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Ethyl *N,N*-dimethyl- and *N,N*-dimethylamidophosphoric acids sodium salts. Preparation and hydrolysis

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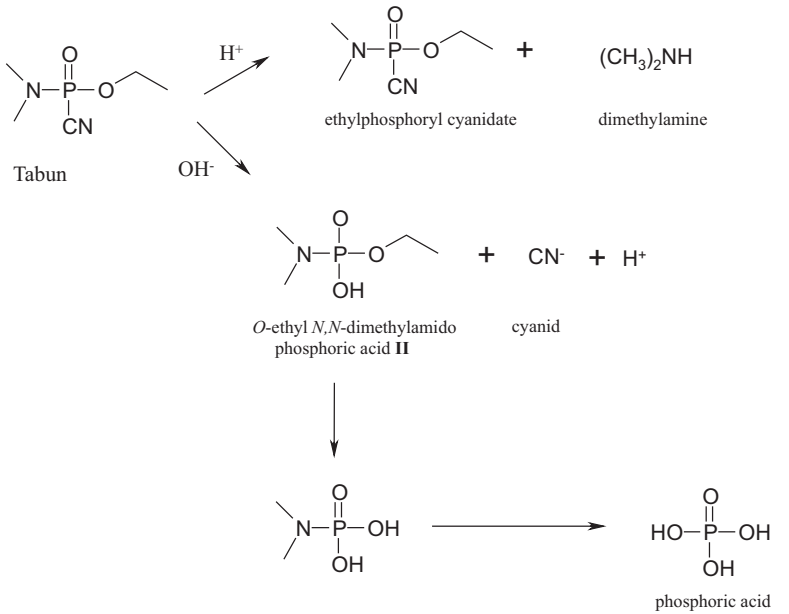
Abstract: Sodium salts of ethyl *N,N*-dimethyl- and *N,N*-dimethylamidophosphoric acids I and II were obtained and their hydrolysis to respective acids was investigated. The salts and acids were characterized by spectral methods (MS, FT/IR, ^{1}H, ^{13}C, ^{31}P NMR).

Keywords: ethyl *N,N*-dimethylamidophosphoric acid, *N,N*-dimethylamidophosporic acid, preparation, sodium salts, hydrolysis

INTRODUCTION

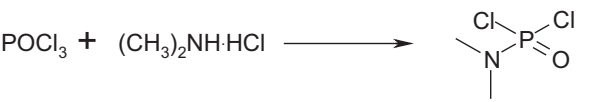
Working in the field of the degradation products of organophosphorous chemical warfare agents (CWA), we synthesized two derivatives of phosphoric acid: ethyl *N,N*-dimethyl- and *N,N*-dimethylamidophosporic acids **I** and **II**, which are formed in the neutral environmental hydrolysis of tabun. The initial step of this hydrolysis is very rapid and leads to hydrogen cyanide and **I**. Further decomposition of the latter to **II** and then, finally, to phosphoric acid, is much slower. Under neutral and basic conditions this is a predominant course of hydrolysis, but under acidic conditions ethylphosphoryl cyanidate and dimethylamine are formed [1, 2]. The possible pathways of tabun hydrolysis are depicted in Scheme 1.



Scheme 1. Hydrolysis of tabun in the environment [1, 2].

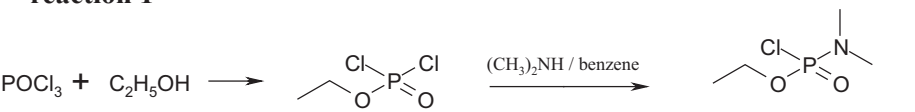
RESULTS

We started from the preparation of *N,N*-dimethylamidophosphoric dichloride **III** (obtained from $POCl_3$ and dimethylamine hydrochloride – reaction 1), and ethyl *N,N*-dimethylamido-chlorophosphate **IV** (obtained by coupling ethyl dichlorophosphate with dimethylamine – reaction 2) [3-5].



