SYNTHESIS OF 2-PROPYLOXAZOLE AND 2-PROPYLOXAZOLE-4-CARBOXYLIC ACID DERIVATIVES

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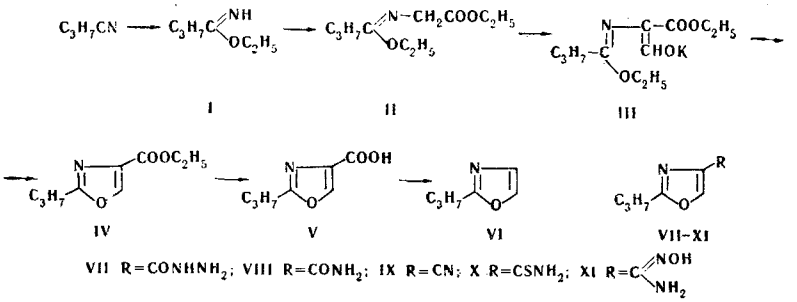
2-Propyloxazole (VI) was obtained in a number of steps starting from butyronitrile. The hydrazide and amide were obtained from ethyl 2-propyloxazole-4-carboxylate; the amide was converted to the nitrile, from which the thioamide and amidoxime were obtained by the usual method. Attempts to convert VI to 2-propylisonicotinic acid or its nitrile by the reaction of VI with acrylic acid or acrylonitrile did not give positive results.

The data available in the literature [1, 2] regarding the possibility of obtaining alkyl(aryl)-substituted isonicotinic acids or their derivatives by the reaction of alkyl(aryl)oxazoles with acrylic acid or acrylonitrile have provided a basis for assuming that 2-propylisonicotinic acid or its nitrile – intermediates in the synthesis of the well-known antitubercular preparation prothionamide (the thioamide of 2-propylisonicotinic acid) – can be obtained from 2- or 4-propyloxazole.

To verify this possibility, we synthesized the previously undescribed 2-propyloxazole (VI). It was also of independent interest to obtain various derivatives of 2-propyloxazole-4-carboxylic acid (VII-XI), which contain groupings that promote tuberculostatic activity; in particular, the thioamide of 2-propyloxazole-4-carboxylic acid (X) can be considered to be the oxazole analog of prothionamide. The synthesis of 2-propyloxazole (VI) was accomplished starting from butyronitrile in analogy with the method described for the preparation of 2-methyl- [3] and 2-amyloxazoles [3, 4].



VII R=CONHNH$_2$; VIII R=CONH$_2$; IX R=CN; X R=CSNH$_2$; XI R=C(NOH)NH$_2$

The base of the imino ester of butyric acid (I) was obtained from butyronitrile via a somewhat modified method [5]. In this case, it was found that the yield of I can be raised from 18% [5] to 64% if the reaction time is increased and the hydrochloride of the imino ester is decomposed under a layer of organic solvent. The condensation of I with the hydrochloride of the ethyl ester of glycine gave ethyl α'-ethoxybutyrylideneaminoacetate (II); II was converted to the potassium salt of ethyl α-(α-ethoxybutyrylideneamino)-β-hydroxyacrylate (III) by the action of potassium alkoxide and ethyl formate.

When III is heated in glacial acetic acid, it cyclizes to form ethyl 2-propyloxazole-4-carboxylate (IV). Saponification of IV with aqueous sodium hydroxide and subsequent decarboxylation of 2-propyloxazole-4-

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carboxylic acid (V) in the presence of cupric oxide gave 2-propyloxazole (VI) as a colorless liquid with a sharp odor. The yield of VI was 10-14% based on butyronitrile.

Attempts to convert VI to 2-propylisonicotinic acid or its nitrile by condensation with acrylic acid or acrylonitrile did not give positive results: when the components were heated in benzene or toluene in the presence of hydroquinone, the reaction mass gradually resinified, and 2-propylisonicotinic acid and its corresponding nitrile were not detected even by chromatography.

Hydrazide VII and amide VIII were obtained from ethyl 2-propyloxazole-4-carboxylate (IV). Amide VIII was converted to nitrile IX by dehydration with phosphorus oxychloride. Thioamide X and amidoxime XI were obtained from IX by the usual method.

Compounds V and VII-XI were investigated of their bacteriostatic activity.* The thioamide of 2-propyloxazole-4-carboxylic acid (X) showed high tuberculostatic activity in vitro. (The minimum bacteriostatic concentration was 0.5 μg/ml.) The activity fell sharply in the presence of serum. The remaining compounds did not have appreciable bacteriostatic properties.

