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The synthesis of the novel tricyclic ring 5-methyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c]-[1,2]benzothiazine 6,6-dioxide (III) is described.

By the reaction of hydrazine and hydroxylamine with the glyoxylate (IV) and ester (V) obtained from III, several polyazadithiasteroid analogues have been synthesized.

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In connection with our studies on new heterocyclic ring systems which are steroidal analogues (1), we now report a synthesis of polynuclear heterocycles incorporating the 1,2-benzothiazine ring into the steroidal skeleton, a structural feature with very interesting pharmacological properties (2).

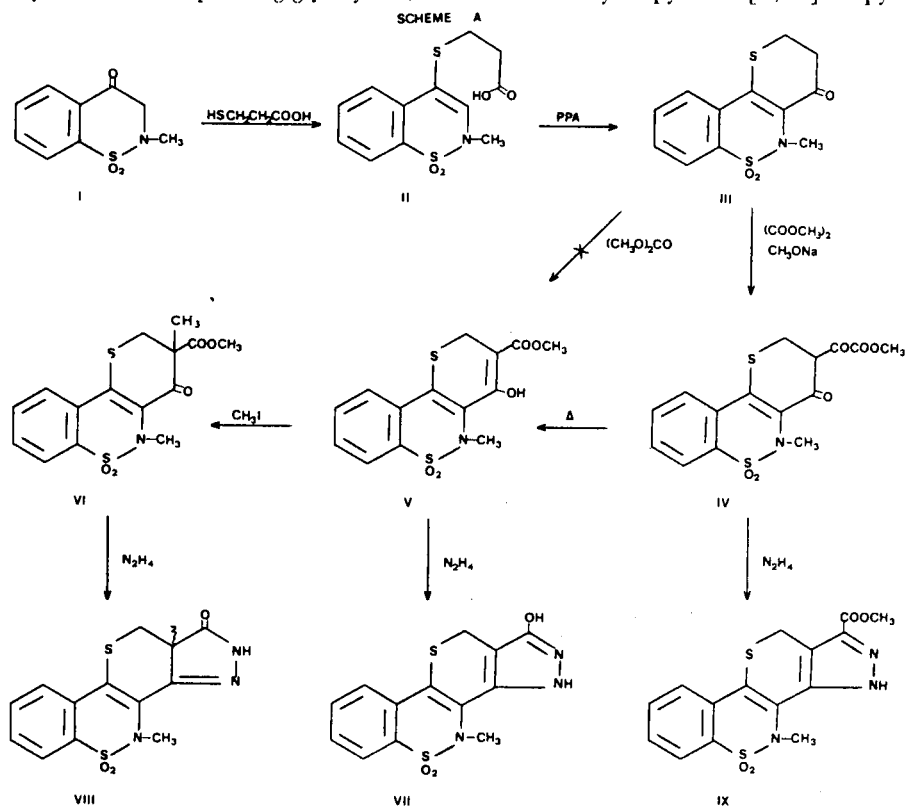
The synthesis of the title compounds outlined in Schemes 1 and 2 was achieved from the known 2-methyl-2H-1,2-benzothiazin-4(3H)one 1,1-dioxide (3), which by acid catalyzed reaction with thioglycolic acid and subsequent cyclodehydration in polyphosphoric acid gave 5-methyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-dioxide (III). Compound III is the starting ketone for the synthesis of the corresponding glyoxylate IV and  $\beta$ -ketoester V as key intermediates for obtaining heterocyclic steroidal analogues.

