropyrazolo-3-yl)-5-methyl-3-nitroisoxazole **5b** a distinct upfield shift of the *N*-methyl was observed.

Compounds **4a,b** were reduced catalytically over palladium on charcoal and the diamino derivatives **6a,b**



a R = H, b R = CH_3, c R = C_2H_5, d R = n-C_3H_7

were obtained in 90-95% yield. The structure of these compounds was confirmed by analytical and spectral data. In particular the ir spectra showed a very complex series of bands in the range 3460-2700 cm^{-1} due to the stretchings of the NH and NH_2 groups which were involved in strong hydrogen bonds and the ^{1}H nmr spectra showed, beside the methyl signals, two broad exchangeable signals at δ 4.31-5.83 due to the NH_2 groups.

The diazotization in hydrochloric acid of the amino compounds **6a,b** and subsequent intramolecular coupling

reaction led to the isoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]-triazepine derivatives **7a,b** in 90% yield.

The structure of the new ring system was confirmed by analytical and spectral data: in the ir spectra very broad bands were observed at 3200-2700 cm^{-1} attributable to the imino group, in the ^1H nmr spectra, instead, it was not possible to observe the NH signal of the triazepine ring because of its high mobility.

The triazepine derivatives **7a,b** as well as the intermediate dinitro derivatives **4a-d** were tested as antibacterials and herbicides at the Diamond-Shamrock Corporation laboratories. Compound **4a** completely inhibited the *Salmonella cholerasuis* bacterium at 25 ppm and the *Clostridium perfringens* bacterium at 50 ppm.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus; ir spectra were determined in bromoform with a Perkin-Elmer 299 spectrophotometer; nmr spectra were obtained with a Varian FT-80 spectrometer (TMS as internal reference); mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage.

3-(5(3)-Methylpyrazole-3(5)yl)-5-methylisoxazole (**2a**).

This compound was prepared using the procedure described previously [7].

Reaction of Substituted Hydrazines on 1-(5-Methylisoxazole-3-yl)butane-1,3-dione (**1**).

To a solution of the diketone **1** [7] (10 mmoles) in ethanol (10 ml), substituted hydrazine was added. The reaction mixture was refluxed for 1 hour, cooled and evaporated to dryness under reduced pressure. The residue was chromatographed on a dry column of silica gel deactivated with water (15%) using light petroleum (bp 50-70°):ethyl acetate 1:1 as eluant.

In the case of methylhydrazine (R = Me), the combined fractions 3-15 (30 ml each) gave 3-(1,5-dimethylpyrazole-3-yl)-5-methylisoxazole (**3b**) as an oil (yield 50%); nmr (deuteriochloroform): δ 2.19 (3H, s, pyrazole CH_3), 2.37 (3H, s, isoxazole CH_3), 4.01 (3H, s, N-CH_3), 6.05 (1H, s, pyrazole CH), 6.21 (1H, s, isoxazole CH); ms: M^+ = 177.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 61.11; H, 6.12; N, 23.70.

The combined fractions 20-50 gave 3-(1,3-dimethylpyrazol-5-yl)-5-methylisoxazole (**2b**) (yield 50%), mp 122° from cyclohexane; nmr (deuteriochloroform): δ 2.30 (3H, s, pyrazole CH_3), 2.45 (3H, s, isoxazole CH_3), 3.83 (3H, s, N-CH_3), 6.43 (1H, s, pyrazole CH), 6.56 (1H, s, isoxazole CH); ms: M^+ = 177.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.90; H, 6.22; N, 23.62.

In the case of ethylhydrazine (R = C_2H_5), the combined fractions 8-10 gave 3-(1-ethyl-5-methylpyrazole-3-yl)-5-methylisoxazole (**3c**) as an oil (yield 32%); nmr (deuteriochloroform): δ 1.48 (3H, t, CH_2-CH_3), 2.20 (3H, s, pyrazole CH_3), 2.37 (3H, s, isoxazole CH_3), 4.30 (2H, q, N-CH_2), 6.11 (1H, s, pyrazole CH), 6.30 (1H, s, isoxazole CH); ms: M^+ = 191.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.71; H, 6.72; N, 21.70.