EXPERIMENTAL

Imino Ester of Butyric Acid (I). Dry hydrogen chloride was passed into an ice-cooled mixture of 32 g (0.46 mole) of butyronitrile, 21.6 g (0.47 mole) of absolute ethanol, and 25 ml of petroleum ether until the gain in weight of the mixture was 16.88 g (0.46 mole). The mixture was allowed to stand at 4-6°C for 20-25 days, the petroleum ether was decanted, and the resulting crystalline hydrochloride of I was cooled and treated under a layer of ether, first with a saturated aqueous solution of potassium carbonate, and then with dry potassium carbonate. The ether layer was periodically decanted and replaced with fresh ether. The combined ether extracts were dried with magnesium sulfate, the solvent was removed by distillation, and the residue was distilled to give 34.6 g (63.8%) of I as a colorless liquid with bp 123-129° [5].

Ethyl (α-Ethoxybutyrylideneamino)acetate (II). A solution of 23.28 g (0.202 mole) of I in 80 ml of cooled diethyl ether was shaken for 1 h with a cooled solution of 28.2 g (0.202 mole) of the hydrochloride of the ethyl ester of glycine in 27 ml of water. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether solutions were washed with water and dried with magnesium sulfate. The solvent was removed, and the residue was distilled to give 20.39 g (50.2%) of II as a colorless liquid with bp 88-90° (0.75 mm), n_D^{20} 1.4384, and d_4^{20} 0.9755. Found: C 59.5; H 9.7; N 7.1%. $C_{10}H_{19}NO_3$. Calculated C 59.7; H 9.5; N 7.0%.

Potassium Salt of Ethyl α-(α-Ethoxybutyrylideneamino)-β-hydroxyacrylate (III). A 4.06 g (0.104 mole) sample of potassium metal was added to 46 ml of dry ether, and 15 ml [11.95 g (0.258 mole)] of absolute ethanol was added dropwise to the mixture. After the potassium had completely dissolved, 125 ml of absolute ether was added, and the reaction mass was cooled to − 9° for 30 min. A cooled mixture of 20.39 g (0.101 mole) of II and 15 ml [13.88 g (0.187 mole)] of ethyl formate was added with stirring. The mixture was stirred for 1 h, 100 ml of absolute ether was added, and the mixture was then allowed to stand for 12 h at 4-6°. The resulting precipitate of III was rapidly removed by filtration, washed with absolute ether, and dried in a vacuum desiccator to give 16.85 g of III. The mother liquor was diluted with ether and cooled for 12 h to give an additional amount of III for an overall yield of 20.65 g (76.5%). The substance is very hydroscopic and rapidly turns red on storage.

Ethyl 2-Propyloxazole-4-carboxylate (IV). A 22.5 g (84.3 mmole) sample of III was added in the course of 10 min to 50 ml of refluxing glacial acetic acid, and the mixture was refluxed for 5 min. The acetic acid was then removed by vacuum distillation, and the residue was cooled and triturated with ether. The precipitated potassium acetate was removed by filtration and washed with ether, and the ether solutions were evaporated. The residue [14.18 g (92.3%)] was distilled to give 11.95 g (77.5%) of IV with bp 115-117° (6.5 mm), n_D^{20} 1.4658, and d_4^{20} 1.0838. Found: C 58.8; H 7.0; N 7.5%. $C_9H_{13}NO_3$. Calculated: C 59.0; H 7.2; N 7.6%.

Technical-grade IV can be used without purification to obtain 2-propyloxazole-4-carboxylic acid.

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2-Propyloxazole-4-carboxylic Acid (V). A mixture of 7.02 g (38.4 mmole) of IV and 20.2 ml of 10% aqueous sodium hydroxide was refluxed for 15 min. The hot solution was treated with charcoal and filtered. The filtrate was cooled and acidified with concentrated hydrochloric acid to pH 3. The resulting precipitate was removed by filtration, washed with a small amount of cold water, and dried in a vacuum desiccator over phosphorus pentoxide to give 4 g of product. The aqueous mother liquor was salted out with sodium chloride to give an additional 0.47 g of V. The overall yield of V with mp 105-107° (benzene–hexane) was 4.47 g (74.87%). The colorless, crystalline substance was quite soluble in water, alcohol, and benzene and insoluble in hexane. Found: C 54.2; H 6.0; N 8.8%. $C_7H_9NO_3$. Calculated: C 54.2; H 5.8; N 9.0%.

