SYNTHESIS OF 2- AND 4-SUBSTITUTED 5,6,7,8-TETRAHYDRO-7-ISOPROPYLPYRIDO[4',3':4,5]THIENO[2,3-d]PYRIMIDINES

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We have already reported the synthesis of condensed 4-substituted pyrano(thiopyrano)-[4',3':4,5]thieno[2,3-d]pyrimidines, which have anticonvulsant activity [1].

Our intention in the work described here was to synthesize tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidines, which differ from the preceding compounds in a single heteroatom. Condensation of 1-isopropyl-4-piperidone with ethyl cyanoacetate or malonodinitrile and sulfur gave 2,3-substituted 4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyridines (II, III).



The IR spectra in the  $3150-3400 \text{ cm}^{-1}$  region contain four (compound II) and two (compound III) free NH<sub>2</sub> bands. Compounds II and III also have bands at 1740 (CO) and 2210 cm<sup>-1</sup> (CN). The intense broad band with two maxima at 1600 and 1650 cm<sup>-1</sup> in II and III and a shoulder at 1720 cm<sup>-1</sup> in II apparently represents the deformation modes of the aromatic nuclei, the ethoxycarbonyl stretching, and also the amino deformation modes. The PMR spectra ( $\delta$ , ppm): II NH<sub>2</sub> 6.12 (2H); 3-CH<sub>2</sub>CH<sub>3</sub> 1.32 (3H, triplet; J 7 Hz); 3-OCH<sub>2</sub> 4.25 (2H, quartet; J 7 Hz); 4- and 5-CH<sub>2</sub> 2.81 (4H); 6-(CH<sub>3</sub>)<sub>2</sub>C 1.18 (6H, doublet; J 6.5 Hz); 6-CH(CH<sub>3</sub>)<sub>2</sub> 2.88 (1H; J 6.5 Hz); III NH<sub>2</sub> 4.61 (2H), 4- and 5-CH<sub>2</sub> 2.65 (4H); 6-CH(CH<sub>3</sub>)<sub>2</sub> 2.82 (1H; J 6.5 Hz); 6-(CH<sub>3</sub>)<sub>2</sub>C 1.18 (6H, doublet; J 1.3 Hz).

When heated with formamide, II and III gave 5,6,7,8-tetrahydro-7-isopropylpyrido[4'3': 4,5]thieno[2,3-d]pyrimidin-4(3H)-one (IV) and 4-amino-5,6,7,8-tetrahydro-7-isopropylpyrido-[4',3':4,5]thieno[2,3-d]pyrimidine (V). The IR spectrum of IV has bands at 1710 cm<sup>-1</sup> (CO) and 1650 cm<sup>-1</sup> (NH); compound V has three free amino bands at 3150, 3250, and 3470 cm<sup>-1</sup>, while the deformation modes of the aromatic nuclei and amino groups appear at 1600 and 1670 cm<sup>-1</sup>.

Reaction of II with benzoyl and p-chlorobenzoyl chloride gave 2-benzoyl- and 2-p-chlorobenzoylamino-3-ethoxycarbonyl-4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyridines (VI, VII).

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When heated in methanolic ammonia VI and VII generated the pyrimidines VIII and IX.

Reaction of III with orthoformate ester in the presence of acetic anhydride gave 2-ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyridine (X), condensation of which with benzylamine led to the 2-benzyl derivative XI. When heated in alcohol in the presence of sodium ethoxide XI cyclized to 4-benzylamino-5,6,7,8-tetrahydroisopropylpyrido[4',3':4,5]thieno[2,3-d]pyrimidine (XII).

Examination of the anticonvulsant properties of II-IX and XII revealed that these compounds do not prevent the convulsant effects of corazole, maximal electroshock, nicotine, or arecoline. They displayed toxic effects in a dose of 200 mg/kg (intraperitoneally).

We also examined the anesthetic and morphine-antagonist properties of these compounds. None, except for XII, had any anesthetic effect. Compound XII showed moderate (up to 40%) analgesic activity in a dose of 30 mg/kg. Increase in the dose to 50 mg/kg caused the development of toxic effects that masked the analgesic activity.

The test compounds were ineffective as opiate antagonists.

## EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on a UR-20 spectrometer with NaCl and LiCl prisms as mulls in vaseline oil. The PMR spectra were measured on a Varian T-60 in chloroform and carbon tetrachloride with tetramethylsilane as internal standard. Shifts are quoted on the  $\delta$  scale.

