401. *An Aldehyde of the Phenothiazine Series.*

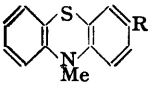
By Ng. Ph. Buu-Hoï and Ng. Hoán.

10-Methylphenothiazine is shown to undergo readily the *N*-methylformanilide aldehyde synthesis, and the compound thus obtained to be 3-formyl-10-methylphenothiazine. From this aldehyde, several styryl derivatives have been prepared for cancer research, and the thiosemicarbazone and its cyclisation products with various α-halogenated fatty acids have been synthesised for testing as antitubercular substances.

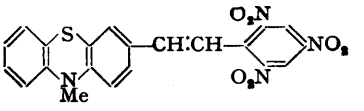
The phenothiazine series offers manifold attractions to pharmacologists, not only because of the several valuable antiseptic and antihistaminic derivatives found therein, but also because the parent compound itself is of strikingly versatile activity. Thus, phenothiazine has been found to be an insecticide (Campbell, Sullivan, and Smith, *J. Econ. Entomol.*, 1934, **27**, 1176), an anthelmintic (Harwood, Jerstad, and Swanson, *J. Parasit.*, 1938, **24**, Suppl., 16), a urinary antiseptic (Thomas, *J. Pharmacol. Exp. Therap.*, 1938, **64**, 280; de Eds and Thomas, *J. Parasit.*, 1942, **28**, 363), and an outstanding tuberculostatic compound (Freedlander, *Proc. Soc. Exp. Biol. Med.*, 1944, **57**, 106; Jouin and Buu-Hoï, *Ann. Inst. Pasteur*, 1946, **72**, 580). This is the more surprising in that the chemical properties of phenothiazine have hitherto been scarcely investigated.

Of its reactions with carbonyl compounds, only Friedel–Crafts acetylation (Baltzly, Harfenist, and Webb, *J. Amer. Chem. Soc.*, 1946, **68**, 2673; Michels and Amstutz, *ibid.*, 1950, **72**, 888) and phthaloylation (Scholl and Seer, *Ber.*, 1911, **44**, 1243) have been investigated. In these reactions, the substituents enter positions 2 and 8, and from these findings Baltzly, Harfenist, and Webb concluded that in the phenothiazine molecule the orientation must be controlled by the sulphur atom rather than by the NH group. The present work shows, however, that 10-methylphenothiazine lends itself to the *N*-methylformanilide aldehyde synthesis to give 3-formyl-10-methylphenothiazine (I) in excellent yield. That the aldehyde group had

entered position 3 exclusively was proved by Wolff–Kishner reduction of (I) to 3 : 10-dimethylphenothiazine (II), which was independently synthesised from 3-methylphenothiazine (Gilman and Shirley, *J. Amer. Chem. Soc.*, 1944, **66**, 891) by *N*-alkylation with methyl sulphate. This result is not surprising, as it had already been shown that in *N*-methylformanilide syntheses with 9-alkylcarbazoles the orientation is controlled by the nitrogen atom and not by the other aromatic nucleus (Buu-Hoï and Hoán, *ibid.*, 1951, **73**, 98). The control exerted by the sulphur atom observed by Baltzly, Harfenist, and Webb in Friedel–Crafts reactions is due to the deactivating effect of *N*-acetylation.



(I; R = CHO.) (II; R = Me.)
(V; R = CH:CAr·CN_2)
(VI; R = CH:CHPh.)

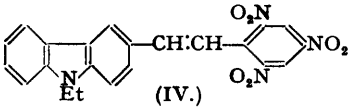


(III.)

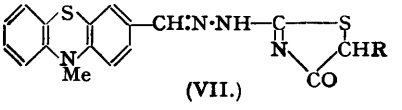
3-Formyl-10-methylphenothiazine lent itself to the usual reactions of aromatic aldehydes. For instance, condensation with 2 : 4 : 6-trinitrotoluene in the presence of piperidine as catalyst (Pfeiffer and Monath, *Ber.*, 1906, **39**, 1306) readily yielded 10-methyl-3-(2 : 4 : 6-trinitrostyryl)-phenothiazine (III). For purposes of comparison, 9-ethyl-3-(2 : 4 : 6-trinitrostyryl)carbazole (IV) was prepared in the same way from 3-formyl-9-ethylcarbazole.

Condensation of 3-formyl-10-methylphenothiazine with various arylacetonitriles in the presence of aqueous potassium hydroxide (see Buu-Hoï and Hoán, *J.*, 1950, 2130; 1951, 251) gave substituted acrylonitriles of general formula (V) (seven individuals were prepared). 10-Methyl-3-styrylphenothiazine (VI), the parent of these acrylonitriles, was obtained by the action of benzylmagnesium chloride on the aldehyde (I), and subsequent dehydration of the resulting secondary alcohol. All these ethylenic compounds have biological interest in connection with Pinck's theory of the possible carcinogenicity of substances of structure analogous to stilbene (Pinck, *Ann. N.Y. Acad. Sci.*, 1948, **50**, 1).

