Preparation of Phenothiazine Derivatives as Possible Anthelmintics.

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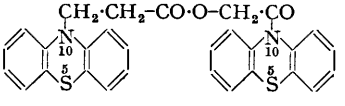
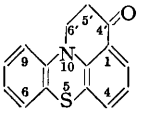
10-Aroyl derivatives of phenothiazine and β-10-phenothiazinylpropionic acid, with salts, esters, and other derivatives have been prepared as possible anthelmintics. The acid is lethal towards liver fluke (*Fasciola hepatica*) *in vitro*.

THE present paper deals with attempts to prepare improved anthelmintics of the phenothiazine type (I). First, we record that we failed to effect ring-closure, by sulphur, of 2 : 4-dinitro- and 4′-methyl-2 : 4-dinitro-diphenylamine (Reitzenstein, *J. pr. Chem.*, 1903, **68**, 256), 4′-chloro-2 : 4-dinitrodiphenylamine (Reverdin and Crépieux, *Ber.*, 1903, **36**, 33), and 2-amino-4-nitrodiphenylamine and its acetyl derivative (Nietzki and Almenräder, *ibid.*, 1895, **28**, 2971). Although a small amount of hydrogen sulphide was formed when 4-chlorodiphenylamine (Chapman, *J.*, 1929, 569) was heated with sulphur, no chlorophenothiazine could be isolated. Hydrogen bromide was evolved with the 4 : 4′-dibromodiphenylamine, but no hydrogen sulphide could be detected; possibly the sulphur removed the bromine from the compound, which would explain the presence of hydrogen bromide.

Ethyl β-10-phenothiazinylpropionate has been reported by Cauquil and Cassadevall (*Compt. rend.*, 1947, **225**, 578). The alkyl esters were more easily obtained by means of the silver salt of the acid. 10-Phenothiazinylcarbonylmethyl β-10-phenothiazinylpropionate (I) was prepared, since a compound with two phenothiazine residues might have interesting anthelmintic properties. Two arylamides of the acid were also prepared.

(I)  (II) 

Since it has been found that compounds with a keto-methylene group showed anthelmintic activity *in vitro* (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219), 5′ : 6′-dihydro-4′-oxopyridino(3′ : 2′ : 1′-1 : 10*a* : 10)phenothiazine (II) and its benzylidene derivative and semicarbazone were prepared. Baldwin (*ibid.*, 1948, **3**, 91) demonstrated anthelmintic activity *in vitro* for benzylidene derivatives of ketones. The benzylidene derivative did not form a phenylhydrazone.

Although the tests of these compounds against liver fluke (*Fasciola hepatica*) and anterior preparations of the roundworm *Ascaris lumbricoides* will be reported in full elsewhere, it may be mentioned that β-10-phenothiazinylpropionic acid was lethal (1 : 3000) and its sodium salt paralysant (1 : 1000) towards liver fluke.

EXPERIMENTAL

10-Benzoylphenothiazine.—A dry benzene solution (50 c.c.) containing phenothiazine (5 g.) and benzoyl chloride (7 g.) was refluxed for 1 hr. After removal of the benzene, the residue was warmed with aqueous potassium hydroxide (20%; 40 c.c.), and the product filtered off, washed with water, and recrystallised from glacial acetic acid as yellow needles of the benzoylated compound (6 g.), m. p. 177—178° (Found: C, 74·8; H, 4·7. Calc. for $C_{19}H_{13}ONS$: C, 75·3; H, 4·3%). Fraenkel (*Ber.*, 1885, **18**, 1844) gives m. p. 170·5°.

10-(2 : 4-Dichlorobenzoyl)phenothiazine.—A xylene solution (25 c.c.) of freshly distilled

2 : 4-dichlorobenzoyl chloride (6 g.) and phenothiazine (5 g.) was refluxed for 45 min. The xylene was distilled off till the solution became turbid. The crystals obtained on cooling recrystallised from ethanol as colourless prisms of the 2 : 4-*dichlorobenzoyl* derivative (4 g.), m. p. 133—134° (Found : C, 61·5; H, 3·1. $C_{19}H_{11}ONCl_2S$ requires C, 61·3; H, 3·0%).

