

AMINO ESTERS OF HETEROCYCLIC DICARBOXYLIC ACIDS

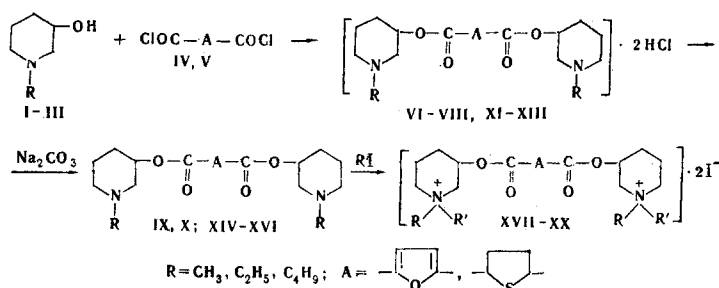
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The corresponding amino esters and their hydrochlorides and quaternary salts were obtained by the condensation of 2,5-furan- and 2,5-tetrahydrothiophenedicarboxylic acid chlorides with 1-methyl-, 1-ethyl-, or 1-butyl-3-hydroxypiperidines.

The amino esters of alicyclic carboxylic acids are of interest as physiologically active substances. Many of them have antispasmodic, antihistamine [1-3], and curare-like activity [4, 5], and some of them lower the blood pressure [6].

In this communication we describe the preparation of new esters of 1-alkyl-3-hydroxypiperidines and 2,5-furan- and 2,5-tetrahydrothiophenecarboxylic acids and their hydrochlorides and diiodides.



The 2,5-bis(1-alkyl-3-piperidyloxycarbonyl)furans were obtained from dichloride IV and 1-alkyl-3-hydroxypiperidines (I-III) in absolute benzene. The amino esters were synthesized as hydrochlorides VI-VIII, which are apparently mixtures of diastereoisomers as indicated by thin-layer chromatography. Free bases IX-X were obtained by the action of 5% sodium carbonate on VI-VIII. The hydrochlorides of the amino esters of 2,5-tetrahydrothiophenedicarboxylic acids (XI-XIII) could be synthesized only under milder conditions in absolute ether at 10-30°.














We intended to obtain free bases XIV-XVI, which are necessary for the synthesis of the quaternary salts, by the action of 5% sodium carbonate on hydrochlorides XI-XIII. Under these conditions we could obtain only base XIV. Compounds XV and XVI were hydrolyzed to the starting compounds. Bases XIV-XVI were obtained in the presence of triethylamine in absolute benzene at 20-80° for 4-5 h. Bis-quaternary salts XVII-XX were obtained as a mixture of diastereoisomers in good yields by alkylation of bases IX-X and XIV-XVI in isopropyl and isobutyl alcohols at 35° or in ether and hexane at room temperature; the presence of a mixture of diastereoisomers was confirmed by separation of diiodide XVII by fractional recrystallization from alcohol into two stereoisomers and by thin-layer chromatography. It must be noted that XVII-XX are obtained in different isomer ratios depending on the reaction conditions. Thus the mixture of isomers obtained by the synthesis of XVII in isopropyl alcohol at 35° for 3 days has mp 204-206°, while the isomer mixture has mp 155-166° when the reaction is carried out in ether or hexane at room temperature for 3-4 h.

The structures of VI-VIII, XI-XIII, and XVII-XX recall the structure of decamethonium iodide $[\text{N}(\text{CH}_3)_3(\text{CH}_2)_{10}\text{N}(\text{CH}_3)_3]2\text{I}^-$, which has pronounced curare-like activity. Tests of VI, VII, XVIIa, XVIII, and *deceased.

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TABLE 1. 2,5-Bis(1-alkyl-3-piperidylloxycarbonyl)furan and Tetrahydrothiophenes

Comp.	R	R'	A	Mp or bp °C (mm)	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
VI	CH ₃			95—112 ^a	C ₁₈ H ₂₈ N ₂ O ₅ · 2HCl	50.92	7.04	6.22	51.07	6.64	6.61	96
VII	C ₂ H ₅			155—160 ^a	C ₂₀ H ₃₀ N ₂ O ₅ · 2HCl	52.86	8.17	6.59	53.22	7.15	6.21	80
VIII	C ₄ H ₉			161.5—170 ^a	C ₂₄ H ₃₈ N ₂ O ₅ · 2HCl	56.72	7.97	5.34	56.79	7.96	5.52	87
XI	CH ₃			97—100 ^a	C ₁₈ H ₃₀ N ₂ O ₄ S · 2HCl · H ₂ O	46.96	7.72	6.74	46.84	7.42	6.31	72
XII	C ₂ H ₅			83—118 ^a	C ₂₀ H ₃₄ N ₂ O ₄ S · 2HCl · H ₂ O	48.60	8.52	6.48	49.09	7.62	5.93	69
XIII	C ₄ H ₉			107—109 ^a	C ₂₄ H ₄₂ N ₂ O ₄ S · 2HCl · H ₂ O	53.62	9.40	5.10	53.38	8.41	5.31	85
XIV	CH ₃			209—212 (1) ^b	C ₁₈ H ₃₀ N ₂ O ₄ S	58.80	8.27	7.75	58.35	8.16	7.56	72
XV	C ₂ H ₅			241—243 (4) ^b	C ₂₀ H ₃₄ N ₂ O ₄ S	60.38	8.88		60.35	8.60		60
XVIIa	CH ₃	CH ₃		236—237 ^c	C ₂₀ H ₃₂ I ₂ N ₂ O ₅	37.58	5.33	4.76	37.86	5.08	4.42	78
XVIIb	CH ₃	CH ₃		213—214 ^b	C ₂₀ H ₃₂ I ₂ N ₂ O ₅	37.93	4.97	4.32	37.86	5.08	4.42	
XVIII	C ₂ H ₅	CH ₃		234.5—235.5 ^d	C ₂₂ H ₃₆ I ₂ N ₂ O ₅	39.83	5.46	4.28	39.90	5.48	4.26	40
XIX	CH ₃	CH ₃		95—112 ^a	C ₂₀ H ₃₂ I ₂ N ₂ O ₄ S	36.86	5.97	4.25	36.71	5.54	4.28	60
XX	C ₂ H ₅	CH ₃		70—78 ^a	C ₂₂ H ₄₀ I ₂ N ₂ O ₄ S	38.71	5.90	4.37	38.72	5.91	4.10	78

