451. *The Reactivity of Organophosphorus Compounds. Part III.* The Decomposition of 2-Diethylaminoethyl Diethyl Phosphate and of* S-*2-Diethylaminoethyl Diethyl Phosphorothioate (" Amiton ").*

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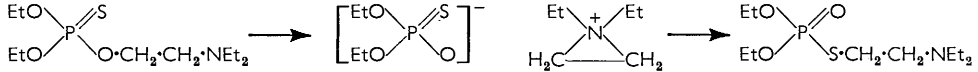
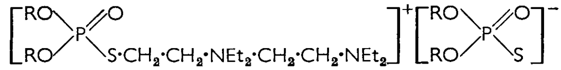
The decomposition, under various conditions, of the compounds named in the title have been investigated. In general, 1,1,4,4-tetraethylpiperazinium salts are formed. Novel reactions of the piperazinium salts which are described include a rearrangement of the bis-(*OO*-diethyl phosphorothioate).

GHOSH and NEWMAN[1] have described the preparation of an extremely toxic[2] insecticide, *S*-2-diethylaminoethyl diethyl phosphorothioate, " Amiton "[3] (III), by the isomerisation of the thiono-isomer (I). The mechanism of the isomerisation has been investigated by Fukoto and Stafford,[2] and that of the analogous 2-dimethylaminoethyl compound by Tammelin.[4] The former workers demonstrated the participation of an ethyleneiminium ion (II) and also reported the formation of a solid decomposition product which contained the 1,1,4,4-tetraethylpiperazinium cation. This was presumably formed by dimerisation involving the ion (II), thus resembling the dimerisation of the " nitrogen mustards."[5]



(I) (II) (III)

Tammelin,[4] on the other hand, suggested that the product might have contained a quaternary salt of the type (IV). None of these workers, however, established the structure of the decomposition product of " Amiton," or the course of the reaction.



(IV)

We have investigated the decomposition of " Amiton " (III) and of the related, relatively non-toxic 2-diethylaminoethyl diethyl phosphate.

At room temperature, 2-diethylaminoethyl diethyl phosphate, prepared by the condensation of diethyl phosphorochloridate and sodium 2-diethylaminoethoxide, slowly deposited hygroscopic colourless crystals of the same elemental composition as the ester. The conversion was faster when the phosphate was heated, alone or with methanol. Since an aqueous solution of the compound gave 1,1,4,4-tetraethylpiperazinium dipicrate, the product is formulated as 1,1,4,4-tetraethylpiperazinium bis(diethyl phosphate) (V). This was confirmed by comparison with a specimen synthesised from potassium diethyl phosphate and 1,1,4,4-tetraethylpiperazinium dichloride. This decomposition is similar to that of 2-dimethylaminoethyl diphenyl phosphate recently reported by Durrant, Turnbull, and Wilson.[6] At 180° and above, an additional reaction, which gave triethyl phosphate (2 equivalents) and 1,4-diethylpiperazine (1 equivalent), occurred. Since the piperazinium salt (V) also gave these products under these conditions, it is concluded that the decomposition of 2-diethylaminoethyl diethyl phosphate at the higher temperature again proceeds through the piperazinium salt (V). This, in turn, is assumed to decompose by a reverse Menschutkin reaction to give the observed products. This reaction closely

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* Part II, *J.*, 1957, 4154; *J.*, 1957, 1079 is regarded as Part I.

[1] Ghosh and Newman, *Chem. and Ind.*, 1955, 118; cf. Calderbank and Ghosh, *J.*, 1960, 637.

[2] Fukoto and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 6083.

[3] Baldit, *Chem. and Ind.*, 1958, 89.

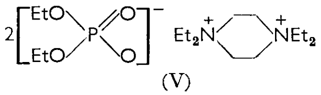
[4] Tammelin, *Acta Chem. Scand.*, 1957, **11**, 1738.

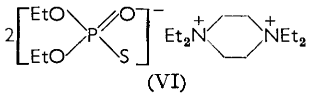
[5] Bartlett, Ross, and Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2971.

