*Preparation of Phenothiazine Derivatives as Possible Anthelmintics. Part II.**

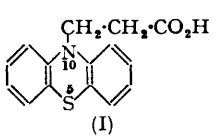
By ALEXANDER MACKIE and ANAND L. MISRA.

[Reprint Order No. 5845.]

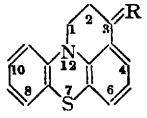
Some derivatives of 2:3-dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine have been prepared.

SINCE β-10-phenothiazinylpropionic acid (I) showed distinct anthelmintic activity towards liver fluke *in vitro* (Mackie and Cutler, Part I *), it appeared desirable to prepare some derivatives of this acid, and also related compounds containing a ketomethylene group, which had been shown to induce anthelmintic activity *in vitro* (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219).

Derivatives of 2 : 3-dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine (II*a*) (Smith, *J. Org. Chem.*, 1950, **15**, 1125), *e.g.*, (II*b*), (II*c*), and (II*d*), have been prepared.

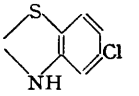


(I)



(II*a*), R = :O

(II*b*), R = :N·NH·C(=NH)·NH·NO$_2$

(II*c*), R = 

(II*d*), R = :N·NH·CO·CH$_2$·N$^+$C$_5$H$_5$}Cl$^-$

In an attempt to prepare β-10-phenothiazinylpropionyl chloride, for the purpose of lengthening the chain (Arndt–Eistert method), only the ketone (II*a*) could be obtained by the action of phosphorus oxychloride on the acid (I) or its sodium salt, or of phosphorus trichloride on the acid. Thionyl chloride gave an uncrystallisable gum. Reaction of the methyl ester with aqueous ammonia over a prolonged period or fusion of the acid (I) with urea (Cherbuliez and Landolt, *Helv. Chim. Acta*, 1946, **29**, 1438) did not produce the amide. Phenothiazine was isolated in the latter reaction. Phenothiazine was also obtained instead of the substituted benziminazole when the acid (I) was treated with *o*-phenylenediamine.

Bromination of the acid (I) in glacial acetic acid and acetic anhydride gave the monobromo-derivative of the ketone (II*a*), whilst similar bromination of the ketone (II*a*) appeared to give a difficultly separable mixture of its mono- and di-bromo-derivatives.

A quaternary hexamine salt was isolated from the reaction in chloroform of 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) with hexamine, recrystallisation of which resulted in decomposition to give hexamine hydrochloride as the only product isolated. Since it was considered that the introduction of the diethylaminoethylamino-group into a phenothiazine derivative containing a ketomethylene group might yield a compound showing anthelmintic properties (cf. Mauss *et al.*, *Naturwiss.*, 1946, **33**, 253; *Ber.*, 1948, **81**, 19), the chloro-compound was treated with 2-diethylaminoethylamine to form 10-2′-diethylaminoethylaminoacetylphenothiazine.

* Part I, *J.*, 1954, 2577.

For examination of the effect of a long continuous chain on *in vitro* anthelmintic activity, 10-phenothiazinylcarbonylmethyl stearate $C_{12}H_8SN{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}[CH_2]_{16}{\cdot}Me$ was prepared by condensing 10-iodoacetylphenothiazine (Dahlbom, *Acta Chem. Scand.*, 1953, **7**, 873) with sodium stearate.

