Polycondensed Nitrogen Heterocycles. IV. Pyrazolo[1,5-*d*]-*s*-triazolo[3,4-*f*]-*as*-triazine

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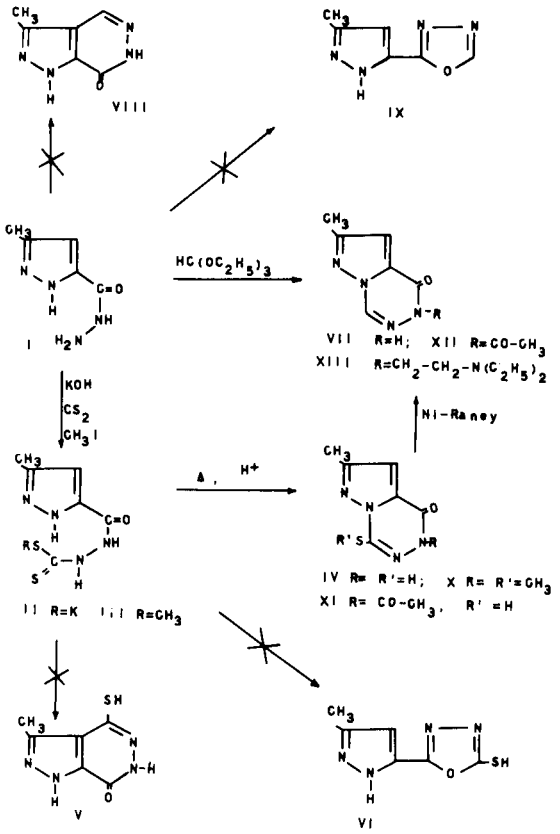
The ease of obtaining dithiocarbazates from the reaction of hydrazides of aromatic acids with carbon disulfide led to the use of this reaction in our program concerning the synthesis of new polycondensed nitrogen heterocycles and the investigation of their pharmacological and microbiological action (1,3).

The reaction of 5(3)-methyl-3(5)pyrazolcarboxylic acid hydrazide (I) and carbon disulfide in alcoholic potassium hydroxide yielded potassium dithiocarbazate (II), which reacted with methyl iodide to yield the methyl derivative III. Heating and acidification of both compounds II and III yielded the same product which was assigned the following formula: 2-methyl-7-mercaptopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (IV).

SCHEME I



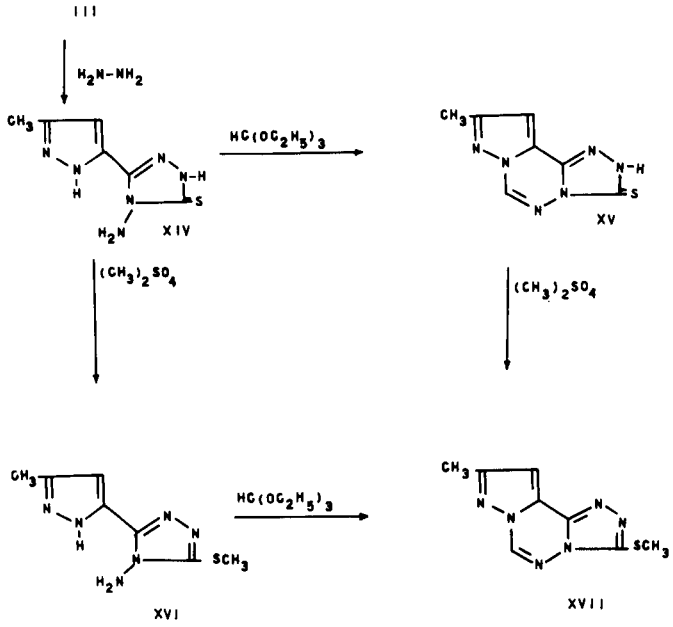
Two other possible structures, 3-methyl-4-mercaptopyrazolo[3,4-*d*]pyridazine (V) and 3(5)-methyl-5(3)-[2-mercapto-1,3,4-oxadiazol-5-yl]pyrazole (VI), ought also to be taken into consideration (4,5,6,7) but the product obtained displays both acidic and basic properties. Its ir spectrum shows a peak at 1670 cm^{-1}, which may be attributed to a carbonyl function.

On treatment with Raney-Ni in ethanol, the mercapto group was easily removed, yielding compound VII, which was also obtained by action of ethyl orthoformate upon hydrazide I.

Although these data do not provide definitive evidence in favour of structure IV, the uv spectrum shows the same pattern and the same peak as those observed in a similar compound which has already been described in the literature (7). This fact helps to confirm the formula 2-methyl-7-mercaptopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one for compound IV.

Compound IV upon reaction with dimethyl sulfate and with acetic anhydride yielded a dimethyl derivative (X) and a monoacetyl derivative (XI), respectively. The acetyl group is placed at position-5- of compound XI

SCHEME II



because the nmr spectrum does not show a band corresponding to the N_5H proton, which does appear in the nmr spectrum of compound IV (Scheme I).