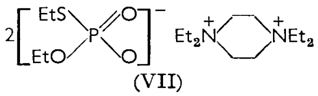
[6] Durrant, Turnbull, and Wilson, *Chem. and Ind.*, 1958, 157.

simulates the decomposition of 1,1,4,4-tetra-alkylpiperazinium dihalides to the corresponding 1,4-dialkylpiperazines.[7]

" Amiton " is more stable than its oxygen analogue and can be stored at room temperature without appreciable decomposition. Prolonged storage at higher temperature caused considerable decomposition to a solid, which by analogy was expected to be 1,1,4,4-tetraethylpiperazinium bis-(*OO*-diethyl phosphorothioate) (VI). It was found, however, that the isomeric 1,1,4,4-tetra-ethylpiperazinium bis-(*OS*-diethyl phosphorothioate) (VII) was the main product, formed with small amounts of the bis-(*OO*-diethyl phosphorothioate) (VI). Complementary experiments showed that the authentic *OO*-isomer (VI) rearranged under the above conditions of storage of " Amiton " to the *OS*-isomer (VII). It is therefore concluded that the decomposition of " Amiton " proceeds by the initial formation of the salt (VI) which rearranges to the *OS*-isomer (VII). Although no direct evidence concerning the mechanism of this rearrangement is available, the observed stability of potassium *OO*-diethyl phosphorothioate under these conditions suggests that intraionic rearrangement of the anion does not occur, and that the tetraethylpiperazinium cation is involved in the reaction as an alkylating agent.


(V)


(VI)


(VII)

Traces of 1,4-diethylpiperazine and triethyl phosphorothiolate also found in the product of decomposition of " Amiton " are attributed to slight decomposition by a reverse Menschutkin reaction of the piperazinium salt, thus resembling the high-temperature decomposition of 2-diethylaminoethyl diethyl phosphate.

The decomposition reactions of " Amiton " and 2-diethylaminoethyl diethyl phosphate described in this paper are therefore assumed to proceed *via* the piperazinium ion. This is at variance with Tammelin's suggestion. In our experiments, no evidence was found for the formation from " Amiton " of the salt (IV). The structure of the solid decomposition product is accommodated by its infrared spectrum and by the absence of free basic groups. Further, alkaline degradation of the salt (IV) would give " Amiton " and/or products of its hydrolysis. Under these conditions the salt isolated from the decomposition of " Amiton " gave only products arising from the degradation of the tetraethylpiperazinium ion.

EXPERIMENTAL

" Amiton " (*S*-2-diethylaminoethyl diethyl phosphorothioate) is an insecticide of very high toxicity and precautions against personal contamination are needed.

The infrared spectra in the region 2—15 μ were obtained by using a Perkin-Elmer Model 21 double-beam spectrophotometer fitted with a rock-salt prism. Those in the region 15—25 μ were recorded on a Hilger H 800 double-beam spectrophotometer fitted with potassium bromide prism. Liquids were examined as capillary films between potassium bromide plates, and solids as Nujol mulls or in potassium chloride or bromide discs.

The reported m. p. determinations on the anhydrous piperazinium salts were carried out in sealed tubes. The hydrated salts exhibited lower m. p.s in sealed tubes but in open tubes two m. p.s were observed, the higher corresponding to that of the anhydrous salt in a sealed tube.

" Amiton," prepared as described by Ghosh and Newman,[1] had b. p. 88°/0·04 mm., n_D^{25} 1·4666 (purity 99%, by titration).

Diethyl phosphorochloridate [8] had b. p. 95°/12 mm. Triethyl phosphorothiolate [9] had b. p. 100°/12 mm., n_D^{25} 1·4555. Triethyl phosphorothionate, prepared by the addition of sulphur to triethyl phosphite, had b. p. 98—100°/13 mm., n_D^{25} 1·4460. 1,1,4,4-Tetraethylpiperazinium dichloride and 1,4-diethylpiperazine were prepared by the methods described by Cadogan.[7]

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[7] Cadogan, *J.*, 1955, 2971.

[8] McCombie, Saunders, and Stacey, *J.*, 1945, 380.

[9] Stirling, *J.*, 1957, 3597.

