RESEARCHES ON ATROPINE-LIKE COMPOUNDS

I. Synthesis and Properties of Aminoesters of Disbustituted Glycolic Acids

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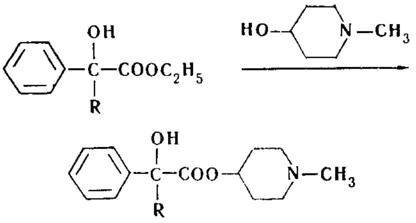
Transesterification of ethyl esters of phenyl-2-thiazolyl and phenyl-p-chlorophenylglycolic acid by N-methyl-4-hydroxypiperidine gives N-methyl-4-piperidyl esters of phenyl-2-thiazolyl– and phenyl-p-chlorophenylglycolic acid. Transesterification of the alkyl esters gives aminoesters of disubstituted glycolic acids in lower yield than reaction of the corresponding acids with halogenoalkylamines.

In the field of atropine-like compounds, great attention centers on aminoesters of disubstituted glycolic acids, as some of them are broad spectrum medicinals [1]. Aminoesters of a disubstituted glycolic acid are usually prepared by reacting them with the appropriate halogenoalkylamines, by reacting a disubstituted chloroacetyl chloride with amino alcohols, and by transesterifying the alkyl esters of a disubstituted glycolic acid in the presence of small quantities of sodium or sodium alkoxide [2,3].

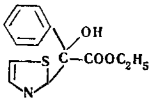
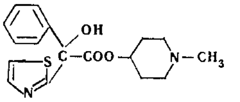
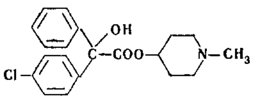
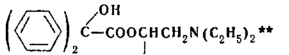
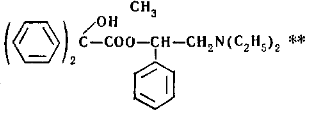
The present paper describes the preparation of new N-methyl-4-piperidyl esters of disubstituted glycolic acids by transesterifying the ethyl esters of phenyl-2-thiazolylglycolic acid and phenyl-p-chlorophenylglycolic acid:



R = p-chlorophenyl, 2-thiazolyl

This method was also used to prepare for comparison some known disubstituted glycolic acid aminoesters, previously synthesized by other methods. It was shown that in a number of cases transesterification of alkyl esters give lower yields of disubstituted glycolic acid aminoesters than treatment of the acids with halogenoalkylamines. However it is known that it is not possible to start with halogenoalkylamines when preparing esters of N-methyl-4-hydroxypiperidine, since the latter compound, unlike N-methyl-3-chloropiperidine, does not react with carboxylic acids.

Esters and Amino Esters of Disubstituted Glycolic Acids

Compound	Mp, °C [bp °C pressure, mm]	Formula	N, %		S, %		Yield, %
			Found	Calculated	Found	Calculated	
	95	$C_{13}H_{13}NO_3S$	5.4	5.31	12.18	12.71	44.3
	135.2	$C_{17}H_{20}N_2O_3S$	8.40	8.43	9.62	9.65	85.3
	144	$C_{20}H_{22}ClNO_3$*	3.86	3.9	—	—	18
	[295 (40)]	$C_{21}H_{27}NO_3$	3.78	4.1	—	—	12
	[190 (0.1)]	$C_{26}H_{29}NO_3$	3.2	3.5	—	—	15

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*Found: C1 9.66%. Calculated: C1 9.9%.

**The hydrochlorides of the last two compounds have previously been prepared by a different method, starting from halogenalkylamines [5,6].

EXPERIMENTAL

Ethyl phenyl-2-thiazolylglycolate. The Grignard reagent was prepared from 10.8 g (0.1 mole) EtBr, 3 9 g (0.15 g at) Mg, 9.84 g (0.06 mole) 2-bromothiazole, and 20 ml dry ether. 27.4 g (1.54 g) ethylbenzoylformate was added at −70°, the temperature gradually raised to room temperature, and the mixture then heated for 2 hr on a water-bath. The products were decomposed with saturated NH_4Cl solution (about 50 ml), extracted with ether (4 × 30 ml), the ether extracts dried over $MgSO_4$, and the ether distilled off. The residue was dissolved in 25 ml HCl (1:1), the acid layer washed with ether, and neutralized with 25% aqueous ammonia. The precipitate was filtered off, and twice recrystallized from benzene-petrol ether (1:1).

N-Methyl-4-piperidyl phenyl-2-thiazolylglycolate. 3.2 g (0.0012 mole) ethyl phenyl-2-thiazolylglycolate, 2 g (0.017 mole) N-methy-4-hydroxypiperidine, and 0.01 g Na were heated together for 4 hr at 120° (20 mm) in a stream of dry nitrogen. The reaction products were dissolved in dilute HCl, washed with ether, neutralized with 25% aqueous ammonia, the precipitate filtered off, washed with water, and dried. It was recrystallized twice from benzene-petrol ether (1:1).

The other aminoesters were prepared similarly (see table).

N-Methyl-4-piperidyl phenyl-2-thiazolylglycolate dimethiodide. 1 5 ml MeI in 17 ml acetone was added to 0.52 g (1.5 mmole) N-methyl-4-piperidyl phenyl-2-thiazolylglycolate, and the mixture left to stand in the dark for 10 days without access of air. The precipitate was filtered off, washed with ether, and dried over $CaCl_2$. Yield 70.3%, mp 165°. Found: I 41.19 N 4.54%. Calculated for $C_{19}H_{26}I_2N_2C_3S$: I 41.18; N 4.55%.

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