Treatment of methyldithiocarbazate (III) with hydrazine yielded 5(3)-methyl-3(5)-[3-thioxo-4-amino-*s*-triazol-5-yl]pyrazole (XIV). This compound reacted with ethyl orthoformate to yield a polycondensed nitrogen heterocycle, which has not been described in literature to date: 9-methyl-3-thioxopyrazolo[1,5-*d*]-*s*-triazolo[3,4-*f*]-*as*-triazine (XV).

The structure of this compound is proved by the fact that on treatment of compound XIV with dimethyl sulfate compound XVI is obtained, which in turn reacts with ethyl orthoformate yielding the same compound XVII obtained by action of dimethyl sulfate on compound XV (Scheme II).

Moreover the thioxo structure of compounds XIV and XV was confirmed by nmr spectra which showed a wide broadened signal at 13.70 and 14.60 δ respectively attributable to a NH proton rather than to a SH proton, and by the uv spectra of compounds XIV and XV which showed a different pattern of those of methyl derivatives XVI and XVII, respectively.

A wide range screening was carried out with most of the products described, in collaboration with the Bristol Laboratories, New York, in order to assay the pharmacological and microbiological properties of such compounds. The only compound which displayed any noteworthy pharmacological action, *i.e.* an antinflammatory action, was 2,5-dimethyl-7-methylmercaptopyrazolo[4,5-*d*]-*as*-triazin-4(5*H*)one (X).

EXPERIMENTAL

All melting points (Kofler) are uncorrected; ir (nujol mull): Perkin-Elmer Infracord 137 spectrophotometer; uv (ethanol): Beckmann DB (with recorder) spectrophotometer; nmr: Jeol C-60H spectrometer (TMS as internal reference). Microbiological and pharmacological tests were performed by Bristol Laboratories, Syracuse, New York.

Potassium 5(3)-Methyl-3(5)-pyrazolyldithiocarbazate (II).

To a solution of 2.8 g. (0.05 mole) of potassium hydroxide in 100 ml. of absolute ethanol was added 7 g. (0.05 mole) of 5(3)-methyl-3(5)-pyrazolcarboxylic acid hydrazide (8), the mixture stirred for 30 minutes with 4 ml. (0.07 mole) of carbon disulfide; the yellow solid (10.35 g.) was filtered and washed with dry ether.

Methyl 5(3)-Methyl-3(5)-pyrazolyldithiocarbazate (III).

A mixture of II (11.5 g.) (0.05 mole), 150 ml. of water and 3.1 ml. (0.05 mole) of methyl iodide was stirred for one hour; the white solid obtained (9.8 g.) was filtered and recrystallized from ethanol, m.p. 191°.

Anal. Calcd. for $C_7H_{10}N_4OS_2$: C, 36.52; H, 4.38; N, 24.34. Found: C, 36.62; H, 4.50; N, 24.30.

2-Methyl-7-mercaptopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (IV).

The solution of II in water or of III in dilute aqueous base was heated for 15 minutes, cooled and acidified with hydrochloric acid; the solid was filtered and recrystallized from water m.p. 188°; ir cm^{-1}, 3130 (NH), 1670 (CO); uv mμ, λ max 286 and 242; nmr (acetone-d_6) δ, 2.40 (s, 3H, CH_3), 6.62 (s, 1H, C_3H), 12.5 (broad, 1H, N_5H); it was not possible to observe the SH proton.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.55; H, 3.51; N, 30.51.

2,5-Dimethyl-7-methylmercaptopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)-one (X).

To a solution of IV (3.65 g.) (0.02 mole) in 50 ml. of water containing 2.52 g. (0.045 mole) of potassium hydroxide was added 4.3 ml. (0.045 mole) of dimethyl sulfate. The mixture was rapidly stirred and in a few minutes a rose-colored solid separated. White scales from water, m.p. 97°; uv mμ, λ max 264 and 304 (sh); nmr (acetone-d_6) δ, 2.24, 2.81 and 4.13 3x (s, 3H, CH_3), 6.68 (s, 1H, C_3H).

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.51; H, 4.86; N, 26.44.

2-Methyl-5-acetyl-7-mercaptopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (XI).

Compound IX (1 g.) was refluxed for ten minutes with 10 ml. of acetic anhydride; after removal of solvent under reduced pressure, the residue was washed with water, filtered and recrystallized from ethanol 50%, m.p. 196°; nmr (acetone-d_6) δ, 2.65 and 2.74 2x (s, 3H, CH_3), 6.82 (s, 1H, C_3H); no evidence for the SH proton was possible.

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.71; H, 3.56; N, 24.80.

2-Methylpyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (VII).

A mixture of 5 g. of I and 50 ml. of triethyl orthoformate was heated under reflux for 18 hours. The excess orthoformate was removed by heating under reduced pressure; the residue was washed with water, filtered and recrystallized from ethanol, m.p. 282°. It was soluble in dilute aqueous base and was reprecipitated by acid; ir cm^{-1}, 3200 (NH), 1700 (CO); uv mμ, λ max 264 and 225 (sh); nmr (DMSO) δ, 2.44 (s, 3H, CH_3), 7.02 (s, 1H, C_3H), 8.92 (s, 1H, C_7H), 12.40 (s, 1H, NH).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.24; H, 4.22; N, 37.04.

