

Short Communications

 Some Tetrazole Derivatives of
Phenothiazine

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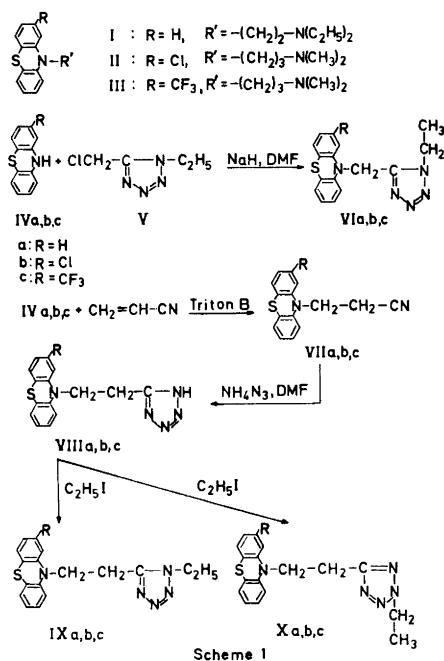
It has been proved that chlorpromazine,¹ diethazine,² and triflupromazine,² respectively, in combination with atropine constitute a much better protection against organophosphorus poisoning than atropine alone.

As part of the research on anticholinergic agents in this laboratory we want to report the preparation of a number of new tetrazole derivatives (VI, VIII, IX, and X) of phenothiazine (IVa), 2-chlorophenothiazine (IVb), and 2-trifluoromethylphenothiazine (IVc), respectively. The structure of compound VI is related to that of diethazine, while the structures of IX and X are related to those of the promazines.

The 10-[(1-ethyl-5-tetrazolyl)methyl]phenothiazines (VIa,b,c) were prepared by *N*-alkylating the corresponding phenothiazines IVa,b,c, with 1-ethyl-5-chloromethyltetrazole³ (V) using DMF as a reaction medium.

A possible route to VIa,b,c involves as an intermediate step the preparation of 10-phenothiazinyl acetonitrile by alkylation of the sodium salt of IV with chloroacetonitrile. Attempts to alkylate IVa failed though 2-chlorophenothiazine (IVb) has been reported⁴ to undergo cyanomethylation at the nitrogen atom.

The 10-[2-(1- and 2-ethyl-5-tetrazolyl)ethyl]phenothiazines (IXa-c and Xa-c) were prepared from the corresponding phenothiazines (IVa-c) by cyanoethylation with acrylonitrile⁵⁻⁷ followed by reaction with ammonium azide in DMF⁸ to give



N-[2-(5-tetrazolyl)ethyl]phenothiazines (VIIIa-c). Finally, the sodium salts of VIIIa-c were alkylated with ethyl iodide forming isomer mixtures of IXa-c and Xa-c. The isomers were separated either by crystallization or by preparative layer chromatography. The 1-isomers (IXa-c) were solids while the 2-isomers (Xa-c) were oily substances. Attempts to distil, e.g., Xa at 0.5 mmHg led to decomposition.

The structures of the compounds VIa-c were assigned on the basis of elementary analysis, IR- and ¹H NMR-spectra. Absorption of VIb-c in the infrared region of 800 cm⁻¹ - 835 cm⁻¹ indicated a 2-substituted phenothiazine.⁹ The structural assignment was confirmed by the synthesis,

Table 1. Tetrazole derivatives of phenothiazine.