2-Propyloxazole (VI). A mixture of 8.83 g (56.9 mmole) of V and 2 g of cupric oxide was heated slowly in the smoky flame of a gas burner in vacuo at 50 mm. In the process, 5.39 g (85.5%) of technical-grade VI distilled off. It was purified by distillation at atmospheric pressure over solid potassium hydroxide to give 3.57 g (56.55%) of VI as a colorless substance with a sharp odor and bp 123-124°, n_D^{20} 1.4396, and d_4^{20} 0.9658. Found: C 64.9; H 8.3; N 12.6%. C_9H_9NO. Calculated: C 64.8; H 8.2; N 12.6%.

Hydrazide of 2-Propyloxazole-4-carboxylic Acid (VII). A 0.35 ml (7.2 mmole) sample of hydrazine hydrate was added to a solution of 1 g (5.45 mmole) of IV in 2 ml of absolute ethanol, and the mixture was heated at 50° for 3 h. It was then cooled to 0° for 12 h, and the solvent was removed by distillation. The residue was triturated with ether, and the resulting precipitate was removed by filtration to give 0.65 g (70.3%) of VII with mp 77-78° (from hexane–ethyl acetate). The colorless, crystalline material was very readily soluble in water and alcohol. Found: C 49.6; H 6.6; N 24.6%. $C_7H_{11}N_3O_2$. Calculated: C 49.7; H 6.6; N 24.8%.

Amide of 2-Propyloxazole-4-carboxylic Acid (VIII). A mixture of 7.51 g (41.1 mmole) of IV and 20 ml of 25% ammonium hydroxide was saturated with gaseous ammonia and allowed to stand at 20° for 2 days. The reaction mass was cooled with ice, and the precipitate was removed by filtration and washed with cooled 25% ammonium hydroxide to give 6.0 g (95%) of VII with mp 157-159° (from water). The colorless, crystalline substance was quite soluble in alcohol and hot water. Found: C 54.3; H 6.6; N 18.5%. $C_7H_{10}N_2O_2$. Calculated: C 54.5; H 6.5; N 18.2%.

Nitrile of 2-Propyloxazole-4-carboxylic Acid (IX). A mixture of 6 g (39 mmole) of VIII and 16.3 ml [27.3 g (178 mmole)] of phosphorus oxychloride was heated at 100° for 15 min, and the oxychloride was then removed by vacuum distillation. Crushed ice (20 g) was added to the residue. Dry sodium bicarbonate was then added until the mixture was alkaline to universal indicator, and IX was extracted with ether. The solvent was removed to give 4.22 g (79.5%) of technical-grade IX. This was distilled at atmospheric pressure to give a colorless liquid with bp 112-114°, n_D^{20} 1.4650, and d_4^{20} 1.0600. Found: C 61.8; H 5.9%. $C_7H_8N_2O$. Calculated: C 61.8; H 5.9%.

Thioamide of 2-Propyloxazole-4-carboxylic Acid (X). Triethylamine (0.3 ml) was added to a solution of 0.26 g (1.92 mmole) of IX and 2 ml of absolute alcohol, the mixture was cooled with ice, and dry hydrogen sulfide was passed through it for 3-4 h. The resulting precipitate was removed by filtration and washed with 50% alcohol to give 0.3 g (92.5%) of X as colorless crystals that were soluble in water, moderately soluble in alcohol, and melted at 159-160° (from alcohol). Found: C 49.5; H 5.9; N 16.1; S 18.7%. $C_7H_{10}N_2OS$. Calculated: C 49.4; H 5.9; N 16.5; S 18.8%.

Amidoxime of 2-Propyloxazole-4-carboxylic Acid (XI). A solution of 0.26 g (3.75 mmole) of hydroxylamine hydrochloride and 0.39 g of sodium carbonate in 10 ml of water was added to a solution of 0.5 g (3.68 mmole) of IX in 10 ml of ethanol, and the mixture was heated at 70° for 9 h. It was then evaporated to one half its original volume and acidified with acetic acid. The resulting precipitate was removed by filtration and washed with water to give 0.37 g (60%) of XI with mp 125-127° (from ethyl acetate). The colorless plates were quite soluble in water and alcohol. Found: C 49.5; H 6.5%. $C_7H_{11}N_3O_2$. Calculated: C 49.7; H 6.6%.

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