N,N-dimethylaminophosphoric dichloride **III**

reaction 1

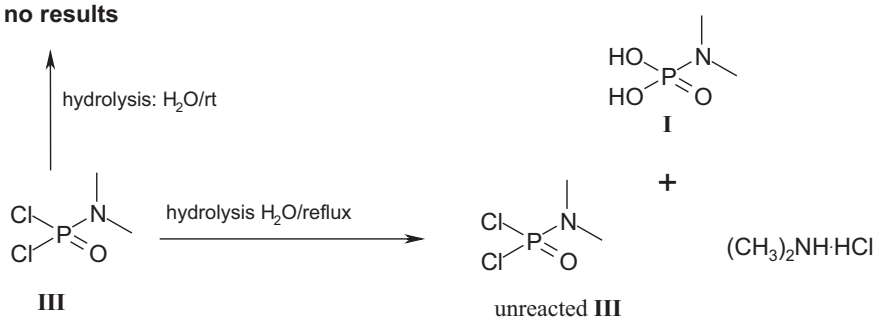


ethyl dichlorophate

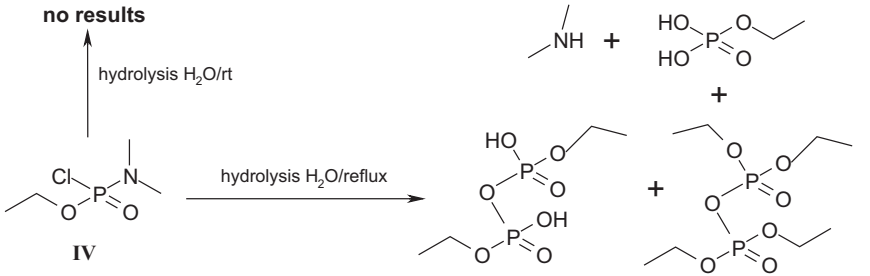
ethyl *N,N*-dimethylamido--chlorophosphate **IV**

reaction 2

The obtained chloroamidates were next hydrolyzed by water, at room temperature. However, the attempts to obtain in this way acid **I** from **III,** and acid **II** from **IV**, failed. When **IV** was stirred with stoichiometric amount of water (1 h, at rt), no progress of hydrolysis was observed, and only a substrate radical ion signal (*m/z* 171, $M^{+\cdot}$) was detected in MS spectra (EI technique). The next trial to hydrolyze **IV** (1h, reflux) resulted in degradation of the sample. MS analysis of post-reaction mixture confirmed a presence of several by-products: dimethylamine(*m/z* 44 $[M-1]^+$, molecular ion *m/z* 45, $M^{+\cdot}$), ethyl phosphate (*m/z* 127 $[M+1]^+$, no molecular ion of *m/z* 126, $M^{+\cdot}$), diethylphosphoric anhydride (*m/z* 290, molecular ion of $M^{+\cdot}$, fragments, *m/z*: 263, 235, 207, 179, 161), and ethylphosphoric anhydride (*m/z* 235 $[M+1]^+$, no molecular ion of *m/z* 234, $M^{+\cdot}$). When the similar conditions (3h, reflux) of hydrolysis were used for *N,N*-dimethylamidophosphoric acid dichloride **III**, MS analysis of post-reaction mixture gave, among the others, a signal of *m/z* 126, which was attributed to the expected diacid **I** as *m/z* $[M+1]^+$ of a molecular ion *m/z*125, $[M^{+\cdot}]$. Schematically, the neutral hydrolysis results of **III** and **IV** are depicted in the Schemes 2 and 3.

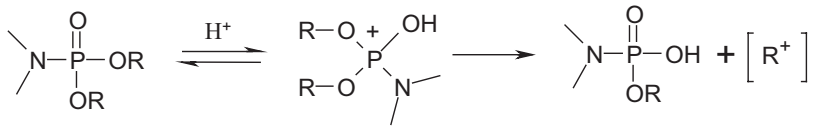


Scheme 2. Neutral water hydrolysis of *N,N*-dimethylamidophosphoric dichloride **III**.



Scheme 3. Neutral water hydrolysis of ethyl *N,N*-dimethylamidochlorophosphate **IV.**

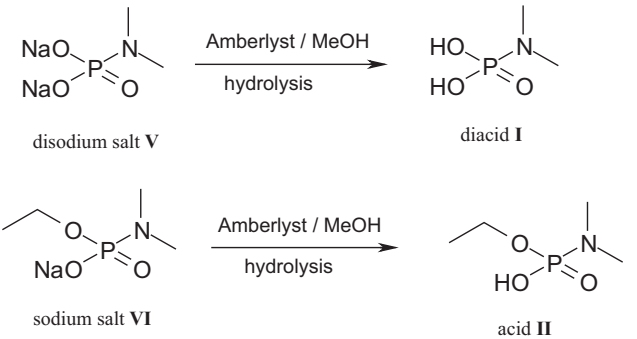
T.A. Modro [6] in 1980 reported a strong acid-catalyzed solvolysis of *O,O*-dialkyl *N,N*-dialkylamidophosphates, leading to monoalkylated *N,N*-dialkylamidophosphoric acids of type **I**. As a strongly acidic, but poorly nucleophilic medium for reaction performance was used trifluoromethanesulphonic acid (Scheme 4). The author explained a mechanism of the presented hydrolysis by the stability of P-N bond and alkyl-oxygen cleavage in the applied conditions.