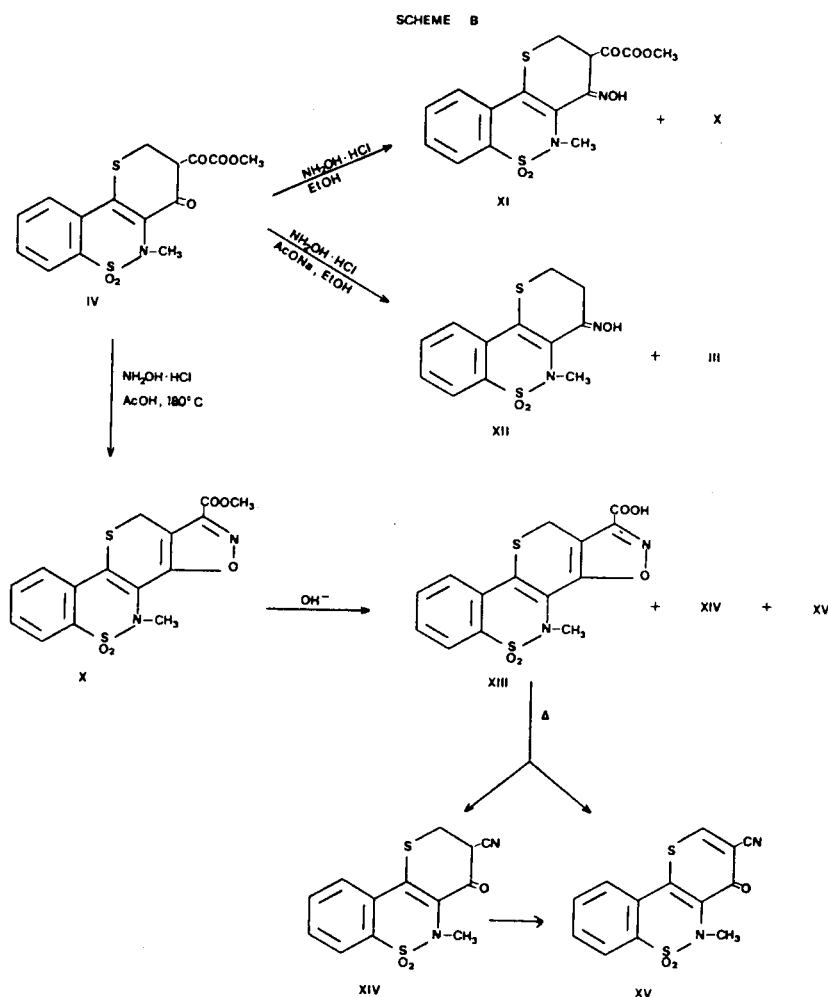
Condensation of dimethyl oxalate with the ketone III furnished in excellent yield the corresponding glyoxylate,

which on heating with soft glass powder at 170° underwent decarbonilation giving the  $\beta$ -ketoester V (4). As indicated by ir and pmr spectra, this ester exists in the tautomeric enol form. Compound V was then converted to 3-carbomethoxy-3,5-dimethyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-dioxide (VI) by treatment with sodium methoxide and methyl iodide.

Compounds V and VI on heating with an ethanolic solution of hydrazine afforded 4,11-dihydro-4-methyl-1-hydroxy-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]benzothiazine 5,5-dioxide (VII) and the racemic 7-methyl-7,15,16-triaza-6,11-dithia-1,3,5,8,14-estrapentaen-17-one 6,6-dioxide (VIII), respectively, whose structures are in agreement with pmr and ir data.

The glyoxylate IV by treatment with an ethanolic solution of hydrazine hydrate in the presence of acetic acid furnished in good yield 4,11-dihydro-4-methyl-1-carbomethoxy-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]-





benzothiazine 5,5-dioxide (IX). The reaction of IV with hydroxylamine hydrochloride gave different products depending on the experimental conditions. Heating the reaction mixture at  $170^\circ$  in acetic solution for a few minutes afforded 4-methyl-1-carbomethoxy-4*H*,11*H*-isoxazolo[4,5-*c*]thiopyrano[3,2-*c*][1,2]benzothiazine 5,5-dioxide (X), while under milder conditions, by carefully heating the reaction mixture to reflux in ethanolic or acetic solution for 1 hour, compound X (55%) and the oxime XI (35%) usually resulted. When compound IV was reacted with hydroxylamine under mildly basic conditions (e.g. in ethanolic solution containing an excess of sodium acetate) a mixture of two products was obtained, which separated by column chromatography on silica gel. These products were identified as the ketone III (44.3%), and the oxime XII (47.3%).

