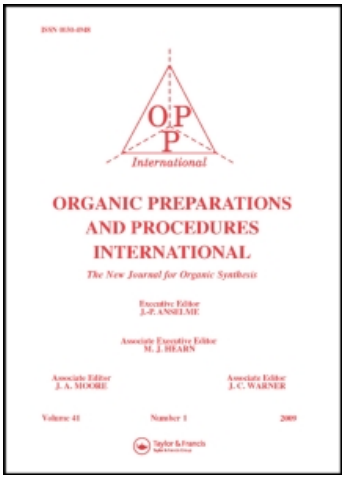

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SYNTHESIS OF SOME 1,2,4-THIADIAZOLO[2,3-a]PYRIDINE DERIVATIVES AND ITS AZA ANALOGUES

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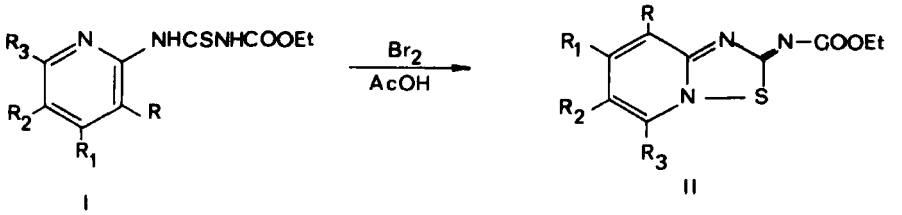
The first derivative of the 2H-1,2,4-thiadiazolo[2,3-a] pyridine ring system was reported forty years ago.[1,2] Recently several derivatives of 1,2,4-thiadiazolo[2,3-a]pyridin-4-ium salts were prepared from the corresponding N-pyridylthioureas and bromine or sulfuryl chloride.[3,4] On the other hand, 2H-1,2,4-thiadiazolo[2,3-b]pyridazin-2-ones could be obtained from 3-aminopyridazines and chlorothioformyl chloride.[5]

Our interest and studies on heterocyclic thiourea derivatives[6-8] prompted us to investigate the possibility of oxidative cyclization of N-carbethoxy-N'-azinylthioureas. We



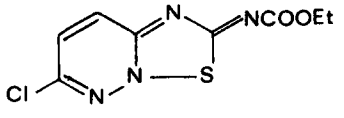
I II

	a	b	c	d	e	f
R =	H	Me	H	H	H	CO_2Et
R_1 =	H	H	Me	Me	H	H
R_2 =	H	H	H	H	Me	H
R_3 =	H	H	Me	H	H	H

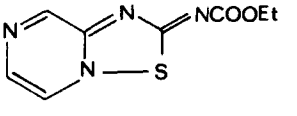
have recently shown that N-ethoxycarbonyl-N'-(2-pyridyl) thioureas, prepared from the corresponding 2-aminopyridines and ethoxycarbonyl isothiocyanate, are cyclized in the presence of sodium ethoxide into the corresponding pyrido[1,2-a]-1,3,5-triazines or pyrido[2,3-d]- and pyrido[3,2-d]pyrimidines.[7] Similarly, the corresponding pyridazino[2,3-a]-1,3,5-triazine derivatives are obtained.[8]

We like to describe the conversion of some carbethoxythiourea derivatives (I) into the corresponding thiadiazolopyridines (II). Oxidative cyclization takes place with bromine in acetic acid at about 10° and subsequent warming up to room temperature. The structures of the obtained products are supported by analytical data, mass and nmr spectra. When compared to uncyclized compounds (I), the signal for H_8 and in particular that for H_5 is shifted downfield in the cyclic compounds (II). In a similar manner also derivatives of 2H-1,2,4-thiadiazolo(2,3-b)pyridazine (III) and of the so far unknown 2H-1,2,4-thiadiazolo(2,3-a)pyrazine (IV) were obtained.

The obtained thiadiazolopyridines (II) are sensitive to acids or alkali like the parent 1,2,4-thiadiazole.[9] In this manner, compound IIa upon treatment with alkali, even in cold and with very dilute aqueous solution of sodium hydroxide, is transformed into 2-cyanaminopyridine. Moreover, the attempted reduction (in the presence of palladium or platinum catalyst)



III



IV

of the exocyclic double bond led to the cleavage of the $S-N_4$ bond and IIa was transformed back into the thiourea derivative Ia.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are corrected. Nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (TMS as internal standard) and mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L mass spectrometer.

General Procedure.- To a solution of ethoxycarbonylthiourea (I, 0.005 mole) in glacial acetic acid (25 ml) cooled to 10°, was added portionwise with stirring a solution of bromine (0.005 mole) in glacial acetic acid (10 ml). After addition was complete, stirring was continued at room temperature for 45 min. The reaction mixture was poured into iced water and neutralized with aqueous ammonia to pH 5. The precipitated product was filtered and crystallized from methanol. Yields ranged from 20-73%.

