# Poly Condensed Nitrogen Heterocycles. V. Two Novel Ring Systems: Pyrazolo[5,1-*c*]-1,2,4-thiadiazine and Pyrazolo[3,4-*c*]-1,2-thiazine (1).

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The title compounds were obtained by reaction of aminopyrazoles IV and VII with ω-acetophenonesulfonyl chloride (II, R = $C_6H_5$). In agreement with the general pattern of the distribution of electron density in the pyrazole nucleus, this work confirms that the position 4 of ring is the favoured site of electrophilic attacks.

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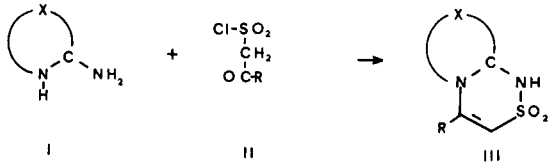
*S,S*-Dioxythiadiazine and thiazine derivatives have been found to possess interesting pharmaceutical and microbiological properties. In connection with our investigation on poly condensed heterocycles (2-6) it was of interest to us to extend our work to the synthesis of new series of compounds containing a *S,S*-dioxy-1,2,4-thiadiazine nucleus (III).

We supposed that the sequence of atoms NCN of 1,2,4-thiadiazines could be furnished by heterocyclic amines of type I and that the ring closure could be realized by means of reaction of I with sulfonyl chlorides of type II.

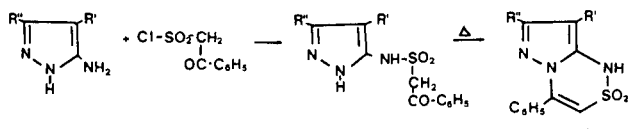
SCHEME I



I II III

We report here compounds obtained by means of reaction of 3(5)-aminopyrazoles (IV) with ω-acetophenonesulfonyl chloride (II, R = $C_6H_5$).

SCHEME II



IV a,b,c V a,b,c VI a,b,c

a R'=$C_6H_5$ R''=$CH_3$ b R',R''=$(CH_2)_4$ c R',R''=$(CH_2)_5$

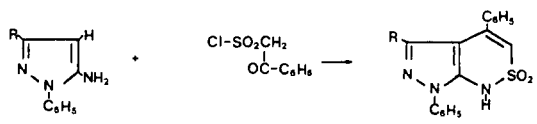
When the position 4 of 3(5)aminopyrazoles (IVa,b,c) was blocked, reaction products were the corresponding monothiamides (Va,b,c). Evidence for monothiamides derivatives, besides analytical data, were the ir spectra which showed two NH and one CO stretching bands at about 3 and 6 μ respectively, and nmr spectra which showed a signal at δ ~5 for two methylene protons and two signals at δ ~9 and 12 for two NH protons, exchangeable with deuterium oxide.

Attempts to cyclize monothiamides under various conditions failed. However, successful ring closure was achieved by heating the monothiamides five degrees above their melting points in Dowtherm A: *S,S*-dioxypyrazolo-[5,1-*c*]-1,2,4-thiadiazines (VIa,b,c), a novel ring system, was obtained.

Evidences for the assigned structures were analytical data, ir spectra, which did not show any CO stretching, nmr spectra, which showed a sharp singlet absorption peak at δ ~6-7 for a CH proton and the mass spectra.

The reaction takes a different path when position 4 of 3(5)aminopyrazoles is free and position 1 is blocked (VIIa,b). In the case of VIIb the corresponding monothioamides were not isolated and pyrazolo[3,4-*c*]-1,2-thiazines (VIIIa,b) a new ring system was obtained directly.

SCHEME III



VII a,b VIIIa, b

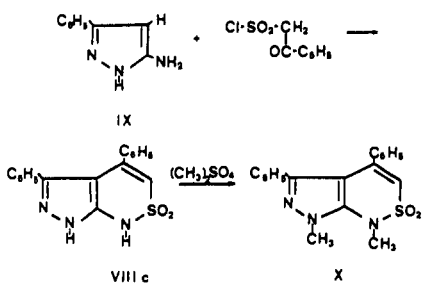
a R=$CH_3$ ; b R=$C_6H_5$

Evidently the carbon atom at position 4, because of the general pattern of the distribution of electron density in the pyrazole nucleus, retains its anionic properties and

and this is the favoured site of electrophilic attack of the enol form of II.

This assertion is confirmed by the fact that the reaction between II and 3(5)phenyl-5(3)aminopyrazole (IX), in which positions 1 and 4 are both free, led directly to a product that by analytical, spectral and chemical evidences must also be regarded as the pyrazolo[3,4-*c*]-1,2-thiazine (VIIIc).