Alkaline hydrolysis of X with an alcoholic solution of sodium hydroxide (10%) yielded a mixture containing the acid (XIII) (67%), and ketonitriles XIV (22.2%) and XV (10.7%). Evidence for the fully aromatic structure of ketonitrile XV was obtained from its pmr spectrum (trifluoroacetic acid), which showed a singlet for the C-2

proton at  $\delta$  9.60, and from the mass spectrum. The pmr spectrum (trifluoroacetic acid) of ketonitrile XIV, however showed a multiplet centered at  $\delta$  3.87 for the methylene group and a quartet centered at  $\delta$  4.65 for the C-3 proton (ABX system). The formation of ketonitriles XIV and XV gives support to the isoxazole structure assigned to X, and shows the instability of ketonitrile XIV, which spontaneously dehydrogenates to give the stable XV. Attempts to separate the mixture of ketonitriles XIV and XV by crystallization or by column chromatography on silica gel led almost exclusively to the formation of the aromatic ketonitrile XV (5).

#### EXPERIMENTAL

Melting points were determined in capillary tubes (Buchi melting point apparatus) and are uncorrected. Ir spectra were measured with a Perkin-Elmer (model 247) spectrophotometer in chloroform unless otherwise specified. Pmr spectra were obtained with a Joel model C60 HL spectrometer in the indicated solvents. Chemical shifts and coupling constants were measured in ppm ( $\delta$ ) and J (Hz) with respect to TMS. The mass spectrum was obtained on a Varian MAT 311 A.

The purity of the analytical samples was checked by tlc (silica gel).

**$\beta$ -(2-Methyl-2H-1,2-benzothiazin-4-ylthio 1,1-Dioxide)propionic Acid (II).**

A solution of 2-methyl-2H-1,2-benzothiazin-4(3H)one 1,1-dioxide (3) (21.1 g., 0.100 mole), 3-mercaptopropionic acid (10.6 g., 0.100 mole) and *p*-toluenesulfonic acid monohydrate (1.33 g., 0.007 mole) in dry benzene (200 ml.) was refluxed for 16 hours under a Dean-Stark trap. The benzene solution was cooled and extracted with three 70 ml. portion on 2*N* sodium carbonate. The combined alkaline extracts were acidified with dilute hydrochloric acid to give 18.5 g. of crude product, recrystallization of which from hexane-ethyl acetate gave II as white prisms, m.p. 130-131° (61.8% yield).

*Anal.* Calcd. for  $C_{12}H_{13}NO_4S_2$ : C, 48.16; H, 4.35; N, 4.68. Found: C, 48.31; H, 4.21; N, 4.73.

**5-Methyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-Dioxide (III).**

A mixture of 6 g. of acid (II) and 30 g. of polyphosphoric acid was stirred and heated at 100-110° for 2 hours. After cooling, the syrupy material was poured into crushed ice. The precipitated solid was filtered, and washed first with 10% aqueous sodium carbonate and then with water. Recrystallization from hexane-ethyl acetate afforded yellow prisms, m.p. 172-173° (95% yield); pmr (deuteriochloroform):  $\delta$  3.30 (A<sub>2</sub>) and 2.95 (B<sub>2</sub>) [m, 4H (A<sub>2</sub>B<sub>2</sub> system), CH<sub>2</sub>-CH<sub>2</sub>], and 2.98 (s, 3H, N-CH<sub>3</sub>); ir:  $\nu$  1660 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{12}H_{11}NO_3S_2$ : C, 51.24; H, 3.91; N, 4.98. Found: C, 51.27; H, 3.76; N, 5.07.

