SYNTHESIS AND PROPERTIES OF 2-AMINO-3-ETHYCARBONYLTHIENO[2,3-b]QUINUCLIDINES

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Some quinuclidines possess pronounced m- and n-choline blocking, antiarrhythmic, antihistaminic, and antiinflammatory activity. Some compunds of this chemical type have found application in medicine as drugs for the treatment of cardiovascular, allergic and other conditions (such as the ganglion-blockers imequin and temequin [2], and the histamine H_1 receptor blocker fencarol [1]).

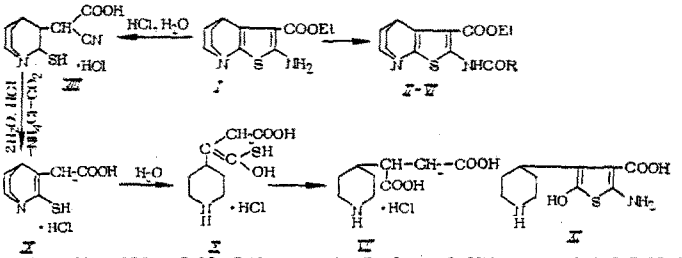
We have synthesized and examined the chemical and biological properties of some thieno-[2,3-b]quinuclidines. This class of compounds is described only in the patent literature [4], which reports the synthesis of some 3-substituted 2-aminothieno[2,3-b]quinuclidines, and states that these compounds display analgesic and antiinflammatory activity.

2-Amino-3-ethoxycarbonythienol[2,3-b]quinuclidine (I) and its derivatives at the amino-group (II-VI) have been prepared, and their chemical properties, antihistaminic and antiinflammatory activity, effects on arterial pressure (AP), and acute toxicities examined.

Compound (I) was obtained by the reaction between 3-oxoquinuclidine, cyanoacetic acid and sulfur in alcoholic solution in the presence of morpholine. The reaction was accompanied by considerable resinification, the yield of the aminoester (I) being 46%. Acylation of (I) with acetic anhydride and acid chlorides in benzene in the presence of triethylamine has given the 2-acylamino-3-ethoxycarbonylthienol[2,3-b]quinuclidines (II-VI).

In order to obtain the amino acid from the amino ester (I), the hydrolysis of (I) was examined under a variety of conditions. It was found that the ester group did not undergo hydrolysis either in boiling 0.1 N HCl nor in 0.1 N NaOH, but although the starting ester (I) was recovered virtually unchanged from the acid solution, when (I) was boiled with caustic alkali, considerable amounts of resin and H_2S were formed, i.e., (I) underwent degradation, so that the (I) was recovered only to the extent of 20%.

More extensive cleavage of the tricyclic system occurred when the ester (I) was boiled in concentrated hydrochloric acid, (piperid-4-yl)succinic acid (VII) and NH_4Cl being isolated from the reaction mixture.



R = Ph (II); Me (III); $C_6H_2(OMe)_3$-3, 4, 5 (IV); $CHPh_2$ (V); $CH_2OC_6H_4Cl$-4 (VI).

The reaction sequence proposed for the conversion of the aminoester (I) into (piperid-4-yl)succinic acid (VII) includes cleavage of the tricycle at the S—C(2) bond to give the nitrile (VIII). Similar reactions have been reported in the alkaline hydrolysis of several 2-aminothiophens containing an electric-acceptor group in the 3-position [3]. The nitride (VII) then undergoes hydrolysis and decarboxylation to the quinclidine (IX); cleavage of the quinuclidine ring to the intermediate (IX) followed by loss of a molecule of H_2S and addition of a molecule of water to the resulting ketene gives the diacid (VII). Also possible is initial cleavage of the quinnuclidine ring to give the (piperid-4-yl)thienyl compound (XI), which subsequently undergoes cleavage as shown above.

EXPERIMENTAL CHEMICAL PART

2-Amino-3-ethoxycarbonylthieno[2,3-b]quinuclidine (I). A mixture of 20 g (160 mmole) of

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3-oxoquinuclidine, 18.18 g (160 mmole) of ethyl cyanoacetate, 5.12 g (160 mmole) of sulfur, 40 ml of morpholine, and 80 ml of absolute ethanol was heated for 4 h at 60°C. The mixture was evaporated under reduced pressure, and the residue treated with 100 ml of 25% potassium carbonate and extracted with ethyl acetate. After removal of the ethyl acetate, the residue was again triturated with ethyl acetate, to give 11.8 g (29.3%) of (I), mp 140-141°C (from ethyl acetate). IR spectrum, ν_{max}, cm^{-1}: 1650 (C=$COOC_2H_5$), 3300, 3405 (NH_2). Found, %: C 56.88; H 6.53; N 11.20; S 13.03. $C_{12}H_{16}N_2O_2S$. Calculated, %: C 57.12; H 6.39; N 11.10; S 12.71.