R = CH_3, C_2H_5, i-C_3H_7

Scheme 4. Strong acid catalyzed hydrolysis of dialkylphosphoroamidates [6].

The acids of the type **I** and **II**, not possessing sterically demanding groups are not very stable and easily undergo the degradation [6-10]. According to the work of Quin and Jankowski [7] we converted chloroamidates **III** and **IV** to their sodium salts **V** and **VI** by a basic hydrolysis. The reaction proceeds easily and efficiently for both of them, as was expected. Structures of the resulted products were confirmed by MS ESI (negative ions polarity) – for **V** it was detected at *m/z* 124 $(M-2Na+H)^-$ and 170 $(M-H)^-$, for **VI** it was detected at *m/z* 152 $(M-Na)^-$. The obtained salts underwent next a careful acidic hydrolysis, carried out by direct passing a methanol solution of **V** or **VI** through a layer (height 20 cm, diameter 10 mm) of ion exchange resin Amberlyst 15, what led to the acids **I** and **II**, respectively (reaction 3).



reaction 3

Structure of the acids was confirmed by MS EI spectra: *m/z* 126 $[M+1]^+$ for **I** (what is in accordance with a previous MS data for this acid obtained in the neutral hydrolysis, described above), and *m/z* of a molecular ion 153 $[M^{+\cdot}]$, attributed to the acid **II** [11]. Unfortunately, for the MS spectra of acid **II**, there were also detected the additional low intensity signals descending from the by-products (*m/z* 113, *m/z* 141, *m/z* 245, *m/z* 288). Additionally, we derivatized an acid **II** with trimethylsilyldiazomethane, and the obtained *O*-ethyl-*O*-methyl *N,N*-dimethyl-amidophosphonate structure was confirmed by GC/MS (*m/z*: molecular ion of 167 $[M^{+\cdot}]$).

The LC ESI/MS analysis of acids **I** and **II** was reported by Smith and Shih in the article from 2005 [11]. The authors, among the other data, presented the spectra of ethyl *N,N*-dimethylamidophosphoric acid **II** (the observed signals of *m/z* 154 derived from $[M+H]^+$, *m/z*176 $[M+Na]^+$, *m/z*198 $[(M-H+Na]^+$.

SUMMARY

On the basis of the existing literature data concerning a chemistry of *N,N*-dialkylamidophosphoric acid derivatives, we obtained sodium salts **V** and **VI.** Acidic hydrolysis of them done with Amberlyst 15 H^+/methanol led to respective acids **I** and **II.** Both synthesized salts and acids were characterized by spectral methods (MS ESI, MS EI, FT/IR, ^1H, ^{13}C, ^{31}P NMR).

EXPERIMENTAL

General procedures

All reagents were of commercial quality: $POCl_3$ (>95%), (97%), dimethylamine (>99%), dimethylamine hydrochloride, trimethylsilyldiazomethane/diethyl ether solution, were from Sigma-Aldrich, Amberlyst 15 H^+ form (20-50 mesh) – from Fluka, benzene p.a., ethanol, methanol, ethyl acetate p.a. – from POCh, anhydrous magnesium sulfate p. a., sodium hydroxide p.a., P_2O_5 and hexane (fraction from petroleum) – from Chempur. GC: Hewlett-Packard HP 6890 apparatus, injector coc type, detector FID, column Megabore HP-1 (15 m x 0.53 mm), film thickness 1.50 μm, temperature programme: 70 °C (3 min) – 240 °C (20°/min) – 240 °C (5 min), detector temperature 270 °C. MS EI, 70 eV, ion source temperature 250 °C, selective mass detector of Agilent Technologies MSD type 5975B, coupled with device HPP7 of Scientific Instrument Services for direct sample introduction. GC/MS EI, 70 eV, ion source temperature 230 °C:

selective mass detector of Agilent Technologies MSD type 5975B, coupled with gas chromatograph Agilent Technologies 6890N Network GC System, equipped with split/splitless detector; capillary column DB-5MS (30 m x 0.25 mm, film 0.25 μm), conditions 50 °C (3 min) – 240 °C (10 °/min), injector temp. 240 °C, detector temp. 240 °C, inert gas: helium, split: 50/1.