**5-Methyl-3-carbomethoxycarbonyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-Dioxide (IV).**

To a suspension of sodium methoxide (prepared freshly from 1.9 g. of sodium and dry methanol) in dry benzene (60 ml.) was added under nitrogen, a solution of dimethyl oxalate (9.5 g., 0.080 mole) in dry benzene (40 ml.), followed by a solution of the ketone (III) (11.24 g., 0.040 mole) in dry benzene (100 ml.). As the condensation proceeded, a red-brown solid gradually precipitated. The mixture was stirred under nitrogen at room temperature for 3 hours, and then ice-cold water was added. The benzene layer was separated and washed with 10% sodium hydroxide. The combined alkaline extracts were chilled and acidified with dilute hydrochloric acid. The glyoxylate (IV) which separated as a greenish-yellow precipitate was filtered and recrystallized from ethyl acetate, m.p. 180-181° (87% yield).

*Anal.* Calcd. for  $C_{15}H_{13}NO_6S_2$ : C, 49.04; H, 3.54; N, 3.81. Found: C, 49.23; H, 3.47; N, 4.01.

**5-Methyl-3-carbomethoxy-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine (V).**

A powdered mixture of the glyoxylate (IV) (2 g.) and soft glass powder was heated around 160° until the evolution of carbon monoxide ceased. The mixture was cooled, extracted with acetone, and the extract after treatment with charcoal was filtered and evaporated to dryness. The orange-brown residue was recrystallized from ethyl acetate, m.p. 156-157° (70% yield); pmr (deuteriochloroform):  $\delta$  3.70 (s, 2H, S-CH<sub>2</sub>), 3.80 (s, 3H, COOCH<sub>3</sub>), 3.05 (s, 3H, N-CH<sub>3</sub>) and 12.80 (s, 1H, OH); ir:  $\nu$  1650 conjugated (CO-O) and 3560 cm<sup>-1</sup> chelated (OH).

*Anal.* Calcd. for  $C_{14}H_{13}NO_5S_2$ : C, 49.56; H, 3.83; N, 4.13. Found: C, 49.66; H, 3.84; N, 4.23.

**3-Carbomethoxy-3,5-dimethyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine (VI).**

To a solution of sodium methoxide (0.6 g. sodium in 50 ml. of dry methanol) was added 1 g. of V, followed by methyl iodide (14 ml.), and the mixture was refluxed for 24 hours. The cold reaction mixture was diluted with water and acidified with acetic acid. The acid solution was extracted with chloroform, and the combined organic layers were washed with water and dried over sodium sulphate to give 0.850 g. of an oily residue, which was extracted with several portions of a 95:5 hexane/ethyl acetate mixture. From the resulting solution, a crystalline product (0.520 g.) was obtained, m.p. 123-124° (50% yield); pmr (trifluoroacetic acid):  $\delta$  1.78 (s, 3H, CH<sub>3</sub> at C-3), 3.85 (A) and 3.60 (B) [q, 2H (AB system), J = 13 Hz, S-CH<sub>2</sub>], 3.05 (s, 3H, N-CH<sub>3</sub>) and 3.95 (s, 3H, COOCH<sub>3</sub>).

*Anal.* Calcd. for  $C_{15}H_{15}NO_5S_2$ : C, 50.99; H, 4.24; N, 3.96. Found: C, 50.76; H, 4.35; N, 3.91.

**4,11-Dihydro-4-methyl-1-hydroxy-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]benzothiazine 5,5-Dioxide (VII).**

A solution of V (1 g.) in ethanol (80 ml.), to which 95% hydrazine hydrate (0.5 ml.) had been added, was refluxed for 18 hours. The product precipitated on cooling was recrystallized from acetic acid, m.p. 320° (45% yield); pmr (DMSO-*d*<sub>6</sub>):  $\delta$  3.95 (s, 2H, S-CH<sub>2</sub>), 3.10 (s, 3H, N-CH<sub>3</sub>) and ~11 (broad s, 1H, OH); ir (nujol):  $\nu$  1640 (C=N) and 3285 cm<sup>-1</sup> (NH; OH).

*Anal.* Calcd. for  $C_{13}H_{11}N_3O_3S_2$ : C, 48.60; H, 3.43; N, 13.08. Found: C, 48.39; H, 3.29; N, 13.09.