The mother liquors after removal of the basic ester (I) were acidified with alcoholic hydrogen chloride to give 7.9 g (17.1%) of (I) hydrochloride, mp 240-241°C (from 95% ethanol). IR spectrum, ν_{max}, cm^{-1}: 1673 ($COOC_2H_5$), 2528, 2612, 2730, (NH), 3140, 3209, 3380 (NH_2). Found, %: C 49.64; H 5.85; Cl 11.27; N 9.94; S 10.92. $C_{12}H_{16}N_2O_2S \cdot HCl$. Calculated, %: C 49.89; H 5.93; Cl 12.28; N 9.70; S 11.10.

2-Acetylamino-3-ethylcarbonylthieno[2,3-b]quinuclidine (III). A solution of 10 g of (I) in 100 ml of acetic anhydride was boiled for 17 h, evaporated under reduced pressure, and the residue treated with 100 ml of 25% potassium carbonate and extracted with ether. The ether was removed until crystallization commenced, then the mixture was chilled for 20 h at 4°C and the solid filtered off to give 10.2 g (87%) of (III), mp 93-95°C (from ethyl acetate). Found, %: C 57.48; H 6.06; N 9.38; S 10.89. $C_{14}H_{18}N_2O_3S$. Calculated, %: C 57.12; H 6.16; N 9.52; S 10.89.

Hydrochloride, mp 213-214°C (from propan-2-ol). Found %: C 50.62; H 5.55; N 8.48. $C_{14}H_{13}N_2O_3 \cdot HCl$. Calculated, %: C 50.83; H 5.79; N 8.47.

2-Benzoylamino-3-ethocycarbonylthieno[2,3-b]quinuclidine (II). A mixture of 1.26 g (5 mmole) of (I), 0.7 g (5 mmole) of benzoyl chloride, 0.5 g (5 mmole) of triethylamine, and 25 ml of benzene was boiled for 6 h. The reaction mixture was then treated with 40 ml of 25% potassium carbonate solution, and extracted with benzene. Following removal of the benzene, the residue was triturated with ethyl acetate. Yield 1.5 g (84%), mp 159-160° (from ethyl acetate). Found %: C 64.12; H 5.64; N 8.11. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 64.02; H 5.65; N 7.86.

Hydrochloride, mp 219-221°C (decomp.). Found, %: Cl 8.92; N 6.73; S 7.82 $C_{19}H_{20}N_2O_3S$. Calculated, %: Cl 8.62; N 6.81; S 7.80.

2-(3,4,5-Trimethoxybenzoylamino)-3-ethoxycarbonylthieno[2,3-b]quinuclidine (IV) was obtained as in the preceding preparation, by reacting (I) with 3,4,5-trimethoxybenzoyl chloride. Yield 89%, mp 191-193°C (from ethyl acetate). Found %: C 59.13; H 5.60; N 6.49; S 6.93. $C_{22}H_{26}N_2O_6S$. Calculated, %: C 59.18; H 5.87; N 6.27; S 7.18.

Hydrochloride, mp 222-223°C. Found, %: Cl 7.48; N 5.85. $C_{22}H_{26}N_2O_6S \cdot HCl$. Calculated, %: Cl 7.36; N 5.80.

2-(Diphenylacetylamino)-3-ethoxycarbonyl[2,3-b]quinuclidine (V) was obtained as for (IV) by reacting the aminoester (I) with diphenylacetyl chloride. The reaction products were extracted with chloroform, the solvent distilled off, and the residue dissolved in acetone, the acetone solution treated with alcoholic hydrogen chloride, and the oily product which separated was triturated with 2-propanol. Yield of (V) hydrochloride 74%, mp 211-213°C (from 95% ethanol). Found, %: C 64.70; H 5.64; Cl 7.23; N 6.16; S 6.70. $C_{20}H_{26}N_2O_3S \cdot HCl$. Calculated, %: C 64.65; H 5.63; Cl 7.34; N 5.80; S 6.64.

2-(4-Chlorophenoxyacetylamino)-3-ethoxycarbonyl[2,3-b]quinuclidine (VI). A mixture of 2.52 g (10 mmole) of the aminoester (I), 2.25 g (11 mmole) of 4-chlorophenoxyacetyl chloride, 1.31 g (13 mmole) of triethylamine, and 50 ml of benzene was heated for 3 h at 70°C, cooled, and treated with 25% potassium carbonate. The benzene layer was separated, the aqueous layer extracted with chloroform, the solvents removed, and the residue triturated with ehter to give 3.6 g (85.5%) of product, mp 163-165°C (from 2-propanol). Found, %: C 57.18; H 5.02; Cl 8.61; N 6.89; S 7.43. $C_{20}H_{21}ClN_2O_4S$. Calculated, %: C 57.07; H 5.03; Cl 8.42; N 6.65; S 7.62.

