THE SYNTHESIS OF CHLORACISIN ANALOGS

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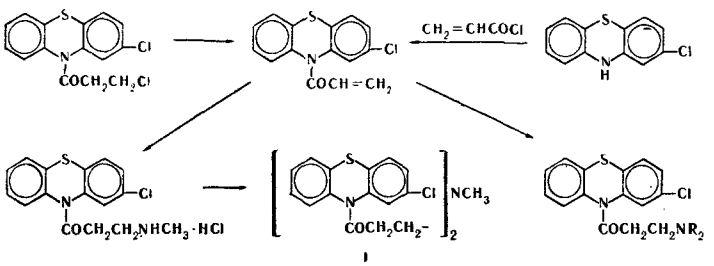
UDC 547.869.2.07:542.951

Reaction of 2-chlorophenothiazine with acryloyl and methacryloyl chloride, and dehydrochlorination of 10-(β-chloropropionyl)-2-chlorophenothiazine, has given 10-acryloyl- and 10-methacryloyl-2-chlorophenothiazine. The latter reacts with secondary amines to give chloracisin and its analogs.

Among the many phenothiazine derivatives, the β-dialkylaminopropionyl derivatives are of special interest. For example, 2-chloro-10-(β-diethylaminopropionyl)phenothiazine has found practical application under the name chloracisin [1]. According to patent information, the close analog of chloracisin, 2-chloro-[β-(β-hydroxyethyl-1-piperazinyl)propionyl]phenothiazine, and its 3,4,5-trimethoxybenzoate, may be used as spasmolytic, sedative, and hypotensive agents [2]. Only one method for the preparation of this type of compound is described in the literature, namely by alkylation of secondary amines with 10-(β-chloropropionyl)-2-chlorophenothiazine [2-7].

We have found that chloracisin and its β-dialkylamino analogs, as well as derivatives containing an α-methyl group, can be synthesized by the addition of secondary amines to the activated double bonds of 10-acryloyl- and 10-methacryloyl-2-chlorophenothiazines [8]. The latter compounds have not previously been described, but they are readily obtained by acylation of 2-chlorophenothiazine with acryloyl and methacryloyl chlorides. We also obtained 10-acryloyl-2-chlorophenothiazine by dehydrochlorination of 10-(β-chloropropionyl)-2-chlorophenothiazine.

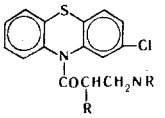


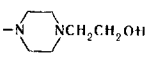
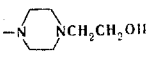
Both 10-acryloyl- and 10-methacryloyl-2-chlorophenothiazine were reacted with equimolecular amounts of secondary amines in organic solvents, or in an excess of the lower-boiling secondary amines. The resulting tertiary amines were not usually isolated, but were characterized as their hydrochlorides. In the reaction of 10-acryloyl-2-chlorophenothiazine with ethylenimine, an addition compound was obtained which crystallized readily (VIII). Treatment of this with HCl resulted in fission of the ethylenimine ring with the formation of 10-[β-(β-chloroethylamino)propionyl]-2-chlorophenothiazine (IX).

Some experiments were also carried out relating to the addition of primary amines to the double bond of 10-acryloyl-2-chlorophenothiazine. N-Phenyl-ethylenediamine yielded a stable addition product which was isolated as the hydrochloride V; but the hydrochloride of the product from the addition of methylamine was converted during isolation or on standing into N,N-bis-[β-(2-chloro-10-phenothiazinyl)propionyl]methylamine (I).

Kirov Academy of Military Medicine, Leningrad. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 5, pp. 601-604, May, 1970. Original article submitted July 1, 1968.