**Racemic 7-Methyl-7,15,16-triaza-6,11-dithia-1,3,5,8,14-estrapenten-17-one 6,6-Dioxide (VIII).**

The  $\beta$ -ketoester (VI) (0.5 g.) was refluxed in methanol (20 ml.) with 95% hydrazine hydrate (0.3 ml.) for 7 hours. The reaction mixture was allowed to stand at room temperature overnight and then poured into ice-water. The yellow precipitate was recrystallized from ethyl acetate, m.p. 280-282° (45% yield); pmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.50 (s, 3H, CH<sub>3</sub> at C-18), 3.55 (A) and 2.82 (B) [q, 2H (AB system), J = 12Hz, -SCH<sub>2</sub>], 3.04 (s, 3H, N-CH<sub>3</sub>), and ~12 (broad s, 1H, NH); ir (nujol):  $\nu$  3150 (NH), 1710 (NH-C=O) and 1675 cm<sup>-1</sup> (C=N).

*Anal.* Calcd. for  $C_{14}H_{13}N_3O_3S_2$ : C, 50.15; H, 3.88; N, 12.54. Found: C, 49.98; H, 3.96; N, 12.43.

**4,11-Dihydro-4-methyl-1-carbomethoxy-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]benzothiazine 5,5-Dioxide (IX).**

A solution of glyoxylate (IV) (1 g.) in ethanol (150 ml.) and acetic acid (20 ml.) was added with 95% hydrazine hydrate (0.5 ml.) and refluxed for 3 hours. The reaction mixture was concentrated, diluted with ice-water and the precipitate that separated was filtered to give 0.800 g. of solid. It was recrystallized from ethanol, m.p. 255-257° (76% yield); pmr (trifluoroacetic acid):  $\delta$  3.14 (s, 3H, N-CH<sub>3</sub>), 3.85 (s, 3H, COOCH<sub>3</sub>) and 4.30 (s, 2H, S-CH<sub>2</sub>).

*Anal.* Calcd. for  $C_{15}H_{13}N_3O_4S_2$ : C, 49.58; H, 3.58; N, 11.57. Found: C, 49.65; H, 3.70; N, 11.61.

**Reaction between 5-Methyl-3-carbomethoxycarbonyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-Dioxide (IV) and Hydroxylamine Hydrochloride.**

a) A mixture of the glyoxylate (IV) (0.5 g., 0.0014 mole) and hydroxylamine hydrochloride (0.2 g., 0.0028 mole) in acetic acid (10 ml.) was quickly heated on an oil-bath maintained at 180° and refluxing continually for 15 minutes. The brown solution was allowed to cool to room temperature and the solid which had separated was collected by filtration and washed with methanol. Recrystallization from acetic acid gave 0.420 g. (79% yield) of 4-methyl-1-carbomethoxy-4H-isoxazolo[4,5-c]thiopyrano[3,2-c]-

[1,2]benzothiazine 5,5-dioxide (X), m.p. 245; pmr (trifluoroacetic acid):  $\delta$  3.30 (s, 3H, N-CH<sub>3</sub>), 4.10 (s, 3H, COOCH<sub>3</sub>) and 4.36 (s, 2H, S-CH<sub>2</sub>).

*Anal.* Calcd. for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>: C, 49.45; H, 3.29; N, 7.69. Found: C, 49.35; H, 3.24; N, 7.63.

(b) The above reaction was performed by refluxing the mixture in ethanol (50 ml.) or acetic acid (10 ml.) for 1 hour. The solution then was poured into ice-water and the resulting precipitate filtered and washed with water. The dried precipitate (0.510 g., m.p. 105-120°) was chromatographed on silica gel (benzene-ethyl acetate 9.8/0.2) to give X (0.290 g., 55%) and 0.220 g., (35%) of 5-methyl-3-carbomethoxycarbonyl-4-oxoimido-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-dioxide (XI), which was recrystallized from hexane-ethyl acetate, m.p. 163°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C, 47.24; H, 3.41; N, 7.34. Found: C, 47.11; H, 3.60; N, 7.29.