Compound	M.p. ^a	% Yield	Formula	Analysis			
				% C Calc. Found	% H Calc. Found	% N Calc. Found	% S Calc. Found
VIa	189–190° (A)	62	C ₁₆ H ₁₅ N ₅ S	62.12 62.02	4.89 5.06	22.64 22.69	10.35 10.51
VIb	160–162° (A)	46	C ₁₆ H ₁₄ F ₃ N ₅ S	55.89 56.00	4.10 4.20	20.38 20.62	9.33 9.40
VIc	128–129° (A)	40	C ₁₇ H ₁₄ F ₃ N ₅ S	54.12 54.18	3.74 3.70	18.56 18.59	8.50 8.67
VIIIa	198–199° (B)	62	C ₁₅ H ₁₃ N ₅ S	61.01 60.88	4.43 4.61	23.71 23.77	10.85 10.67
VIIIb	180–182° (B)	58	C ₁₅ H ₁₂ ClN ₅ S	54.64 54.48	3.67 3.77	21.24 21.17	9.73 9.83
VIIIc	152–153° ^b	42	C ₁₆ H ₁₂ F ₃ N ₅ S	52.89 52.22	3.30 3.34	19.28 19.01	8.81 8.57
IXa	109.5–110.5° (C)	36	C ₁₇ H ₁₇ N ₅ S	63.15 63.38	5.29 5.41	21.66 21.90	9.90 9.87
IXb	97–99° (A)	32	C ₁₇ H ₁₆ ClN ₅ S	57.05 56.90	4.51 4.50	19.57 19.63	8.96 8.89
IXc	124.5–125.5° (A)	24	C ₁₈ H ₁₆ F ₃ N ₅ S	55.25 55.20	4.13 4.27	17.90 17.92	8.19 8.39
Xa	oil ^c	52	C ₁₇ H ₁₇ N ₅ S	63.15 63.20	5.29 5.46	21.66 21.48	9.90 9.89
Xb	oil	48	C ₁₇ H ₁₆ ClN ₅ S	57.05 57.10	4.51 4.70	19.57 19.40	8.96 9.12
Xc	oil	46	C ₁₈ H ₁₆ F ₃ N ₅ S	55.25 55.05	4.13 4.23	17.90 17.80	8.19 8.48

^a Recrystallization solvent given in parentheses; A, ethanol; B, isopropanol-water 1:1; C, ethanol-water 1:1.

^b Recrystallized from benzene-petroleum ether as recrystallization from B yielded a product with 1 mol of isopropanol of crystallization. M.p. 65–66°.

^c Distillation at 0.5 mmHg led to decomposition at 180°C.

as 1-ethyl-5-chloromethyltetrazole used for the alkylation of IVa-c was prepared by an unequivocal method of Cosgrove and La Forge.³

The structural assignments of the 10-[2-(1- and 2-ethyl-5-tetrazolyl)ethyl]-

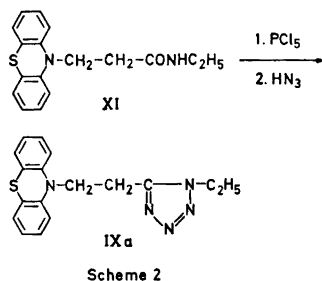
Table 2. ¹H NMR data of the ethyl group attached to the tetrazole ring in VIa-c, IXa-c and Xa-c.

Compound	Chemical shifts (τ -values)	
	^a –N–CH ₂ –C	^b –C–CH ₃
VIa	5.62*	8.70 (t)
VIb	5.63*	8.63 (t)
VIc	5.60*	8.62 (t)
IXa	5.93*	8.65 (t)
IXb	5.93*	8.63 (t)
IXc	5.90*	8.62 (t)
Xa	5.42*	8.43 (t)
Xb	5.45*	8.43 (t)
Xc	5.42*	8.43 (t)

* q, $J_{ab} = 7$ Hz.

phenothiazines (IXa-c and Xa-c) were based on the ¹H NMR-spectra (see Table 1) as it is known¹⁰ that the signals of the protons of the methyl or methylene groups directly attached to a nitrogen atom in the tetrazole ring occur at a higher field for the 1-isomers compared to those of the 2-isomers. From the chemical shifts listed in Table 2 we ascribe the 1-isomer structure to IXa-c and the 2-isomer structure to Xa-c. In addition to that it has to be mentioned that IXb-c and Xb-c showed absorption in the infrared region of 800–835 cm⁻¹. This structural assignment was confirmed in one case (IXa) by an unequivocal synthesis involving treatment of *N*-ethyl-3-(10-phenothiazinyl)propanamide (XI) with phosphorus pentachloride and subsequent addition of hydrazoic acid.³ The product so formed in poor yield (< 1%) was proved to be identical with IXa by IR analysis. XI was obtained by converting 3-(10-phenothiazinyl)propanoic acid into the corresponding acid chloride¹¹ followed by reaction with ethyl amine.

Experimental. The IR-spectra were recorded on a Perkin-Elmer 337 spectrophotometer (KBr discs) and the ¹H NMR-spectra were recorded in CDCl₃ at 60 MHz on a Varian A 60



spectrometer, using tetramethylsilane as an internal standard.