Gilman and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 5424) obtained 10-phenylacetylphenothiazine by condensing phenothiazine with phenylacetyl chloride in dioxan. When glacial acetic acid was used as the condensing medium, 10-acetylphenothiazine was isolated in good yield with the liberation of hydrogen chloride. 10-Phenylacetylphenothiazine gave phenothiazine and not 10-acetylphenothiazine when refluxed in glacial acetic acid saturated with hydrogen chloride. Chloroacetylation of phenothiazine was effected in dry benzene (Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302) and in dioxan (Gilman and Nelson, *loc. cit.*), but when glacial acetic acid was used as solvent 10-acetylphenothiazine resulted. It appears that phenylacetyl chloride and chloroacetyl chloride react in presence of glacial acetic acid to give the mixed anhydrides $CH_2Ph{\cdot}CO{\cdot}O{\cdot}COMe$ and $CH_2Cl{\cdot}CO{\cdot}O{\cdot}COMe$ respectively, which in turn react with the hydrogen chloride liberated, to give in each case acetyl chloride (Watson and Gregory, *J.*, 1929, 1373). This would explain the formation of acetylphenothiazine in these reactions, since phenothiazine is readily acetylated with acetyl chloride in glacial acetic acid. Condensation of phenothiazine with some aroyl chlorides, however, proceeds smoothly in glacial acetic acid (Part I).

Experimental

2 : 3-*Dihydro*-3-(*nitroamidinohydrazono*)-1H-*pyrido*[3,2,1-kl]*phenothiazine* (II*b*).—2 : 3-Dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine (II*a*) (Smith, *J. Org. Chem.*, 1950, **15**, 1125) (4 g.) was added to a boiling glacial acetic acid solution of aminonitroguanidine (4 g. in 50 c.c.) (Phillips and Williams, *J. Amer. Chem. Soc.*, 1928, **50**, 2465) (cf. Whitmore, Revukas, and Smith, *ibid.*, 1935, **57**, 706). The mixture was heated for 0·5 hr., a yellow crystalline precipitate being formed. After cooling and filtration the residue was washed in turn with hot ethanol and ether, and dried. Recrystallisation from pyridine afforded golden-yellow plates of the *hydrazono*-derivative (2·5 g.), m. p. 234—235° (decomp.) (Found: C, 54·3; H, 4·0. $C_{16}H_{14}O_2N_6S$ requires C, 54·2; H, 4·0%).

5′-*Chloro*-2 : 3-*dihydro*-1H-*pyrido*[3,2,1-kl]*phenothiazine*-3-spiro-2′-*benzothiazoline* (II*c*).—A pyridine solution of the ketone (II*a*) (2·6 g. in 5 c.c.) was added to 2-amino-4-chlorothiophenol hydrochloride in pyridine (Lankelma and Knauff, *J. Amer. Chem. Soc.*, 1931, **53**, 310) (2 g. in 5 c.c.). The mixture was refluxed on the water-bath for 8 hr., and after cooling, acidified with dilute hydrochloric acid. The supernatant liquid was decanted, and the red gum which remained was extracted in turn with ethanol and boiling light petroleum (b. p. 60—80°). The solid residue crystallised from acetone as scarlet shining needles of the spiro-*compound* (0·8 g.); m. p. 206—207° (Found: C, 64·0; H, 3·2. $C_{21}H_{15}N_2ClS_2$ requires C, 63·9; H, 3·8%) (cf. Lankelma and Sharnoff, *ibid.*, 1932, **54**, 379).

2 : 3-*Dihydro*-3-(*pyridinoacetylhydrazono*)-1H-*pyrido*[3,2,1-kl]*phenothiazine Chloride* (II*d*).—A suspension of the ketone (II*a*) (1·25 g.) and Girard reagent P (1 g.) in absolute ethanol (15 c.c.) containing 10% acetic acid was refluxed for 3 hr. The product which separated was filtered off, washed with hot absolute ethanol, and recrystallised from chlorobenzene–light petroleum (b. p. 40—60°) as yellow prisms (0·3 g.), m. p. 299—300° (Found: C, 70·6; H, 4·0; N, 10·3%). No definite structure could be assigned to this compound. Crystals separated from the filtrate after storage in ice overnight. These were recrystallised from ethanol–methanol, the *pyridinoacetylhydrazono*-compound being obtained as yellow stellate needles (0·7 g.), m. p. 192—194° (Found: N, 13·0. $C_{22}H_{19}ON_4ClS$ requires N, 13·3%).