10-p-*Nitrobenzoylphenothiazine.*—*p*-Nitrobenzoyl chloride (5 g.) was added gradually to an acetic acid solution of phenothiazine (5 g. in 25 c.c.) and the mixture heated for 15 min. Next morning, the product was filtered off and washed in turn with ethanol and acetone. Recrystallisation from xylene afforded bright yellow rectangular plates (3·5 g.), m. p. 225—226°, of the *nitrobenzoyl* derivative (Found : C, 65·9; H, 3·5. $C_{19}H_{12}O_3N_2S$ requires C, 65·5; H, 3·5%).

10-(3 : 5-*Dinitrobenzoyl*)*phenothiazine.*—This *compound* was similarly obtained. Recrystallisation from xylene afforded yellow plates (40% yield), m. p. 265—266° (Found : C, 58·1; H, 2·9. $C_{19}H_{11}O_5N_3S$ requires C, 58·0; H, 2·8%).

10-p-*Anisoylphenothiazine.*—*p*-Anisoyl chloride (9 g.) was added gradually to phenothiazine (10 g.) and pyridine (10 c.c.). A vigorous reaction ensued on warming and the colourless crystals formed on cooling were washed with ethanol and recrystallised from glacial acetic acid. Colourless rectangular prisms of the p-*anisoyl* derivative (13 g.), m. p. 173—174°, were obtained (Found : C, 71·9; H, 4·7. $C_{20}H_{15}O_2NS$ requires C, 72·1; H, 4·2%).

β-10-*Phenothiazinylpropionic Acid.*—This compound was prepared by Smith's method (*J. Org. Chem.*, 1950, **15**, 1125). The sodium salt, obtained by titration, crystallised from absolute ethanol–acetone as colourless needles, m. p. 262—263° (decomp.). The 1-*phenylethylammonium* salt formed colourless needles, m. p. 156—158° (Found : C, 70·5; H, 5·8. $C_{23}H_{24}O_2N_2S$ requires C, 70·4; H, 6·1%), and the S-*benzylthiuronium* salt was obtained as colourless needles, m. p. 160° (both from aqueous ethanol) (Found : C, 63·1; H, 5·2. $C_{23}H_{23}O_2N_3S_2$ requires C, 63·2; H, 5·3%). The *piperazonium* salt crystallised from absolute ethanol as colourless needles, m. p. 190—191° (Found : C, 63·5; H, 5·9. $C_{34}H_{36}O_4N_4S_2,H_2O$ requires C, 63·2; H, 5·9%).

The silver salt of the acid, an alkyl iodide, and sodium-dried benzene were refluxed on the water-bath for 2 hr. After removal of the silver iodide, the filtrate was extracted with aqueous sodium hydrogen carbonate and evaporated. The residue was a red oil which solidified on cooling and was purified by recrystallisation from ethanol (charcoal). The *esters*, except the ethyl ester, are tabulated : all formed colourless needles, except the *iso*propyl (colourless rectangular plates) and the *sec.*-butyl (colourless prisms) ester. The *n*-heptyl ester became greenish-blue in light.