The combined fractions 15-36 gave 3-(1-ethyl-3-methylpyrazole-5-yl)-5-methylisoxazole (**2c**) (yield 68%), mp 68-70° from cyclohexane; nmr (deuteriochloroform): δ 1.43 (3H, t, CH_2-CH_3), 2.33 (3H, s, pyrazole CH_3), 2.47 (3H, s, isoxazole CH_3), 4.20 (2H, q, N-CH_2), 6.46 (1H, s, pyrazole CH), 6.60 (1H, s, isoxazole CH); ms: M^+ = 191.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.68; H, 6.79; N, 21.78.

In the case of propylhydrazine (R = C_3H_7), was only isolated 3-(1-propyl-3-methylpyrazole-5-yl)-5-methylisoxazole (**2d**) (yield 93%), mp 58-60° from cyclohexane; nmr (deuteriochloroform): δ 0.96 (3H, t, CH_2-CH_2-CH_3), 1.90 (2H, m, CH_2-CH_2CH_3), 2.30 (3H, s, pyrazole CH_3), 2.43 (3H, s, isoxazole CH_3), 4.06 (2H, t, N-CH_2), 6.46 (1H, s, pyrazole CH), 6.56 (1H, s, isoxazole CH); ms: M^+ = 205.

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.36; H, 7.37; N, 20.47. Found: C, 64.48; H, 7.39; N, 20.58.

3-(3-methyl-4-nitro-1-R-pyrazole-5-yl)-5-methyl-4-nitroisoxazoles **4a-d**.

The compounds **2a-d** (10 mmoles) were dissolved in concentrated sulphuric acid (10 ml) and the solution was cooled at -20° with stirring. Nitric acid (d = 1.4, 1.7 ml, 24 mmoles) was added dropwise and the mixture was stirred at -20° for 1 hour. Then it was allowed to stir to rt overnight. The reaction mixture was warmed on steam bath for 30 minutes, cooled and poured into ice/water. The solid was collected, air dried and recrystallized.

3-(3-methyl-4-nitro-1*H*-pyrazole-5-yl)-5-methyl-4-nitroisoxazole (**4a**).

This compound was obtained in 90% yield, mp 204° from ethanol; ir: 3360 (NH) cm^{-1}; nmr (deuteriochloroform): δ 2.66 (3H, s, pyrazole CH_3), 2.93 (3H, s, isoxazole CH_3), 11.65 (1H, broad, exchangeable NH); ms: M^+ = 253.

Anal. Calcd. for $C_6H_7N_5O_5$: C, 37.95; H, 2.79; N, 27.66. Found: C, 37.88; H, 2.69; N, 27.58.

3-(3-methyl-4-nitro-1-methylpyrazole-5-yl)-5-methyl-4-nitroisoxazole (**4b**).

This compound was obtained in 94% yield, mp 160° from ethanol; nmr (deuteriochloroform): δ 2.75 (3H, s, pyrazole CH_3), 2.95 (3H, s, isoxazole CH_3), 3.96 (3H, s, N-CH_3); ms: M^+ = 267.

Anal. Calcd. for $C_5H_9N_5O_5$: C, 40.45; H, 3.40; N, 26.21. Found: C, 40.58; H, 3.49; N, 26.48.

3-(3-methyl-4-nitro-1-ethylpyrazole-5-yl)-5-methyl-4-nitroisoxazole (**4c**).

This compound was obtained in 94% yield, mp 158-160° from ethanol; nmr (deuteriochloroform): δ 1.51 (3H, t, CH_2-CH_3), 2.73 (3H, s, pyrazole CH_3), 2.91 (3H, s, isoxazole CH_3), 4.25 (2H, q, N-CH_2); ms: M^+ = 281.

Anal. Calcd. for $C_{10}H_{11}N_5O_5$: C, 42.71; H, 3.94; N, 24.90. Found: C, 42.58; H, 3.99; N, 24.88.

3-(3-methyl-4-nitro-1-propylpyrazole-5-yl)-5-methyl-4-nitroisoxazole (**4d**).

This compound was obtained in 95% yield, mp 100-102° from ethanol; nmr (deuteriochloroform): δ 0.94 (3H, t, CH_2-CH_2CH_3), 1.92 (2H, m, CH_2-CH_2-CH_3), 2.70 (3H, s, pyrazole CH_3), 2.89 (3H, s, isoxazole CH_3), 4.13 (2H, t, N-CH_2); ms: M^+ = 295.