SCHEME IV



In fact the nmr spectrum showed only a signal at δ 6.55 for one methinic proton and two broad signals at δ ~13 and 11 which disappeared on treatment with deuterium oxide. On the other hand, this compound with dimethyl sulphate gives a dimethyl derivative X, which can only be a pyrazolo[3,4-*c*]-1,2-thiazine.

In conclusion, when position 1 of the aminopyrazoles is free and the position 4 is blocked the reaction with ω-acetophenonesulphonyl chloride gives monothiamides that only under vigorous conditions may cyclize into a pyrazolo[5,1-*c*]-1,2,4-thiadiazine (VI).

Furthermore, when position 4 is free the products obtained were pyrazolo[3,4-*c*]-1,2-thiazines (VIII) and this is in agreement with the general pattern of the distribution of the electron density in the pyrazole nucleus.

Several of the compounds listed in the tables were tested by Bristol Laboratories, Syracuse, New York. However, none showed encouraging biological and pharmacological activities.

Table I

| | R′ | R″ | M.p. °C | Formula | Analysis Calcd. C | H | N | Found C | H | N | Crystallization Solvent |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Va | $C_6H_5$ | $CH_3$ | 173-174 | $C_{18}H_{17}N_3O_3S$ (a) | 60.84 | 4.82 | 11.83 | 60.84 | 5.04 | 11.73 | benzene-ethanol |
| Vb | -$(CH_2)_4$- | | 214-216 | $C_{15}H_{17}N_3O_3S$ (b) | 56.42 | 5.37 | 13.16 | 56.56 | 5.50 | 13.13 | ethanol-water |
| Vc | -$(CH_2)_5$- | | 190-191 | $C_{16}H_{19}N_3O_3S$ (c) | 57.65 | 5.75 | 12.61 | 57.61 | 5.99 | 12.71 | ethanol |

(a) Ir: $cm^{-1}$ 3440 and 3340 (2 x NH) 1690 (CO); nmr: δ 2.25 (3H, s, $CH_3$) 5.10 (2H, s, $CH_2$) 7.00-8.20 (10H, m, 2 x $C_6H_5$) 9.55 (1H, s, NH) 12.60 (1H, s, NH). (b) Ir: $cm^{-1}$ multiple bands at 3250-3400 (2 x NH), 1690 (CO), nmr: δ 1.50-2.50 (8H, m, $(CH_2)_4$), 4.90 (2H, s, $CH_2$) 7.40-8.10 (5H, m, $C_6H_5$) 9.50 (broad, NH), 12.05 (broad NH). (c) Ir: $cm^{-1}$ multiple bands at 3250-3400 (2 x NH) 1690(CO); nmr: δ 1.30-2.50 (10H, m, $(CH_2)_5$), 4.95 (2H, s, $CH_2$) 9.40 (1H, s, NH) 12.12 (1H, s, NH).

Table II

| | R′ | R″ | M.p. °C | Formula | Analysis Calcd. C | H | N | Found C | H | N | Crystallization Solvent |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VIa | $C_6H_5$ | $CH_3$ | 270-271 | $C_{18}H_{15}N_3O_2S$ (a) | 64.09 | 4.48 | 12.46 | 64.25 | 4.40 | 12.69 | Ethanol-water |
| VIb | -$(CH_2)_4$- | | 258-259 | $C_{15}H_{15}N_3O_2S$ (b) | 59.79 | 5.02 | 13.95 | 59.89 | 5.21 | 14.08 | Ethanol-water |
| VIc | -$(CH_2)_5$- | | 247-248 | $C_{16}H_{17}N_3O_2S$ (c) | 60.94 | 5.43 | 13.33 | 60.94 | 5.64 | 13.38 | Ethanol |

(a) Mass spectrum: $M^+$ = 337, 322, 272, 258, 245, 232, 204, 168, 129, 115, 102 m/e; nmr*: δ 2.20 (3H, s, $CH_3$) 7.00 (1H, s, CH) 7.30-7.80 (10H, m, 2 x $C_6H_5$). (b) Mass spectrum: $M^+$ = 301, 273, 236, 222, 209, 196, 149, 116, 103 m/e; nmr*: δ 1.50-2.70 (8H, m, $(CH_2)_4$) 6.78 (1H, s, CH) 7.30-7.70 (5H, m, $C_6H_5$). (c) Mass spectrum: $M^+$ = 315, 286, 261, 250, 236, 222, 196, 170, 102 m/e; nmr*: δ 1.30-2.70 (10H, m, $(CH_2)_5$) 6.78 (1H, s, CH) 7.40-7.70 (5H, m, $C_6H_5$). *It was not possible to observe the NH proton in the nmr spectra.