In view of the known tuberculostatic properties of aldehyde thiosemicarbazones (Domagk, Behnisch, Mietzsch, and Schmidt, *Naturwiss.*, 1946, **33**, 315) on the one hand, and of phenothiazine on the other, 3-formyl-10-methylphenothiazine thiosemicarbazone was prepared. Con-



(IV.)



(VII.)

densation of this with α-halogenated fatty acids (cf. Chabrier, *Bull. Soc. chim.*, 1947, **14**, 797; Chabrier and Cattelain, *ibid.*, 1950, **17**, 48; Wilson *et al.*, *J.*, 1922, **121**, 876; 1923, **123**, 799; 1926, 253) led easily to 3-formyl-10-methylphenothiazine 4-keto-2-thiazolinylhydrazones of general formula (VII). These substances, listed in the Table in the Experimental section, unlike the starting thiosemicarbazone, are but feebly tuberculostatic.

Experimental.

3-Formyl-10-methylphenothiazine (I).—Redistilled 10-methylphenothiazine (60 g.; prepared by methylation of phenothiazine with methyl sulphate and sodium hydroxide in acetone), *N*-methylformanilide (42 g.), phosphorus oxychloride (42 g.), and *o*-dichlorobenzene (60 c.c.) were heated for 4 hours on a steam-bath to 90—95°. After cooling, an aqueous solution of sodium acetate (180 g. in 400 c.c. of water) was added, and the solvent and *N*-methylaniline were removed by steam-distillation. The residual oil was taken up in toluene, the toluene solution dried (Na_2SO_4), the solvent removed, and the residue vacuum-fractionated. *3-Formyl-10-methylphenothiazine* (80%) formed from methanol long silky yellow needles, m. p. 89°, b. p. 270—280°/13 mm., giving a brown colour with sulphuric acid (Found : C, 69·6; H, 4·6. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·5%). The corresponding semicarbazone formed from ethanol fine greenish-yellow needles melting at 232° and resolidifying into a red mass, m. p. 276°. The *thiosemicarbazone* crystallised from ethanol in fine yellow needles, m. p. 227° (Found : N, 17·5. $C_{15}H_{14}N_4S_2$ requires N, 17·8%). On nitration with fuming nitric acid (*d*, 1·49) in acetic acid at 0°, 3-formyl-10-methylphenothiazine gave a compound crystallising from acetic acid in fine yellow prisms, m. p. 279°, probably the corresponding nitrosulphoxide.

3 : 10-Dimethylphenothiazine (II).—(*a*) A mixture of the foregoing aldehyde (3 g.), 85% hydrazine hydrate (3 g.), potassium hydroxide (3 g.), and diethylene glycol (50 c.c.) was cautiously refluxed with removal of water until the temperature reached 195—200°, refluxing being then continued for a further hour. After cooling, the mixture was diluted with much water, and the precipitated *dimethyl* derivative

collected and recrystallised from ethanol (yield, 90%); it formed long, shiny, colourless, sublimable needles, m. p. 148° (Found: C, 73·7; H, 5·7. $C_{14}H_{13}NS$ requires C, 74·0; H, 5·7%).

(*b*) A solution of 3-methylphenothiazine (21 g.) in acetone (250 c.c.) containing sodium hydroxide (6 g., dissolved in some water) was shaken with methyl sulphate (18 g.), and the acetone removed by distillation. The residue was taken up in benzene, the benzene solution washed thoroughly with water and dried (Na_2SO_4), the solvent removed, and the 3 : 10-dimethylphenothiazine purified by vacuum-distillation (b. p. 240°/13 mm.).

10-*Methyl*-3-(2 : 4 : 6-*trinitrostyryl*)*phenothiazine* (III).—A solution of 3-formyl-10-methylphenothiazine (2·4 g.) and 2 : 4 : 6-trinitrotoluene (2·3 g.) in ethanol was refluxed for 6 hours with 3 drops of piperidine. After cooling, the precipitated *trinitrostyryl* compound was collected and recrystallised from *o*-dichlorobenzene, giving fine violet needles, m. p. 264°; the halochromic coloration with sulphuric acid was brown (Found: C, 55·8; H, 3·2. $C_{21}H_{14}O_6N_4S$ requires C, 56·0; H, 3·1%).

9-*Ethyl*-3-(2 : 4 : 6-*trinitrostyryl*)*carbazole* (IV).—Similarly prepared from 9-ethyl-3-formylcarbazole (2·3 g.), 2 : 4 : 6-trinitrotoluene (2·3 g.), and piperidine in ethanol, this *compound* formed from toluene fine red needles, m. p. 255°, giving with sulphuric acid an orange colour, becoming rapidly green (Found: C, 61·0; H, 3·9. $C_{22}H_{16}O_6N_4$ requires C, 61·1; H, 3·7%).