2-Diethylaminoethyl Diethyl Phosphate.—Sodium (14·5 g.) in dry benzene (250 ml.) was boiled with 2-diethylaminoethanol (72 g.) for 2 hr. The solution of the sodium salt was decanted from unchanged sodium, and diethyl phosphorochloridate (104 g.) in dry benzene (200 ml.) was added at room temperature in 1 hr. Precipitation of sodium chloride was induced by addition of light petroleum (b. p. 40—60°), and the mixture was filtered through kieselguhr. Removal of the solvents followed by distillation gave a forerun of triethyl phosphate followed by a fraction, b. p. 75—80°/0·01 mm., which on redistillation gave *2-diethylaminoethyl diethyl phosphate* (80 g.), b. p. 87°/0·02 mm., n_D^{25} 1·4288 (Found: C, 47·2; H, 9·6. $C_{10}H_{24}NO_4P$ requires C, 47·4; H, 9·55%). The product deposited colourless crystals on prolonged storage at room temperature.

Preparation of 1,1,4,4-*Tetraethylpiperazinium Bis(diethyl Phosphate).*—Potassium diethyl phosphate (7 g.), dissolved in the minimum amount of methanol, was added to 1,1,4,4-tetraethylpiperazinium dichloride (5 g.) in methanol (15 ml.). The mixture was boiled for 5 min., cooled, filtered, evaporated to a small volume, and diluted with acetone (300 ml.). This solution was reduced to 25 ml. by evaporation and allowed to cool. The resultant hygroscopic needles were recrystallised from acetone–methanol and dried over P_2O_5 at 70°/0·1 mm., to give 1,1,4,4-*tetraethylpiperazinium bis(diethyl phosphate)* as hygroscopic prisms (7 g.), m. p. 205—206° (decomp.) (Found: C, 47·0; H, 9·4. $C_{20}H_{48}N_2O_8P_2$ requires C, 47·4; H, 9·55%).

Preparation of 1,1,4,4-*Tetraethylpiperazinium Bis-(*OO*-diethyl Phosphorothioate).*—Potassium *OO*-diethyl phosphorothioate was prepared by the hydrolysis of triethyl phosphorothionate as described by Martin.[10] The product, recrystallised from ethanol, had m. p. 196—197°. The potassium salt (20·6 g.) in methanol (30 ml.) was added to 1,1,4,4-tetraethylpiperazinium dichloride (13·5 g.) in methanol (60 ml.). The mixture was boiled for a few minutes, cooled, filtered, evaporated to a small volume, diluted with acetone (400 ml.), and again evaporated to a small volume. When cool, colourless needles (m. p. 90—116°) of a *dihydrate* separated. The m. p. was not improved by recrystallisation (Found: C, 42·7; H, 9·0. $C_{20}H_{48}N_2O_6P_2S_2,H_2O$ requires C, 43·1; H, 9·0%). The product was dried over P_2O_5 at 70°/0·1 mm. to give anhydrous 1,1,4,4-*tetraethylpiperazinium bis-(*OO*-diethyl phosphorothioate)* (50%), m. p. 148° (Found: C, 44·8; H, 9·2; N, 5·6. $C_{20}H_{48}N_2O_6P_2S_2$ requires C, 44·6; H, 9·0; N, 5·2%).

Preparation of 1,1,4,4-*Tetraethylpiperazinium Bis-(*OS*-diethyl Phosphorothioate).*—*Triethyl phosphorodithiolate.* Ethyl phosphorodichloridate (27 g.) in ether (dried over Na; 50 ml.) was added dropwise during 30 min. to an ice-cold stirred mixture of ethanethiol (20 g.) and anhydrous triethylamine (50 ml.) in dry ether (100 ml.). The mixture was boiled under reflux for 2 hr. and left at room temperature overnight. Evaporation of the filtered solution gave *triethyl phosphorodithiolate* (28 g.), b. p. 102—103°/0·3 mm., n_D^{25} 1·5160 (Found: C, 33·7; H, 7·05. $C_6H_{15}O_2PS_2$ requires C, 33·6; H, 7·05%).