TABLE 1. Analogs of Chloracisin



Compound	R	R′	mp, °C	Molecular formula	Solvent for recrystallization	Found, %		Calculated, %		Yield, %
						N	S	N	S	
I	H		183—5*	$C_{31}H_{25}Cl_2N_3O_2S_2$	Dimethylformamide + ethanol	7,2	—	6,9	—	70
II	H		186	$C_{19}H_{19}ClN_2OS \cdot HCl$	Dichloroethane + benzene	—	8,0	—	8,1	80
III	H		239†	$C_{19}H_{19}ClN_2O_2S \cdot HCl$	Aqueous ethanol	—	8,0	—	7,8	97
IV	H		215*	$C_{21}H_{24}ClN_3O_2S \cdot 2HCl$	Aqueous ethanol	8,0	6,3	8,6	6,5	100
V	H	—$NHCH_2CH_2NHC_6H_5$	205—6*	$C_{23}H_{22}ClN_3OS \cdot 2HCl$	Ethanol + acetone	8,3	—	8,5	—	93
VI	CH_3	—$N(CH_3)_2$	225—7	$C_{18}H_{19}ClN_2OS \cdot HCl$	Absolute ethanol + petroleum ether	—	8,7	—	8,4	—
VII	CH_3	—$N(C_2H_5)_2$	226	$C_{20}H_{23}ClN_2OS \cdot HCl$	Chloroform + n-hexane	6,9	—	6,8	—	98
VIII	CH_3		110	$C_{18}H_{17}ClN_2OS$	n-Hexane	8,3	9,6	8,1	9,3	97
IX	CH_3	—$NHCH_2CH_2Cl$	211*	$C_{18}H_{18}Cl_2N_2OS \cdot HCl$	—	—	8,0	—	7,7	30
X	CH_3		237*	$C_{20}H_{21}ClN_2OS \cdot HCl$	Ethanol	—	7,4	—	7,8	95
XI	CH_3		244*	$C_{21}H_{23}ClN_2OS \cdot HCl$	Aqueous ethanol	—	7,4	—	7,6	—
XII	CH_3		235	$C_{22}H_{25}ClN_2OS \cdot HCl$	Chloroform	6,3	7,1	6,4	7,3	—
XIII	CH_3		233	$C_{20}H_{21}ClN_2O_2S \cdot HCl$	Ethanol	6,3	—	6,6	—	90
XIV	CH_3		231	$C_{22}H_{26}ClN_3O_2S \cdot 2HCl$	Aqueous ethanol	8,0	—	8,3	—	94

*With decomposition.

†Literature value: mp 225° C [2].

EXPERIMENTAL

10-Acryloyl-2-chlorophenothiazine. A) A 52-g (0.22 mole) quantity of 2-chlorophenothiazine, 300 ml of dry benzene, and 23 g (0.255 mole) of acryloyl chloride [9] were boiled under reflux for 10 hr. The solvent and the excess acid chloride were removed in vacuo, and the residue was recrystallized from ethanol to give 54 g (85%) of product, mp 124-126° C.

B) A 32.4-g (0.1 mole) quantity of 10-(β-chloropropionyl)-2-chlorophenothiazine, 150 ml of ethanol, and 16 ml of triethylamine were boiled for 1 hr. The precipitate which separated on cooling was filtered off and washed successively with 20 ml of 1:1 aqueous ethanol and 20 ml of ethanol, giving 25.6 g (89%) of 10-acryloyl-2-chlorophenothiazine, mp 125-127° C. A mixed mp with material prepared by method A) gave no depression. Found, %: N 5.0; S 11.1. Calculated for $C_{15}H_{10}ClNOS$, %: N 4.9; S 11.1.

10-Methacryloyl-2-chlorophenothiazine. A 65.2-g (0.28 mole) quantity of 2-chlorophenothiazine, 150 ml of dry toluene, and 35.7 g (0.34 mole) of methacryloyl chloride were boiled for 4 hr, then the solvent and excess acid chloride were removed in vacuo on a boiling water bath. The residue was recrystallized from acetone to give 59.3 g (70%) of 10-methacryloyl-2-chlorophenothiazine, mp 119° C. Further recrystallization from aqueous acetone gave mp 122° C. Found, %: N 4.7. Calculated for $C_{16}H_{12}ClNOS$, %: N 4.7.

2-Chloro-10-(β-morpholinopropionyl)phenothiazine Hydrochloride (III). A mixture of 5.75 g (0.02 mole) of 10-acryloyl-2-chlorophenothiazine, 1.75 g (0.02 mole) of dry morpholine, and 40 ml of benzene was boiled for 4 hr. The solvent was removed in vacuo, and the residue was dissolved in 50 ml of dry ether. A solution of HCl in absolute alcohol was added to the solution, dropwise with cooling, until the mixture became acid to Congo red. The product which separated (8.0 g) was filtered off, washed with ether, and dried.

2-Chloro-10-[β-(β-hydroxyethyl-1-piperazinyl)isobutyryl]phenothiazine Hydrochloride (XIV). A mixture of 6.03 g (0.02 mole) of 10-methacryloyl-2-chlorophenothiazine, 2.6 g (0.02 mole) of N-(β-hydroxyethyl)piperazine, and 10 ml of ethanol was boiled for 5 hr. The mixture was cooled, 50 ml of absolute ether added, and saturated with dry HCl until acid to Congo red. The product (8.8 g) was filtered off and washed with ether.

The remaining compounds were prepared in a manner similar to III and XIV, and are listed in the table.

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