Compound IIa, mp. 213-215°. Mass spectrum: m/e 223 (M^+).
Nmr (DMSO-d_6, 110°): τ = 1.15 (ddd, H_5), 2.80 (ddd, H_6), 2.05 (deg ddd, H_7), 2.40 (ddd, H_8), 5.72 (q, CH_2), 8.70 (t, CH_3); $J_{5,6}$ = 6.5, $J_{5,7}$ = 1.5, $J_{5,8}$ = 0.9, $J_{6,7}$ = 7.0, $J_{7,8}$ = 7.6, $J_{6,8}$ = 1.5, J_{Et} = 7.2 Hz.
Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.43; H, 4.06; N, 18.83.
Found: C, 48.51; H, 4.41; N, 18.72.

Compound IIb, mp. 225-227°. Mass spectrum: m/e 237 (M^+).
Nmr ($CDCl_3$): τ = 1.75 (d, H_5), 3.0 (deg dd, H_6), 2.47 (qd, H_7), 7.47 (d, 8-Me), 5.58 (q, CH_2), 8.65 (t, CH_3); $J_{5,6}$ = 6.2, $J_{6,7}$ = 6.4, $J_{7,8\text{-Me}}$ = 1.0, J_{Et} = 7.2 Hz.
Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.63; H, 4.67; N, 17.72.
Found: C, 50.82; H, 5.04; N, 17.99.

Compound IIc, mp. 181-183°. Mass spectrum: m/e 251 (M^+).
Nmr (DMSO-d_6, 100°); τ = 2.95 (s, H_6), 2.58 (s, H_8), 7.34

(s, 5-Me), 7.55 (s, 7-Me), 5.67 (q, CH_2), 8.70 (t, CH_3); J_{Et} = 7.2 Hz.
Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.58; H, 5.22; N, 16.73.
Found: C, 52.95; H, 5.41; N, 16.61.

Compound IId, mp. 180-181°. Mass spectrum: m/e 237 (M^+).
Nmr (DMSO-d_6): τ = 1.16 (d, H_5), 2.83 (dd, H_6), 2.45 (m, H_8), 7.52 (d, 7-Me), 5.75 (q, CH_2), 8.72 (t, CH_3); $J_{5,6}$ = 6.5, $J_{6,8}$ = 2.0, $J_{8,7\text{-Me}}$ = 1.0, J_{Et} = 7.2 Hz.
Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.63; H, 4.67; N, 17.72.
Found: C, 50.68; H, 4.98; N, 17.67.

Compound IIe, mp. 197-200°. Mass spectrum: m/e 237 (M^+).
Nmr (DMSO-d_6): τ = 1.16 (d, H_5), 2.84 (qd, H_7), 2.48 (dd, H_8), 7.55 (d, 6-Me), 5.75 (q, CH_2), 8.72 (t, CH_3); $J_{5,7}$ = 1.5, $J_{5,8}$ = 0.8, $J_{7,8}$ = 7.2, $J_{7,6\text{-Me}}$ = 1.5, J_{Et} = 7.2 Hz.
Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.63; H, 4.67; N, 17.72.
Found: C, 50.88; H, 4.80; N, 17.57.

Compound IIf, mp. 217-220°. Mass spectrum: m/e 295 (M^+). Nmr (DMSO-d_6, 106°): τ = 1.0 (dd, H_5), 2.77 (dd, H_6), 1.72 (dd, H_7, 5.57 and 5.70 (q, CH_2), 8.60 and 8.67 (t, CH_3); $J_{5,6}$ = 6.2, $J_{6,7}$ = 7.5, $J_{5,7}$ = 1.5, J_{Et} = 7.0 Hz.
Anal. Calcd. for $C_{12}H_{13}N_3O_4S$: C, 48.81; H, 4.44; N, 14.23.
Found: C, 49.12; H, 4.90; N, 14.10.

Compound III, mp. 225°. Mass spectrum: m/e (258) (M^+).
Anal. Calcd. for $C_8H_7ClN_4O_2S$: C, 37.14; H, 2.73; N, 21.66.
Found: C, 37.42; H, 3.02; N, 21.95.

Compound IV, mp. 222-225°. Mass spectrum: m/e 224 (M^+).
Nmr (DMSO)-d_6, 110°): τ = 1.07 (dd, H_5), 1.70 (d, H_6), 0.88 (d, H_8), 5.65 (q, CH_2), 8.67 (t, CH_3); $J_{5,6}$ = 4.8, $J_{5,8}$ = 1.5, J_{Et} = 7.2 Hz.
Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.86; H, 3.60; N, 24.99.
Found: C, 43.14; H, 3.84; N, 25.06.

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