 $\frac{2-\text{Amino}-3-\text{ethoxycarbonyl}-4,5,6,7-\text{tetrahydro}-6-\text{isopropylthieno}[3,4-b]pyridine (II). A suspension of I (14.1 g, 0.1 mole), ethyl cyanoacetate (11 g, 0.1 mole), and sulfur powder (3.2 g, 0.1 mole) in 96% ethanol (100 ml) was heated to 40°C and diethylamine (2 ml) in ethanol (15 ml) was added dropwise with stirring over a period of 30 min. The temperature was raised to 60°C. The mixture was stirred until the sulfur had completely dissolved. It was then cooled and poured into cold water (250 ml). The yellow crystals were filtered off, washed twice with water, and dried in a vacuum desiccator to give II (20.0 g 74.62%), mp 35-36°C (from methanol-water). Found, %: N 10.36, S 11.87. C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S. Calculated, %: N 10.43, S 11.96. Hydrochloride: mp 125-126°C (from alcohol).$ 

 $\frac{2-\text{Amino}-3-\text{cyano}-4,5,6,7-\text{tetrahydro}-6-\text{isopropylthieno}[3,4-b]\text{pyridine (III)}. A mixture of I (7.05 g, 0.05 mole), sulfur powder (1.6 g, 0.05 mole), and malonodinitrile (3.3 g, 0.05 mole) in 96% ethanol (70 ml) was warmed to 35°C in a stream of nitrogen with stirring and diethylamine (1 ml) in ethanol (10 ml) was added dropwise over a period of 15 min. Stirring was continued until the sulfur had completely dissolved. The reaction mixture was left overnight at room temperature. The precipitated crystals were filtered off and washed with hexane to give III (6.77 g, 61.25%), mp 168-169°C (from alcohol). Found, %: N 18.90; S 14.45. C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>S. Calculated, %: N 18.98, S 14.48.$ 

5,6,7,8-Tetrahydro-7-isopropylpyrido[4',3';:4,5]thieno[2,3-d]pyrimidin-4(3H)-one (IV). A mixture of II (5.36 g, 0.02 mole) and formamide (15 ml) was refluxed in a stream of nitrogen for 5 h, left overnight at room temperature, and then diluted with water. The precipitated crystals were filtered off, washed with acetone, and dried in a vacuum desiccator to give IV (2.54 g, 51.20%), mp 259-261°C. Found, %: N 16.77, S 12.69. C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>OS. Calculated, %: N 16.85; S 12.85.

4-Amino-5,6,7,8-tetrahydro-7-isopropylpyrido[4',3':4:5]thieno[2,3-d]pyrimidine (V). A mixture of III (2.2 g, 0.01 mole) and formamide (10 ml) was refluxed for 4 h. The reaction mixture was cooled, diluted with ethanol (15 ml), and left overnight at room temperature. The precipitate was filtered off, washed with ethanol, and dried in a vacuum desiccator to give V (1.1 g, 45.0%), mp 198-199.5°C. Found, %: N 22.45, S 12.83. C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>S. Calculated, %: N 22.56, S 12.90.

<u>2-Benzoyl-</u> and 2-p-Chlorobenzoyl-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyridine (VI, VII). To a solution of II (0.01 mole) in dry benzene (30 ml) was added triethylamine (2.0 g, 0.02 mole) and benzoyl or p-chlorobenzoyl chloride (0.01 mole) was slowly added dropwise. The reaction mixture was refluxed for 5 h and then cooled. The precipitated crystals of triethylamine hydrochloride were filtered off. The filtrate was evaporated under slight vacuum and the thick residue crystallized on addition of ether. The crystals were filtered off and washed with ether. The yield of VI was 62.09%, mp 123-124°C (from alcohol). Found, %: N 7.28, S 8.33.  $C_{20}H_{24}N_2O_3S$ . Calculated, %: N 7.51, S 8.60. The yield of VII was 73.89%, mp 149-150°C (from alcohol). Found, %: Cl 8.56, N 6.73, S 7.69. C<sub>20</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>. Calculated, %: Cl 8.71, N 6.88, S 7.87. IR spectrum, ν, cm<sup>-1</sup>: 1620, 1650, 1670 (NH, CO, C=N) and 3250 (NH). PMR spectrum (δ, ppm): VI NH 6.85; C<sub>6</sub>H<sub>5</sub> 7.2-8.2 (5H, multiplet); VII NH 7.42.