10-*Methyl*-3-*styrylphenothiazine* (VI).—To an ethereal solution of benzylmagnesium chloride (from 3·2 g. of benzyl chloride and 0·6 g. of magnesium), 3-formyl-10-methylphenothiazine (5 g.) was added in small portions. After 10 minutes' boiling, the reaction mixture was worked up in the usual way, and the crude carbinol obtained dehydrated with 98% formic acid. The *styryl* compound formed (4 g.) from acetic acid fine greenish-yellow prisms, m. p. 152°, giving with sulphuric acid a violet-red colour (Found: C, 79·7; H, 5·5. $C_{21}H_{17}NS$ requires C, 80·0; H, 5·4%).

β-(10-*Methyl*-3-*phenothiazinyl*)-α-*phenylacrylonitrile* (V; Ar = Ph).—A solution of 3-formyl-10-methylphenothiazine (2·4 g.) and phenylacetonitrile (1·3 g.) in warm ethanol was shaken with some drops of 30% aqueous potassium hydroxide; the oily *product* which separated quickly solidified after cooling, and yielded on recrystallisation from ethanol–benzene fine orange needles (2·8 g.), m. p. 120° (Found: C, 77·7; H, 4·9. $C_{22}H_{16}N_2S$ requires C, 77·7; H, 4·7%). This and the following acrylonitriles (all crystallised from ethanol–benzene) gave with sulphuric acid a violet halochromic colour.

β-(10-*Methyl*-3-*phenothiazinyl*)-α-p-*tolylacrylonitrile*, obtained as above from (I) (2·4 g.) and *p*-tolylacetonitrile (1·4 g.), formed fine orange needles, m. p. 117° (Found: C, 77·6; H, 5·0. $C_{23}H_{18}N_2S$ requires C, 77·9; H, 5·1%).

β-(10-*Methyl*-3-*phenothiazinyl*)-α-2-*naphthylacrylonitrile* [from β-naphthylacetonitrile (1·8 g.)] formed orange prisms, m. p. 199° (Found: C, 79·8; H, 4·8. $C_{26}H_{18}N_2S$ requires C, 80·0; H, 4·6%).

α-p-*Fluorophenyl*-β-(10-*methyl*-3-*phenothiazinyl*)*acrylonitrile* formed long orange-yellow needles, m. p. 154° (Found: C, 73·6; H, 4·2. $C_{22}H_{15}N_2SF$ requires C, 73·7; H, 4·1%).

α-p-*Chlorophenyl*-β-(10-*methyl*-3-*phenothiazinyl*)*acrylonitrile* was obtained as fine orange leaflets, m. p. 202° (Found: C, 70·4; H, 4·1. $C_{22}H_{15}N_2SCl$ requires C, 70·7; H, 4·0%).

α-p-*Bromophenyl*-β-(10-*methyl*-3-*phenothiazinyl*)*acrylonitrile* [from *p*-bromophenylacetonitrile (cf. Buu-Hoï and Hoán, *J.*, 1951, 251)] crystallised in fine orange leaflets, m. p. 204° (Found: C, 62·9; H, 3·8. $C_{22}H_{15}N_2SBr$ requires C, 63·0; H, 3·6%).

α-p-*Iodophenyl*-β-(10-*methyl*-3-*phenothiazinyl*)*acrylonitrile*.—The *p*-iodophenylacetonitrile used was prepared from 4-iodobenzyl chloride (the product of chloromethylation of iodobenzene) and sodium cyanide in acetone. The *acrylonitrile* formed fine orange leaflets, m. p. 172° (Found: C, 56·4; H, 3·1. $C_{22}H_{15}N_2SI$ requires C, 56·6; H, 3·2%).

Preparation of the 4-*Keto*-2-*thiazolinylhydrazones* (VII).—A suspension in acetic acid of 3-formyl-10-methylphenothiazine thiosemicarbazone was refluxed for 6 hours with the theoretical amount of the appropriate α-halogenated fatty acid in the presence of sodium acetate; after cooling, the precipitate formed was collected and recrystallised several times from acetic acid or toluene. The *products* thus obtained (see Table), as well as the starting thiosemicarbazone, were extremely difficult to burn and gave very poor carbon and hydrogen analyses.

4-*Keto*-2-*thiazolinylhydrazones* (VII).

R.	Acid used.	M. p.	Formula.	N, %. Found.	Reqd.
H	Chloroacetic	307°	$C_{17}H_{14}N_4OS_2$	15·5	15·8
Et	α-Bromobutyric	257	$C_{19}H_{18}N_4OS_2$	14·4	14·6
Pr^i	α-Bromo*iso*valeric	288	$C_{20}H_{20}N_4OS_2$	13·8	14·1
Bu^n	2-Bromohexanoic	249	$C_{21}H_{22}N_4OS_2$	13·3	13·6
n-$C_{14}H_{29}$	α-Bromopalmitic	207	$C_{31}H_{42}N_2OS_4$	10·1	10·2
n-$C_{16}H_{33}$	α-Bromostearic ...	200	$C_{33}H_{46}N_4OS_2$	9·9	9·7

Full biological results of the tuberculostatic and anthelmintic tests, performed by Professor M. Welsch (Liège) with the compounds described in this work, will be published elsewhere. Our thanks are due to Miss P. F. Boshell, M.A. (Oxon.), for assistance with this work.

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