MS ESI (negative Q1 MS scan type): apparatus of Applied Biosystems, model 4000 QTRAP, FT/IR: Jasco FT/IR 420 apparatus, method – KBr pellets or film between KBr plates. ^{1}H, ^{13}C, ^{31}P NMR: INOVA-500, "varian500" (operating at 500 MHz for proton, 200 MHz for phosphorous and 125 MHz for carbon spectra), analyses performed in deuterated chloroform or deuterated methanol, TMS as internal reference.

***N,N-*(dimethyl)amidophosphoric dichloride III**

Phosphorous oxychloride $POCl_3$ (3.12 mol, 478.3 g, 285.6 mL) and dimethylamine hydrochloride (0.6 mol, 48.9 g) were placed in 750 mL glass reactor, equipped with reflux condenser connected with HCl absorber, mechanical stirrer and thermometer. The mixture was kept under reflux (temp. rose from 90 to 105 °C) for 8.5 h. The excess of $POCl_3$ was distilled off (40 °C/200 mm Hg), and a crude product was purified by repeated fractional distillation to give 53.9 g of *N,N*-(dimethyl)amidophosphoric dichloride (b.p. 82 °C/15 mmHg, yield 55.3% n_D^{20} 1.4634; GC/MS EI, *m/z*: molecular ion 161($M^{+\cdot}$), 126(100%), 117, 110, 97, 90, 83, 76, 66, 60, 47; purity by GC: 98.6%; FT/IR [cm^{-1}]: 558 (P-Cl), 726, 992, 1264, 1309 (P=O), 1460 (CH_3), 2930, 3415 (low :$(CH_3)_2N$); NMR [ppm]: ^{31}P: 16.6(s,1P); ^{13}C: 36.55(s, 1C), 36.58(s, 1C); ^{1}H: 2.86 (s, 3H), 2.89 (s, 3H).

Ethyl dichlorophosphate

Phosphorous oxychloride $POCl_3$ (1.18 mol, 182.4 g, 109.0 mL) was placed in 750 mL glass reactor, equipped with mechanical stirrer, dropping funnel and thermometer and cooled to 0 °C (ice bath). Keeping the temperature below 5 °C, ethanol (58.6 g, 1.27 mol, 63.5 mL) was then carefully dropped to intensively stirred $POCl_3$ (for 1.5 h). Reaction was continued for the next 2 h at this temperature, and left overnight at rt. Product was purified by distillation to obtain 109.9 g (b.p. 61- 64 °C/p17 mmHg, n_D^{20} 1.4341, yield 57.7%).

Ethyl (*N,N*-dimethyl)amidochlorophosphate IV

A solution of ethyl dichlorophosphate (0.51 mol, 83.0 g) in 250 mL of benzene was placed in 750 mL glass reactor, equipped with mechanical stirrer, dropping funnel and thermometer, and cooled to -5 °C (ice/NaCl bath). Next, 23.0 g (0.51 mol) of 20% (w/v) dimethylamine solution in benzene was carefully

dropped, at temperature 0-5 °C. The mixture was then stirred for 3 h at rt and filtrated through the Schott funnel. Solvent was distilled off. From 68.3 g of the residual mixture after distillation was obtained 54.3 g of pure product (b.p. 66-70 °C/0.3 mmHg, purity by GC: 95.9%, yield 62%, n_D^{20} 1.4391). GC/MS EI, *m/z*: molecular ion ($M^{+\cdot}$)171, 1Cl, 142, 136, 126, 108, 92, 44 (100%); FT/IR [cm^{-1}]: 528 (P-Cl), 720, 788, 1000, 1040 (P-OAlk), 1181, 1265, 1305 (P=O), 1457(CH_3), 2939 (CH_2), 3500, 3585 (low $(CH_3)_2N$); NMR [ppm]: ^{31}P: 15.2 (s, 1P); ^{13}C: 15.3(s, 1C), 36.08(s, 1C), 36.09(s, 1C), 63.8(s, 1C, CH_2); ^{1}H: 1.38(t, 3H, J= 7.2), 2.71(s, 3H), 2.74(s, 3H), 4.21 - 4.28(m, 2H).