Table III

| | R | M.p. °C | Formula | Analysis Calcd. C | H | N | Found C | H | N | Crystallization Solvent |
|---|---|---|---|---|---|---|---|---|---|---|
| VIIIa | $CH_3$ | 258-260 | $C_{18}H_{15}N_3O_2S$ (a) | 64.09 | 4.48 | 12.46 | 64.14 | 4.65 | 12.42 | Ethanol |
| VIIIb | $C_6H_5$ | 232-234 | $C_{23}H_{17}N_3O_2S$ (b) | 69.16 | 4.29 | 10.52 | 69.16 | 4.23 | 10.65 | Ethanol |
| VIIIc | | 293-294 | $C_{17}H_{13}N_3O_2S$ (c) | 63.15 | 4.05 | 13.00 | 63.32 | 4.05 | 13.00 | Methanol-water |

(a) Mass spectrum: $M^+ = 337$; ir: 3230 $cm^{-1}$ (NH); nmr: δ 2.40 (3H, s, $CH_3$), 6.26 (1H, s, thiazine CH) 7.30-8.00 (10H, m, 2 x $C_6H_5$) 11.30 (1H, s, NH). (b) Mass spectrum: $M^+ = 399$; ir: 3240 $cm^{-1}$ (NH); nmr: δ 6.40 (1H, s, thiazine CH) 7.20-8.40 (15H, m, 3 x $C_6H_5$) 11.10 (1H, s, NH). (c) Mass spectrum: $M^+ = 322$; nmr: δ 6.65 (1H, s, CH) 6.80-7.30 (10H, m, 2 x $C_6H_5$) ~13 and ~11 (broad, 2 x NH).

## EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ir spectra were determined in nujol mulls (unless otherwise specified) with a Perkin Elmer Infracord 137 spectrophotometer. The nmr spectra (DMSO-$d_6$, unless otherwise specified) were obtained with a Jeol C-60H spectrometer (TMS as the internal reference). A 270 Perkin Elmer mass spectrometer was employed for determination of the low resolution 70 eV mass spectra.

General Procedure for Monothiamides (Va,b,c).

A mixture of aminopyrazoles IVa (7) b (8) c (8) (10 mmoles) and ω-acetophenonesulfonyl chloride II (9) (10 mmoles) in chloroform (100 ml.) and 10 mmoles of triethylamine was refluxed for 5 hours. The solution was evaporated under reduced pressure and the resulting product was boiled in water (100 ml.) for 10 minutes. After cooling, the mixture alkalinized with aqueous sodium hydroxide (20%) was stirred for 30 minutes, filtered and acidified with concentrated hydrochloric acid. The resulting precipitate was crystallized twice. The title compounds are listed in table I.

General Procedure for *S,S*-Dioxypyrazolo[5,1-c]-1,2,4-thiadiazines (VIa,b,c).

Monothiamides Va,b,c (1 g.) were dissolved in 5 ml. of Dowtherm A and heated five degrees above their melting points for 10 minutes in a current of nitrogen. Products VIa,b were purified by adding ether, filtering and crystallizing the resulting precipitate. Product VIc was obtained as a crystalline mass which was recrystallized. The title compounds are listed in table II.

*S,S*-Dioxypyrazolo[3,4-c]-1,2-thiazines (VIIIa,b,c).

Compound VIIIc was directly obtained by refluxing equimolar amounts of 3(5)phenyl-5(3)aminopyrazole IX (10), II and triethylamine in chloroform by the general procedure described above for monothiamides. The same procedure was employed for VIIIb using 1,3-diphenyl-5-aminopyrazole IVf (11) as the starting pyrazole. Compound VIIIa was obtained by refluxing the corresponding monothiamide, obtained by reaction of VIIa (12) and II, in acetic acid (50 ml.) for 3 hours followed by addition of water; the resulting precipitate was recrystallized. The title compounds are listed in table III.

1-Phenyl-3-methyl-5-(ω-acetophenonesulfonylamido)pyrazole.

The product melted at 135-138° (ethanol); ir: $cm^{-1}$ 3380 (NH); nmr: δ 1.80 (3H, s, $CH_3$) 4.78 (2H, s, $CH_2$), 6.75 (1H, s, CH) 7.40-7.90 10H, m, (2 x $C_6H_5$).

*Anal.* Calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.93; H, 4.80; N, 11.71.

Dimethyl Derivative of VIIIc (X).

Ten mmoles of VIIIc was dissolved in 2% aqueous sodium hydroxide (20 ml.) and dimethyl sulfate (25 mmoles) was added. After stirring one hour, a white precipitate was obtained which was crystallized from acetone-water, m.p. 192°; mass spectrum: $M^+ = 351$; 302, 286, 272, 253, 245, 227, 210, 202, 189, 143, 135, 127, 118, 102 m/e; nmr (deuteriochloroform): δ, 3.58 (3H, s, $CH_3$) 3.80 (3H, s, $CH_3$), 7.32 (1H, s, CH), 6.85-7.25 (10H, m, 2 x $C_6H_5$).

*Anal.* Calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.96; H, 4.72; N, 12.28.

## REFERENCES AND NOTES

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