A mixture of IV (1g.), 150 ml. of ethanol and 1 g. of W_2 Raney Nickel (9) was refluxed with stirring for one hour. After removal of the nickel by filtration, the filtrate was evaporated under reduced pressure. The residue was recrystallized from ethanol, m.p. 282°. This compound was identical with a sample of 2-methylpyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (VII).

2-Methyl-5-acetylpyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (XII).

Compound VII (2 g.) was refluxed for 10 minutes with 10 ml. of acetic anhydride; after removal of solvent under reduced pressure, the residue was washed with water, filtered and recrystallized from acetone, m.p. 169°; ir cm^{-1}, 1700 (CO), 1760 ($CO-CH_3$); nmr (acetone-d_6) δ, 2.43 and 2.63 2x (s, 3H, CH_3), 7.09 (s, 1H, C_3H), 8.65 (s, 1H, C_7H).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.16; N, 29.16. Found: C, 49.72; H, 4.26; N, 29.06.

2-Methyl-5-ethyldiethylaminopyrazolo[1,5-*d*]-*as*-triazin-4(5*H*)one (XIII).

A mixture of VII (1.5 g.) (0.01 mole), 5 ml. of water, 0.67 g.

(0.012 mole) of potassium hydroxide and 2 g. (0.012 mole) of 2-diethylaminoethyl chloride hydrochloride was stirred for 30 minutes, the emulsion was extracted with ether, the extract dried (sodium sulfate) and evaporated, m.p. 56°; chloride m.p. 222°; ir cm^{-1}, 1690 (CO).

Anal. Calcd. for $C_{12}H_{19}N_5O$·HCl: C, 50.43; H, 7.05; N, 24.51. Found: C, 49.93; H, 7.02; N, 23.93.

5(3)-Methyl-3(5)-[3-thioxo-4-amino-*s*-triazol-5-yl]pyrazole (XIV).

A solution of III (23 g.) (0.1 mole) in 150 ml. of ethanol was refluxed with 6 ml. (0.12 mole) of hydrazine. In a few minutes a white precipitate was obtained; the refluxing was continued for 3 hours, the precipitate filtered and recrystallized from water, m.p. 222°; ir cm^{-1}, 3150 to 3380 (NH and NH_2); uv mμ, λ max 258 and 220 (sh); nmr (DMSO) δ, 2.32 (s, 3H, CH_3), 5.72 (s, 2H, NH_2), 6.49 (s, 1H, CH), 13.09 (s, 1H, NH) *ca.* 13.70 (broad, 1H; NH).

Anal. Calcd. for $C_6H_8N_6S$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.61; H, 4.10; N, 42.96.

3-Thioxo-9-methylpyrazolo[1,5-*d*]-*s*-triazolo[3,4-*f*]-*as*-triazine (XV).

Compound XIV (2 g.) was refluxed for 10 hours with 35 ml. of triethyl orthoformate. The excess orthoformate was removed by heating under reduced pressure and the residue recrystallized from water, m.p. 318°; ir (potassium bromide), 2900 cm^{-1} (NH); uv mμ, λ max 284 and 268; nmr (DMSO) δ 2.47 (s, 3H, CH_3); 7.19 (s, 1H, $C_{10}H$), 9.29 (s, 1H, C_6H), 14.60 (broad, 1H, N_2H); Mass: 206 (M^+), 107, 91, 78, 65, 51, 42, 28, 18 m/e.

Anal. Calcd. for $C_7H_6N_6S$: C, 40.78; H, 2.93; N, 40.77. Found: C, 40.75; H, 3.04; N, 40.60.

5(3)Methyl-3(5)-[3-methylmercapto-4-amino-*s*-triazol-5-yl]pyrazole (XVI).

A mixture of compound XIV (0.01 mole), 0.012 mole of potassidum hydroxide in 50 ml. of water and 0.012 mole of dimthyl sulfate was stirred for 1 hour; the precipitate was filtered and recrystallized from ethanol-water, m.p. 248°; uv mμ, λ max 259 and 218 (sh).

Anal. Calcd. for $C_7H_{10}N_6S$: C, 40.00; H, 4.80; N, 39.88. Found: C, 40.26; H, 4.90; N, 39.76.

3-Methylmercapto-9-methylpyrazolo[1,5-*d*]-*s*-triazolo[3,4-*f*]-*as*-triazine (XVII).

A mixture of compound XV (0.01 mole), 0.012 mole of potassium hydroxide in 50 ml. of water and 0.012 mole of dimethyl sulfate was stirred for 5 minutes; the precipitate was filtered and recrystallized from ethanol-water, white scales, m.p. 214°; uv mμ, λ max 252 and 273 (sh); nmr (DMSO) δ, 2.48 and 2.78 2x (s, 3H, CH_3), 7.23 (s, 1H, $C_{10}H$), 9.42 (s, 1H, C_6H).

Anal. Calcd. for $C_8H_8N_6S$: C, 43.64; H, 3.66; N, 38.17. Found: C, 43.80; H, 3.72; N, 38.17.

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