The melting points were determined with a hot stage microscope (Mikroskop-Heiztisch 350, Ernst Leitz, G.m.b.H., Wetzlar) and the microanalyses were made by Preben Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen.

Phenothiazine and 2-chlorophenothiazine were commercially available while 2-trifluoromethylphenothiazine was prepared according to the method of Smith.⁵

10-[2-(1-Ethyl-5-tetrazolyl)methyl]-phenothiazines (VIa-c). General procedure. To a stirred suspension of 0.022 mol of sodium hydride (50 % in mineral oil) in 10 ml of DMF, a solution of 0.020 mol of the phenothiazine in 10 ml of DMF was added dropwise at room temperature under nitrogen. After the hydrogen evolution had ceased (2 h) a solution of 0.020 mol of 1-ethyl-5-chloromethyltetrazole in 15 ml of DMF was added dropwise during 10 min. The mixture was heated at 100° for 4–4½ h and after cooling to room temperature the reaction mixture was filtered and evaporated under reduced pressure. The residue was taken up in a mixture of 100 ml benzene and 50 ml ethyl acetate and the organic layer was washed with successive portions of water until the aqueous layer became colourless. After drying over magnesium sulphate, decolourizing with charcoal and filtration the benzene-ethyl acetate layer was evaporated and the residue was recrystallized from ethanol. Yields together with physical and analytical data are summarized in Table 1.

10-[2-(5-Tetrazolyl)ethyl]phenothiazines (VIIa-c). General procedure. To a solution of the β -phenothiazinyl-propionitrile⁵⁻⁷ in DMF was added 10 % excess of sodium azide and ammonium chloride, respectively, and the suspension was heated with stirring at 110° for 24–30 h. After cooling to room temperature the reaction mixture was filtered and evaporated under reduced pressure. The

residue was treated with water and the solution was adjusted to pH 10 with 50 % aqueous sodium hydroxide. The precipitate (unreacted nitrile) was removed by filtration and washed with ice cold water. The combined filtrates were acidified with concentrated hydrochloric acid to pH 2 with cooling and stirring. The tetrazole formed was collected, washed with several portions of ice cold water, and recrystallized from isopropanol-water 1:1. Yields together with physical and analytical data are summarized in Table 1.

10-[2-(1- and 2-Ethyl-5-tetrazolyl)ethyl]-phenothiazines (IXa-c and Xa-c). General procedure. To a cold solution of 0.010 mol of VIII was added ethyl iodide (0.011 mol) in 20 ml of acetone, 0.011 mol of sodium hydroxide, and 5 ml of water. The mixture was refluxed for 2½ h and after cooling to room temperature 35 ml of benzene was added. The organic layer was separated, washed with three 10 ml portions of water and dried over magnesium sulphate. Upon evaporation an isomer mixture was obtained in almost quantitative yield. The isomers were separated by crystallization (Table 1) or by preparative layer chromatography on 1 mm silica gel plates using benzene-ethyl acetate 90:10 as an eluent.

1. Wills, J. H. *J. Med. Pharm. Chem.* **3** (1961) 353.
2. Coleman, I. W., Little, P. E., Patton, G. W. and Bannard, R. A. B. *Can. J. Physiol. Pharmacol.* **44** (1966) 745–46.
3. Cosgrove, C. E. and La Forge, R. A. *J. Org. Chem.* **21** (1956) 197.
4. Bell, R. B. Belgian Pat. 659, 467 (1965); *Chem. Abstr.* **64** (1966) P 2099a.
5. Smith, N. L. *J. Org. Chem.* **15** (1950) 1125.
6. Kano, H., Makizumi, Y. and Ogata, K. *Ann. Rept. Shionogi Research Lab.* **6** (1956) 15; *Chem. Abstr.* **51** (1957) 6644g.
7. Craig, P. N. and Ullyot, G. E. German Pat. 1,138,729 (1962); *Chem. Abstr.* **59** (1963) 3934b.
8. Finnegan, W. G., Henry, R. A. and Lofquist, R. *J. Am. Chem. Soc.* **80** (1958) 3908.
9. Yale, H. L., Sowinski, F. and Bernstein, J. *J. Am. Chem. Soc.* **79** (1957) 4375.
10. Sørensen, A. K. and Klitgaard, N. A. *To be published.*
11. Godefroi, E. F. and Wittle, E. L. *J. Org. Chem.* **21** (1956) 1163.

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