^aWashed with absolute benzene and ether.^bVacuum distillation.^cRecrystallization from methanol.^dFrom ethanol.

XIX indicate very weak curare-like activity for XVIII, while a maximum toxicity dose of XIX (MTD 200 mg/kg) in mice temporarily lowers the blood pressure and manifests central p-cholinomimetic activity.

EXPERIMENTAL

2,5-Bis(1-methyl-3-piperidylloxycarbonyl)furan Hydrochloride (VI). A solution of 3.4 g (18 mmole) of IV [8, 9] in 15 ml of absolute benzene was added dropwise with stirring at room temperature to 4.96 g (43 mmole) of I in 15 ml of absolute benzene; a precipitate formed immediately. The mixture was refluxed for 4 h, and the crystals were filtered and washed with absolute benzene and ether to give 7.14 g (94.9%) of VI with mp 95–112°. The white, crystalline, very hygroscopic substance was quite soluble in lower alcohols and acetone and slightly soluble in ether and hexane. R_f 0.086, 0.73 (on activity II aluminum oxide in ethyl acetate with development by iodine). Recrystallization from alcohol–ether (1:1) yielded one of the isomers with mp 232–234° and R_f 0.73.

Compounds VII and VIII were similarly obtained (see Table 1).

2,5-Bis(1-methyl-3-piperidylloxycarbonyl)furan (IX). Compound VI [10.58 g (25 mmole)] was added to a solution of 6.4 g (60 mmole) of sodium carbonate in 100 ml of water. The resulting light-yellow oil was extracted with ether and dried with potassium carbonate, and the ether was removed by distillation to give 4 g of an oil.* Found %: N 8.057, 7.69. $C_{18}H_{22}N_2O_5$. Calculated %: N 8.06. Compound IX was used without further purification to obtain diiodide XVII.

Similarly, 5.53 g (73%) of X, from which diiodide XVIII was obtained, was isolated from 9.03 g (20 mmole) of VII.

2,5-Bis(1-methyl-3-piperidylloxycarbonyl)tetrahydrothiophene Hydrochloride (XI). A solution of 4.27 g (20 mmole) of V [10, 11] in 25 ml of absolute ether was added dropwise in the course of 1 h with cold-water cooling to 5.07 g (44 mmole) of I in 25 ml of absolute ether. The mixture was stirred at 30° for 2.5 h, and the precipitate was filtered, washed with absolute ether, and vacuum dried over $CaCl_2$ to give 6.36 g (71%) of the light-yellow crystalline hydrate of XI with mp 97–100° (decomp.). R_f 0.14, 0.66 (ethyl acetate).

Compounds XII and XIII were similarly obtained.

2,5-Bis(1-methyl-3-piperidylloxycarbonyl)tetrahydrothiophene (XIV). A solution of 2.3 g (10 mmole) of V in 15 ml of absolute benzene was added dropwise at room temperature to 2.3 g (20 mmole) of I in 15 ml of absolute benzene and 2.5 g (25 mmole) of triethylamine. The mixture was heated at 70–80° for 2 h. It was then cooled, 75 ml of water was added, and the resulting oil was separated and extracted with ether. The ether was removed by distillation, and the residue was vacuum distilled to give 2.2 g (60%) of XIV with bp 209–212° (1 mm) and n_D^{20} 1.5068. The product was a viscous, dense liquid with an unpleasant odor. R_f 0.80, 0.59 (ethyl acetate).

Compounds XV and XVI were similarly obtained (XVI decomposed on distillation).

2,5-Bis(1,1-dimethyl-3-piperidiniumoxycarbonyl)furan Diiodide (XVII). A solution of 1.36 g of methyl iodide in 7 ml of isopropyl alcohol was added to 2.52 g (7 mmole) of IX, and the mixture was heated at 35° for 3 days to give 3.55 g (78%) of XVII with mp 204–206° as a mixture of diastereoisomers. Two compounds were isolated by fractional recrystallization from ethanol: XVIIa with mp 236–237° (from methanol) and R_f 0.68; XVIIb with mp 213–214° and R_f 0.51 [acetone–water (10:1)].

Compounds XVIII–XX were similarly obtained.

The presence of an ester grouping was confirmed by the presence of the frequency of the C=O valence vibration at 1730–1740 cm^{-1} in the IR spectra of VI–XX.

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* The oil decomposed during vacuum distillation.

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