Sodium *OS*-diethyl phosphorothioate was prepared by a modification of the method of Hudson and Keay:[11] the above ester (2 g.) was shaken at 20° with sodium hydroxide (1 g.) in water (25 ml.). After 30 min., the almost homogeneous mixture was extracted with ether and the aqueous portion was treated with 1,1,4,4-tetraethylpiperazinium dichloride (1·25 g.). The pH was adjusted to 8 and the solution evaporated to dryness. The residue was extracted with hot methanol (2 × 75 ml.), and the extracts were evaporated to a small volume and diluted with acetone. Crystallisation from this mixture of solvents gave 1,1,4,4-*tetraethylpiperazinium bis-(*OS*-diethyl phosphorothioate)* as needles (2 g.), m. p. 203° (after drying over P_2O_5 at 50°/0·01 mm. for 12 hr.), whose infrared spectrum indicated the presence of the $[EtS{\cdot}P(O_2){-}]^-$ moiety and the absence of the $(\rangle POS)^-$ ion (Found: C, 44·7; H, 9·3; N, 5·4. $C_{20}H_{48}N_2O_6P_2S_2$ requires C, 44·6; H, 9·0; N, 5·2%).

Decomposition of 2-Diethylaminoethyl Diethyl Phosphate.—(i) *At* 100°. After 1 hr. at 100° the product was semisolid. The hygroscopic solid so formed was filtered off, washed with cold acetone, and dried (P_2O_5/1 mm.). It had m. p. 205° and its infrared spectrum was identical with that of 1,1,4,4-tetraethylpiperazinium bis(diethyl phosphate) prepared as described above. Treatment with aqueous calcium picrate gave 1,1,4,4-tetraethylpiperazinium dipicrate (m. p. >250°, correct infrared spectrum).

(ii) *At* 180°. After 2 hr. the dark product was allowed to cool, giving a semisolid mass; filtration left crystals which were washed with cold acetone and dried (P_2O_5). These were

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[10] Martin, *J. Amer. Chem. Soc.*, 1945, **67**, 1663.

[11] Hudson and Keay, *J.*, 1956, 3269; cf. Thain, *J.*, 1957, 4694.

1,1,4,4-tetraethylpiperazinium bis(diethyl phosphate). The filtrate was distilled (b. p. 50—100°/10 mm.) and was shown by infrared analysis to be a mixture of triethyl phosphate (2 mol.) and 1,4-diethylpiperazine (1 mol.). This was confirmed by isolation of the neutral and basic portions. The triethyl phosphate had b. p. 86—90°/10 mm., n_D^{25} 1·4040. The base had b. p. 85°/47 mm., n_D^{25} 1·4515 [dimethiodide, m. p. and mixed m. p. 250° (Found: C, 28·2; H, 5·3. Calc. for $C_{10}H_{24}N_2I_2$: C, 28·2; H, 5·7%)].

Decomposition of 1,1,4,4-*Tetraethylpiperazinium Bis*(*diethyl Phosphate*).—(i) *At* 180°. After 4 hr., the product afforded unchanged piperazinium salt, triethyl phosphate, and 1,4-diethylpiperazine.

(ii) *By dry distillation.* Distillation under slightly reduced pressure gave a 75% conversion into 1,4-diethylpiperazine (1 part) and triethyl phosphate (2 parts). The residue was an intractable gum.

Isomerisation of 1,1,4,4-*Tetraethylpiperazinium Bis*-(OO-*diethyl Phosphorothioate*).—The salt (m. p. 148°), in a sealed tube, was kept at 105° for 10 days and then at 115° for a further 7 days. After this time the salt had m. p. 169—178° (Found: C, 44·3; H, 9·3. Calc. for $C_{20}H_{48}N_2O_6P_2S_2$: C, 44·6; H, 9·0%). Recrystallisation from acetone gave needles, m. p. 204° (Found: C, 44·7; H, 9·3; N, 5·4. Calc. for $C_{20}H_{48}N_2O_6P_2S_2$: C, 44·6; H, 9·0; N, 5·2%). The infrared spectrum indicated the presence of the P·SEt and $>PO_2^-$ groups and the absence of the $>POS^-$ anion. This compound was identical (mixed m. p. 203°, and infrared spectrum) with 1,1,4,4-tetraethylpiperazinium bis-(*OS*-diethyl phosphorothioate) prepared as described above. The interpretation of the infrared spectra is, in part, based on unpublished work by one of us (L. C. T.) which has resulted in the following correlations: $[>POS]^-$ 1105—1143 and 580—645 cm.$^{-1}$; P·SEt 1258—1271 cm.$^{-1}$.