Anal. Calcd. for $C_{11}H_{13}N_5O_5$: C, 44.74; H, 4.44; N, 23.72. Found: C, 44.68; H, 4.59; N, 23.88.

Compound **3b** was nitrated with the same procedure to give 3-(1,5-dimethyl-4-nitropyrazole-3-yl)-5-methyl-4-nitroisoxazole (**5b**) (yield 92%) mp 124° from ethanol; nmr (deuteriochloroform): δ 2.60 (3H, s, pyrazole CH_3), 2.95 (3H, s, isoxazole CH_3), 3.84 (3H, s, N-CH_3); ms: M^+ = 267.

Anal. Calcd. for $C_5H_9N_5O_5$: C, 40.45; H, 3.40; N, 26.21. Found: C, 40.37; H, 3.40; N, 26.38.

3-(4-amino-3-methyl-1-R-pyrazole-5-yl)-4-amino-5-methylisoxazoles **6a,b**.

Compounds **4a,b** were reduced on 10% palladium on charcoal in methanol in a Parr apparatus at 45 psi for 12 hours at rt. The catalyst was filtered off and the concentrate solution was allowed to crystallize giving the desired products.

3-(4-amino-3-methyl-1*H*-pyrazole-5-yl)-4-amino-5-methylisoxazole (**6a**).

This compound was obtained in 90% yield, mp 191° dec; ir: 3460-2700 (very broad NH_2 and NH) cm^{-1}; nmr (deuteriochloroform): δ 2.50 (3H, s, pyrazole CH_3), 2.70 (3H, s, isoxazole CH_3), 4.83 and 5.83 (4H, 2 broad exchangeable NH_2), 8.25 (1H, broad, exchangeable NH); ms: M^+ = 193.

Anal. Calcd. for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.88; H, 5.69; N, 36.38.

3-(4-amino-3-methyl-1-methylpyrazole-5-yl)-4-amino-5-methylisoxazole (**6b**).

This compound was obtained in 90% yield, mp 210° dec; ir: 3450, 3400, 3300 and 3240 (broad NH_2) cm^{-1}; nmr (deuteriochloroform): δ 2.33 (3H, s, pyrazole CH_3), 2.78 (3H, s, isoxazole CH_3), 3.93 (3H, s, N-CH_3), 4.31 and 5.27 (4H, 2 broad exchangeable NH_2); ms: M^+ = 207.

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.80. Found: C, 52.00; H, 6.39; N, 33.68.

4,9-Dihydro-3,7-dimethyl-9-R-isoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]-triazepines **7a,b**.

The amines **6a,b** (5 mmoles) were dissolved in concentrate hydrochloric acid (20 ml) and water (20 ml) and the solution was cooled at 0° with stirring. A solution of sodium nitrite (5 mmoles) in water (5 ml) was added dropwise and the reaction mixture was allowed to stir at rt for 4 hours. The solid was collected, air dried and recrystallized.

4,9-Dihydro-3,7-dimethyl-9*H*-isoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]-triazepine (**7a**).

This compound was obtained in 90% yield, mp 320° dec from ethanol; ir: 3200-2760 (very broad NH) cm^{-1}; nmr (dimethylsulfoxide): δ 2.67 and 2.70 (6H, 2s, 2 x CH_3), 14.04 (1H, broad, exchangeable NH); ms: M^+ = 204.

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 47.18; H, 3.89; N, 41.28.

4,9-Dihydro-3,7-dimethyl-9-methylisoxazolo[4,3-*d*]pyrazolo[3,4-*f*][1,2,3]-triazepine (**7b**).

This compound was obtained in 90% yield, mp 300° dec from ethanol; ir: 3100-2700 (broad NH) cm^{-1}; nmr (dimethylsulfoxide) δ 2.68 and 2.88 (6H, 2s, 2 x CH_3), 4.05 (3H, s, N-CH_3); ms: M^+ = 218.

Anal. Calcd. for $C_9H_{10}N_6O$: C, 49.53; H, 4.62; N, 38.52. Found: C, 49.44; H, 4.59; N, 33.48.

Acknowledgements.

This work was supported by funds from C.N.R. and from Ministero P.I.

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