Bromination of β-10-*phenothiazinylpropionic Acid.*—Bromine (2·9 g.) in glacial acetic acid (5 c.c.) was added to β-10-phenothiazinylpropionic acid (I) (Smith, *loc. cit.*) (5 g.), dissolved in a mixture of glacial acetic acid (30 c.c.) and acetic anhydride (10 c.c.). The temperature was kept at 40—50°. The mixture was then refluxed for 2 hr. on the water-bath; a yellow solid separated, which was collected and recrystallised from absolute ethanol. Dull yellow microscopic needles of ?-*bromo*-2 : 3-*dihydro*-3-*oxo*-1H-*pyrido*[3,2,1-kl]*phenothiazine* (1·5 g.), m. p. 247—248°, insoluble in aqueous sodium carbonate, were obtained (Found: C, 54·6; H, 2·9. $C_{15}H_{10}ONBrS$ requires C, 54·2; H, 3·0%).

10-(*Hexaminoacetyl*)*phenothiazine Chloride.*—A mixture of 10-chloroacetylphenothiazine

(Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) (3 g.) and hexamine (1·5 g.) in dry chloroform (15 c.c.) was refluxed on the water-bath for 5 hr. The colourless needles of the *quaternary salt* formed were filtered off, washed with chloroform, refluxed for 0·5 hr. with benzene, collected hot, and dried (3·3 g.), m. p. 172—173° (Found: C, 57·8; H, 5·6. $C_{20}H_{22}ON_5ClS$ requires C, 57·8; H, 5·3%). Recrystallisation of the quaternary salt from ethyl acetate–absolute ethanol afforded colourless prismatic needles of hexamine hydrochloride. m. p. 204—205° (decomp.) (Found: C, 40·9; H, 7·0. Calc. for $C_6H_{12}N_4,HCl$: C, 40·8; H, 7·4%; Locquin (*Bull. Soc. chim.*, 1900, **23**, 663) gives m. p. 188—189° (decomp.).

10-(2-*Diethylaminoethylaminoacetyl*)*phenothiazine*.—A mixture of 2-diethylaminoethylamine (6 g.) and 10-chloroacetylphenothiazine (5·5 g.) in dry benzene (30 c.c.) was refluxed on the water-bath for 10 hr. The resulting solution was shaken with N-hydrochloric acid, and the acid extract made alkaline with aqueous sodium carbonate. The *base*, which separated as an oil, solidified and was filtered off and dried. Recrystallisation from light petroleum (b. p. 40—80°) afforded colourless prisms of the pure base (2 g.), m. p. 79—80° (Found: N, 11·1. $C_{20}H_{25}ON_3S$ requires N, 11·8%) (cf. Dahlbom and Ekstrand, *loc. cit.*).

10-*Phenothiazinylcarbonylmethyl Stearate*.—A hot ethanolic solution of 10-iodoacetylphenothiazine (1·7 g. in 20 c.c.) (Dahlbom, *Acta Chem. Scand.*, 1953, **7**, 873) was added to an aqueous-ethanolic solution of sodium stearate (1·1 g. in 15 c.c.), made slightly acid to litmus. The mixture was refluxed on the water-bath for 3 hr. On cooling, the product was filtered off and recrystallised from ethanol in colourless plates of the *stearate* (1·6 g.), m. p. 73—74° (Found: C, 73·5; H, 8·2. $C_{32}H_{45}O_3NS$ requires C, 73·4; H, 8·6%).

The authors thank the Agricultural Research Council for financial aid, the Council of Scientific and Industrial Research (India) for the award of an Assam Oil Co. Scholarship to one of them (A. L. M.), Professor F. Bell for his interest, Dr. A. A. Cutler for assistance in the preparative work, and Dr. J. W. Minnis for some of the microchemical analyses.

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, November 3rd*, 1954.]