Disodium salt of *N,N*-(dimethyl)amidophosphoric acid V

N,N-(dimethyl)amidophosphoric acid dichloride (4.05 g, 50 mmol) was added to a stirred solution of 4.0 g (0.1 mol) of NaOH in 120 mL of 1:1 water-acetone solution. Mixture was then stirred for 15 min and solvents were evaporated. The solid residue was dried in dessicator over P_2O_5, then product was separated from NaCl by washing crude solid with methanol. After NaCl filtration off, solution was concentrated to dryness, and product was dried in dessicator to costant weight; 4.04 g of expected salt was obtained (yield 95.5%); MS ESI, negative ions: 75, 91, 113, 124 $(M - 2Na + H)^-$, 157, 170 (M - H); FT/IR [cm^{-1}]: 699, 954, 983, 1075, 1115 (P=O), 1160, 1460(CH_3), 1640, 2930, 3302 (strong and wide $(CH_3)_2N$ signals); NMR (deuterated CH_3OH), [ppm]: ^{31}P: 14.18 (s,1P); ^{13}C: 39.76 (s, 2C); ^{1}H: 2.53 (s, 3H), 2.55 (s, 3H).

Sodium salt of ethyl *N,N*-(dimethyl)amidophosphate VI

To 8.6 g (50 mmol) of ethyl *N,N*-(dimethyl)amidochlorophosphate, placed in 250 mL Erlenmayer flask, 4 g (0.1 mmol) of NaOH in 120 mL of 1:1 water-aceton solution was slowly added. The mixture was then stirred for 15 min, solvents were evaporated, and the residue was washed with anhydrous ethanol (50 mL). NaCl was filtered off, and the remaining solution was concentrated to dryness, and product was additionally dried over P_2O_5 in dessicator to obtain finally 8.3 g of expected sodium salt VI (yield 95%). MS ESI, negative ions: 115, 129, 152 $(M - Na)^-$, 221, 255, 283, 301, 353; FT/IR [cm^{-1}]: 769, 940, 989, 1058, 1080 (P-OAlk), 1213(P=O), 1290, 1390, 1460(CH_3), 1640, 2800-2980(CH_2), 3415; NMR (deuterated CH_3OH ,TMS), [ppm],: ^{31}P: 11.36 (s, 1P); ^{13}C: 17.2(s, 1C), 38.23(s, 1C), 38.26(s,1C), 61.28 (s,1C, CH_2); ^{1}H: 1.21(t, 3H, J=7.5), 2.61(s, 3H), 2.63(s, 3H), 3.81-3.84(m, 2H).

Hydrolysis of disodium salt V with Amberlyst 15 to acid I

Amberlyst 15 was first washed exhaustively with methanol and then dried at

120 °C in the oven before use. Amberlyst (1.9 g) prepared, as above described, was placed onto a glass column. Then, a solution of disodium salt **I** (0.53 g) in 20 mL of methanol was poured directly on catalyst. Solution passed through an ionic catalyst was collected, and additional 50 mL of methanol was put on the column to collect next fraction. Both fractions were put together and passed again through a column, following by filtration through a filtrate paper. After concentration on rotavapor 0.36 g of sticky, cloudy white oil was obtained, which was characterized as expected acid I. MS EI, *m/z*: 126 $[M+1]^+$, 96, 82 (100%), 65, 50; IR [cm^{-1}]: 518, 782, 930, 1055, 1180, 1470(CH_3), 1640, 2480 (P-OH), 2788, 2960, 3020, 3400; NMR (TMS, deuterated CH_3OH,) [ppm]: ^{31}P 3.12 (s, 1P), -7.66 -7.81 (d, 1P) – results show that compound is contaminated; ^{13}C: 35.5 (s, 2C); ^{1}H: 3.52(s, 3H), 3.54(s, 3H).

Hydrolysis of sodium salt VI with Amberlyst 15 to acid II

1.14 g of **VI** was dissolved in 5 mL of methanol and poured on the glass column fitted with 2 g of previously washed and dried Amberlyst 15, following by the passing through the column an additional 150 mL of methanol. After concentration of the resulted solution on rotavapor 1.16 g of product was obtained as a bright, oil residue. MS EI, *m/z:* 153(M^{+-}), 138, 124, 108, 82, 65, 44(100%), some other fragment ions detected: *m/z:* 113, 188, 245, 288, 290; FT/IR [cm^{-1}]: 798, 938, 980, 1059 (P-OAlk), 1236(P=O), 1390, 1470(CH_3), 1640, 2470, 2770, 2979(CH_2), 3430; NMR [ppm]: ^{31}P: -1.03 (s, 1P), -1.05, -0.97 – results show that compound is contaminated.

Acknowledgements

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