Hydrochloride, mp 222-224°C. Found, %: C 52.38; H 4.86; Cl 15.5; N 6.11; S 6.92. $C_{20}H_{21}ClN_2O_4S \cdot HCl$. Calculated, %: C 52.52; H 4.85; Cl 15.5; N 6.12; S 7.01.

(Piperid-4-yl)Succinic Acid (VII). A solution of 7 g (24.3 mmole) of (I) hydrochloride in 70 ml of conc. HCl was boiled for 8 h. The mixture was evaporated under reduced pressure, the residue triturated with ether, and the solid filtered off and recrystallized from 60 ml of 80% ethanol, giving 0.7 g (54%) of ammonium chloride. The alcoholic solution was evaporated under reduced pressure, the residue triturated with absolute alcohol, and the crystalline solid filtered off and recrystallized from 40 ml of absolute alcohol. Following filtration from un-

TABLE 1. Pharmacological Activity of Ethoxycarbonyl[2, 3-b] quinuclidines

Compound	Change in AP, % of original level	Histamine intoxication		Carrageenin edema, % of control	LD_{50}, internal, mg/kg
		latent period, sec	lethality, %		
I	18±13	112±15*	100	73±7*	>2000
II	15±9	48±11	100	102±16	>2000
III	10±4	45±9	100	98±11	740±90
IV	39±11*	56±13	100	132±8*	>2000
V	25±5*	58±17	100	82±9	>2000
VI	4±3	43±10	100	66±5*	>2000
Temequin (10 mg/kg)	41±8*	—	—	—	
Fencarol (25 mg/kg)	—	208±16*	0	—	
Acetylsalicylic acid (50 mg/kg)	—	—	—	70±5*	

*$P < 0.05$ compared with controls, by Student's t-criterion.

dissolved solid, on cooling to 4°C for 20 h colorless crystals separated from the alcoholic solution. These were filtered off, and washed with alcohol and ether to give 1.7 g (30%) of piperid-4-ylsuccinic acid hydrochloride, mp 189-191°C. Found, %: C 45.41; H 6.79; Cl 15.34; N 5.88. $C_9H_{15}NO_4 \cdot HCl$. Calculated, %: C 45.48; H 6.78; Cl 14.95; N 5.89.

EXPERIMENTAL PHARMACOLOGICAL PART

The AP was measured by a bloodless method in non-narcotized rats weighing 200-220 g in the caudal artery, using a KN-209 apparatus (Natume, Japan). The activity of the test compounds was measured as the percentage of the control value (one hour before treatment), one hour after treatment.

Antihistamine activity was examined in guinea pigs weighing 250-300 g one hour after treatment with the test compounds. The latent period for the intoxication reaction and the percentage lethality in groups of six animals were determined following inhalation of a 1% solution of histamine hydrochloride for 5 min.

Antiinflammatory (antiexudative) activity was studied in rats weighing 180-200 g, by the effects on edema of the rear extremities induced by carrageenin. For this purpose, 0.1 ml of a 1% suspension of carrageenin in 0.9% sodium chloride was injected subplantarly into the left rear extremity, and the edema measured with a plethysmometer (Ugo Basile) three hours after introduction of carrageenin, expressed as the difference between the volumes of the left and right paws. The test compounds were administered one hour before the injection of carrageenin.

The acute toxicities of the compounds were measured in mice weighing 18-20 g by the gastric route, the LD_{50} values being calculated by the method of Litchfield and Wilcoxon.

In all the experiments, the test compounds were administered internally in a dose of 50 mg/kg as a homogenized aqueous suspension with the addition of Tween-80.

The effects of the compounds on the AP were compared with that of the ganglion-blocker Temequin (2,2,6,6-tetramethylquinuclidine hydrobromide), effects on histamine intoxication with those of the histamine H_1-receptor blocker Fencarol (quinclidin-3-yl diphenyl carbinol hydrochloride), and effects on the exudative activity of carrageenin with acetylsalicylic acid.

The test results are shown in Table 1, from which it will be seen that the greatest activity in terms of AD was shown by (IV), the effect of which was comparable with that of Temequin at a dose of 10 mg/kg. Compound (I) increased the latent period of intoxication with histamine, but it had only half the activity of fencarol in a dose of 25 mg/kg, and did not protect the animals from a lethal outcome. Antiedema activity not inferior to that of acetylsalicylic acid in the same dose (50 mg/kg) was shown by (I) and (VI).

Hence, compounds have been found in this series which possess high hypotentive, antihistamine, and antiexudative activity, which in conjunction with their low toxicities encourages a further search for pharmacologically active compounds in the 3-ethoxycarboylthienol-[2,3-b]quinuclidine group.

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