(c) To a solution of IV (0.750 g., 0.002 mole) in ethanol (150 ml.) was added hydroxylamine hydrochloride (0.150 g., 0.002 mole) and a solution of sodium acetate (0.250 g., 0.003 mole) in water (5 ml.). The mixture was refluxed for 5 hours and then evaporated to ca. 20 ml. at reduced pressure. The cooled solution afforded a crystalline product which was chromatographed on silica gel. Elution with benzene yielded III (0.272 g., 44.3%). Further elution with benzene-ethyl acetate 9/1 afforded 0.306 g. (47.3%) of 5-methyl-4-oximido-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-dioxide (XII), which was recrystallized from ethanol, m.p. 248°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>: C, 48.64; H, 4.05; N, 9.45. Found: C, 48.63; H, 3.96; N, 9.29.

Alkaline Hydrolysis of 4-Methyl-1-carbomethoxy-4H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][1,2]benzothiazine 5,5-Dioxide (X) to afford 4-Methyl-1-carboxy-4H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][1,2]benzothiazine 5,5-Dioxide (XIII), 5-Methyl-3-cyano-4-oxo-4,5-dihydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-Dioxide (XV) and 5-Methyl-3-cyano-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine 6,6-Dioxide (XIV).

To a suspension of X (2 g.) in ethanol (30 ml.), a solution of 10% sodium hydroxide (20 ml.) was added. After refluxing for 30 minutes the formation of a precipitate was obtained. The reaction mixture was refluxed for additional 15 minutes and then sodium salt precipitate was filtered, washed with several portions of ethanol, dissolved in water and the resulting solution acidified with 4N hydrochloric acid to give a precipitate, which was filtered and washed with water to give 1.290 g. of acid (XIII), m.p. 204-206° dec. (from ethanol); pmr (trifluoroacetic acid):  $\delta$  3.35

(s, 3H, N-CH<sub>3</sub>) and 4.45 (s, 2H, S-CH<sub>2</sub>).

*Anal.* Calcd. for C<sub>14</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>: C, 48.00; H, 2.85; N, 8.00. Found: C, 48.32; H, 3.01; N, 8.27.

The aqueous alcoholic filtrate was then combined with alcoholic washings of the sodium salt, diluted with water, acidified with 4N hydrochloric acid and the resulting acid solution extracted with several portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, and evaporated to give 0.550 g. of a solid residue (m.p. 180-185°) which was crystallized from ethanol to give 0.178 g. of the aromatic ketonitrile (XV), m.p. 270° (from acetic acid); pmr (trifluoroacetic acid):  $\delta$  3.32 (s, 3H, N-CH<sub>3</sub>) and 9.60 (s, 1H, C-2); ir (nujol):  $\nu$  2220 (C≡N) and 1630 cm<sup>-1</sup> (C=O); ms: M<sup>+</sup> 304.

*Anal.* Calcd. for C<sub>13</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>: C, 51.31; H, 2.63; N, 9.21. Found: C, 51.27; H, 2.70; N, 9.19.

By concentration of the mother liquors, a precipitate (0.374 g.) constituted mainly of the ketonitrile XIV, m.p. 200-202°, slightly impure because of the ketonitrile XV, was obtained; pmr (trifluoroacetic acid):  $\delta$  3.10 (s, 3H, N-CH<sub>3</sub>), 3.87 (m, 2H, S-CH<sub>2</sub>) and 4.65 (q, 1H, C-3); ir:  $\nu$  2200 (C≡N) and 1680 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>: C, 50.98; H, 3.26; N, 9.15. Found: C, 51.19; H, 3.48; N, 8.95.

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- (4) The direct carbomethoxylation of III with dimethyl carbonate under different conditions failed.
- (5) A mixture of ketonitriles (XIV) and (XV) in yields of 70% and 22%, respectively, was also obtained in the attempt to decarboxylate XIII by heating with soft glass powder.