Decomposition of S-2-*Diethylaminoethyl Diethyl Phosphorothioate* (" *Amiton* ").—(i) *At* 100°. " Amiton " was kept at 100° under nitrogen, samples being withdrawn at intervals for infrared spectroscopy and refractive-index determinations. Some solid was soon deposited but the supernatant liquid showed little change during 20 hr. After a further 29 hr. the sample was semisolid. The solid was water-soluble and gave a good yield of 1,1,4,4-tetraethylpiperazinium dipicrate (m. p. >250°; correct infrared spectrum). The liquid portion was mainly unchanged " Amiton." In another experiment it was shown that " Amiton " was almost completely (80—90%) converted into the piperazinium salt after 18 days at 90°.

(ii) *At* 60°. " Amiton " was stored for 6 months at 60°, after which time it had turned almost completely into a yellow hygroscopic solid. The infrared spectrum was very different from that of " Amiton " or that of 1,1,4,4-tetraethylpiperazinium bis-(*OO*-diethyl phosphorothioate) and indicated the presence of the P·SEt and $>PO_2^-$ moieties. A portion (6 g.), which was not a truly representative sample because of the heterogeneity of the mixture, was treated with water and extracted with ether. The aqueous portion gave 1,1,4,4-tetraethylpiperazinium dipicrate in good yield. The ether solution was extracted with dilute hydrochloric acid and the extracts were combined (A). The ether portion on evaporation left an oil (n_D^{25} 1·4412; 0·1 g.) which had the infrared spectrum of triethyl phosphorothiolate contaminated with *ca.* 5% of triethyl phosphorothionate. The extracts (A) were basified and extracted with chloroform. Evaporation left a red oil (1·65 g.) which had an infrared spectrum interpreted as showing the presence of " Amiton " contaminated with 1,4-diethylpiperazine. This was confirmed by chromatography on paper of this mixture and of a synthetic mixture of the pure components (the solvent system was dimethylformamide and heptane).

Another portion of the decomposition mixture was washed with acetone and filtered, to give colourless crystals which after being dried (P_2O_5 at 80°/18 mm.) had m. p. 140—159°. The infrared spectrum indicated the presence of the P·SEt and $>PO_2^-$ moieties and was identical with the spectrum of the product of isomerisation of 1,1,4,4-tetraethylpiperazinium bis-(*OO*-diethyl phosphorothioate).

A further portion of the decomposition product of " Amiton," dissolved in water, was extracted with ether to remove non-ionic material. The aqueous portion was boiled under reflux with 2N-potassium hydroxide for 4 hr. Ether-extraction gave a red oil, shown to be mixture of 2-diethylaminoethanol and tetraethylethylenediamine, by infrared spectra and by isolation of the methiodides as described below.

Action of Alkali on 1,1,4,4-*Tetraethylpiperazinium Dichloride*.—The salt (30 g.) was treated with 2N-potassium hydroxide (4 equiv.) under reflux for 20 min. The mixture was extracted with ether to give a mixture of bases (12 g.; b. p. 67—100°/20 mm.) which was converted into a mixture of methiodides. These were resolved by fractional crystallisation from methanol into 2-diethylaminoethanol methiodide, m. p. and mixed m. p. 263°, and *NNN'N'*-tetraethylethylenediamine dimethiodide, m. p. and mixed m. p. 203°.

Action of Alkali on 1,1,4,4-*Tetraethylpiperazinium Bis*-(OO-*diethyl Phosphorothioate*).—The salt (6·0 g.) was treated with 2N-potassium hydroxide solution (2 equiv.) and warmed. A gas was evolved and the mixture was worked up as described in the previous experiment, to give the methiodides of 2-diethylaminoethanol and *NNN'N'*-tetraethylethylenediamine. The aqueous portion was acidified and continuously extracted with ether. The extracts gave *OO*-diethyl hydrogen phosphorothioate (correct infrared spectrum).

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