2-Phenyl- and 2-p-Chlorophenyl-5,6,7,8-tetrahydro-7-isopropylpyrido[4',3':4,5]thieno-[2,3-d]pyrimidin-4(3H)-one (VIII, IX). A mixture of VI or VII (0.008 mole) in 25% methanolic ammonia (50 ml) was heated at 100-110°C in a metal bomb for 18 h. After cooling with an ice-salt mixture, the bomb was opened and the contents were poured into an equal volume of ether. The precipitated crystals were filtered off, washed with ether, and dried in a vacuum desiccator. The yield of VIII was 48.25%, mp 225-226°C. Found, %: N 12.77; S 9.69.  $C_{18}H_{19}N_{3}OS$ . Calculated, %: N 12.21, S 9.85. Hydrochloride: mp 210-212°C (from alcohol). The yield of IX was 1.6 g (61.5%), mp 135-136°C (from alcohol). Found, %: Cl 10.12, N 11.72, S 9.14.  $C_{18}H_{18}CIN_{3}OS$ . Calculated, %: Cl 9.84, N 11.67, S 8.90. Hydrochloride: mp 245-247°C (from alcohol). IR spectrum (v, cm<sup>-1</sup>): 1620-1670 (NH, C=N, CO), 3200 (NH).

2-Ethoxymethylene-3-cyano-4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyridine (X). To a solution of III (2.2 g, 0.01 mole) in orthoformate ester (20 ml) was added acetic anhydride (5 drops). The reaction mixture was refluxed for 4 h. The excess orthoformate ester was removed under vacuum and the thick precipitate crystallized after addition of hexane. The crystals were filtered off, washed with hexane, and dried to give X (1.7 g, 62.96%), mp 64-66°C (from alcohol-hexane). Found, %: N 14.97, S 11.43.  $C_{14}H_{19}N_{3}OS$ . Calculated, %: N 15.14, S 11.55. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1630 (C=N), 2210 (CN), 3250 (NH). PMR spectrum ( $\delta$ , ppm): CH 7.82, OCH<sub>2</sub>CH<sub>3</sub> 4.28 (2H, quartet, J 7 Hz), OCH<sub>2</sub>CH<sub>3</sub> 1.39 (3H, triplet, J 7 Hz).

 $\frac{2-\text{Benzylaminomethyleneamino-3-cyano-4,5,6,7-tetrahydro-6-isopropylthieno[3,4-b]pyri$ dine (XI). To a solution of X (1.7 g, 0.006 mole) in ethanol (25 ml) was added benzylamine(0.6 g, 0.006 mole). The reaction mixture was refluxed for 3 h. After cooling the alcoholwas stripped off and the thick residue was crystallized from ethyl acetate -hexane (1:2).The crystals were filtered off, washed, and dried to give XI (1.2 g, 53.0%), mp 54-55.5°C.Found, %: N 16.42, S 9.31. C19H22N4S. Calculated, %: N 16.55, S 9.47. IR spectrum $(v, cm<sup>-1</sup>): 1630 (C=N), 2210 (CN), 3350 (NH). PMR spectrum (<math>\delta$ , ppm): CH 7.62, NCH2 5.18, C<sub>6</sub>H<sub>5</sub> 7.25.

<u>4-Benzylamino-5,6,7,8-tetrahydro-7-isopropylpyrido[4',3':4,5]thieno[2,3-d]pyrimidine</u> (XII). To sodium ethoxide, prepared from ethanol (15 ml) and sodium (0.0017 mole), was added XI (0.7 g, 0.0017 mole). The reaction mixture was refluxed for 4 h. The alcohol was stripped off under vacuum and the thick residue of ethyl acetate was crystallized from ethyl acetate, filtered off, washed with ethyl acetate, and dried to give XII (0.6 g, 85.71%), mp 90-92°C. Found, %: N 16.50, S 9.42.  $C_{19}H_{22}N_4S$ . Calculated, %: N 16.55, S 9.47. Hydrochloride: mp 201-202°C (from alcohol). IR spectrum ( $\nu$ , cm<sup>-1</sup>): 1630 (C=N), 1720 (CO), 3360 (NH).

## LITERATURE CITED

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