β-10-*Phenothiazinylpropionic esters.*

Ester	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H	M. p.	Yield (%)
Methyl	$C_{16}H_{15}O_2NS$	68·1	5·4	67·4	5·3	64—65°	37
n-Propyl	$C_{18}H_{19}O_2NS$	69·1	6·1	69·0	6·1	34—35	42
*iso*Propyl	$C_{18}H_{19}O_2NS$	69·6	6·4	69·0	6·1	74—75	73
n-Butyl	$C_{19}H_{21}O_2NS$	70·1	6·5	69·7	6·4	85—86	74
*iso*Butyl	$C_{19}H_{21}O_2NS$	69·3	6·4	69·7	6·4	73—74	70
sec.-Butyl	$C_{19}H_{21}O_2NS$	69·5	6·4	69·7	6·4	43—44	80
tert.-Butyl	$C_{19}H_{21}O_2NS$	69·2	6·7	69·7	6·4	76	70
n-Amyl	$C_{20}H_{23}O_2NS$	70·7	6·8	70·4	6·7	74—75	68
n-Hexyl	$C_{21}H_{25}O_2NS$	70·7	7·0	70·9	7·0	52—53	36
n-Heptyl	$C_{22}H_{27}O_2NS$	71·7	7·3	71·6	7·3	46—47	70
n-Octyl	$C_{23}H_{29}O_2NS$	72·2	7·8	72·1	7·6	38—39	70

4-*Nitrobenzyl* β-10-*phenothiazinylpropionate* crystallised from xylene–light petroleum (b. p. 60—80°) in bright yellow needles (55%), m. p. 160—161° (Found : C, 64·2; H, 4·5. $C_{22}H_{18}O_4N_2S$ requires C, 65·0; H, 4·4%).

10-*Phenothiazinylcarbonylmethyl* β-10-*Phenothiazinylpropionate.*—An ethanolic solution of the sodium salt of the acid (2 g.) and 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 107) (2 g.) was refluxed on the water-bath for 3 hr. The product which separated afforded colourless rectangular prisms of the *ester* (1 g.), m. p. 179—180°, from toluene–light petroleum (b. p. 40—60°) (Found : C, 67·9; H, 4·1. $C_{29}H_{22}O_3N_2S_2$ requires C, 68·2; H, 4·3%).

β-10-*Phenothiazinylpropion*-p-*toluidide.*—A xylene solution (15 c.c.) of the acid (4 g.) and *p*-toluidine (8 g.) was refluxed for 3 hr. Benzene (20 c.c.) was added to the cooled product, and the benzene–xylene solution washed in turn with dilute hydrochloric acid, water, aqueous sodium hydroxide, and again water. After drying and removal of the benzene, light petroleum

(b. p. 40—60°) was added to the residue. The *toluidide* which separated recrystallised from benzene–light petroleum (b. p. 40—60°) (charcoal) as colourless matted needles (3 g.), m. p. 140° (Found : C, 72·8; H, 5·6. $C_{22}H_{20}ON_2S$ requires C, 73·3; H, 5·6%).

β-10-*Phenothiazinylpropion*-p-*bromoanilide*.—This *derivative* was prepared similarly from the acid (2 g.). Recrystallisation from absolute ethanol (charcoal) gave colourless needles (1 g.), m. p. 193—194° (Found : Br, 18·2. $C_{21}H_{17}ON_2BrS$ requires Br, 18·8%).

5′-*Benzylidene*-5′ : 6′-*dihydro*-4′-*oxopyridino*(3′ : 2′ : 1′-1 : 10a : 10)*phenothiazine*.—5′ : 6′-Dihydro-4′-oxopyridino(3′ : 2′ : 1′-1 : 10*a* : 10)phenothiazine (Smith, *loc. cit.*) (5 g.), benzaldehyde (5 g.), absolute ethanol (70 c.c.), and 5N-sodium hydroxide (3·5 c.c.) were shaken and set aside for 4 hr. ; the precipitated *benzylidene* derivative recrystallised from aqueous methanol in yellow prismatic needles (3·5 g.), m. p. 164° (Found : C, 77·5; H, 5·1. $C_{22}H_{15}ONS$ requires C, 77·4; H, 4·4%).

5′ : 6′-*Dihydro*-4′-*oxopyridino*(3′ : 2′ : 1′-1 : 10a : 10)*phenothiazine Semicarbazone*.—The *semicarbazone* crystallised from chlorobenzene–light petroleum (b. p. 40—60°) as yellow needles, m. p. 237—238° (Found : C, 62·7; H, 4·7; N, 17·6. $C_{16}H_{14}ON_4S$ requires C, 61·9; H, 4·5; N, 18·1%).

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