ACTA CHEMICA SCANDINAVICA 14 (1960) 1353—1356

Organophosphorus Analogues of Tropic Acid Esters

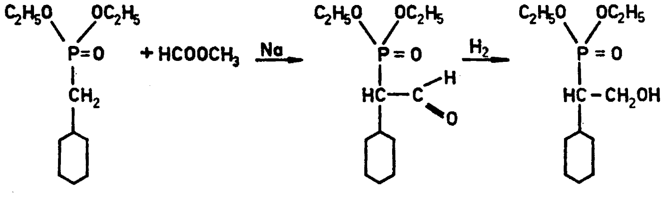
1. 2-Phenyl-2-diethoxyphosphoryl Ethanol

L.-E. TAMMELIN and L. FAGERLIND

Research Institute of National Defence, Dept. 1, Sundbyberg 4, Sweden

Phenyl-diethoxyphosphoryl methane, phenyl-diethoxyphosphoryl acetaldehyde and 2-phenyl-2-diethoxyphosphoryl ethanol have been prepared. Infrared spectra, protolytic titration, refractive index, and violet color reaction with iron(III)ions indicate that the aldehyde shows keto-enol tautomerism. The occurrence of tautomerism and the presence of a strong hydrogen bridge in the enol form, support the view that condensation of phenyl-diethoxyphosphoryl methane and methyl formate with sodium results in phenyl-diethoxyphosphoryl acetaldehyde. Catalytic hydrogenation of the aldehyde consequently yields 2-phenyl-2-diethoxyphosphoryl ethanol.

Organophosphorus analogues of acetylcholine have been shown to be of considerable chemical and pharmacological interest [1]. It thus seemed to be of value to prepare phosphoryl analogues to other pharmacodynamically active compounds. This investigation is part of a study on the preparation of organophosphorus analogues of atropine [2,3]. The main purpose with the present part was to show whether phosphoryl compounds react analogously to carbonyl compounds in the ester condensation and hydrogenation reactions used in preparation of tropic acid ester [4]. The following formulae show the sequence of preparations studied.



Carbon and hydrogen content of the obtained compounds, and the analogous reactions described in syntheses of tropic acid ester [4] *per se*, suggest that the studied reaction sequence really gives rise to 2-phenyl-2-diethoxyphosphoryl ethanol. However, the structure of the parent compound, phenyldiethoxyphosphoryl acetaldehyde, is of major importance for establishing the structure of the phenyldiethoxyphosphoryl ethanol. Thus the aldehyde was made the subject of the following supplementary determinations: Infrared spectrum, acid properties and reaction with iron chloride. Finally, the infrared spectrum of phenyl-diethoxyphosphoryl ethanol was recorded.

EXPERIMENTAL

Syntheses

Phenyl-diethoxyphosphoryl methane. Two moles of ethanol and two moles of triethylamine were dissolved in 1 l of ether in a round bottomed flask with stirring. One mole of benzyl phosphoryldichloride was added (prepared according to Kinnear and Perren [5]). The triethylammonium chloride formed was filtered off, and the ester separated by fractional distillation, b.p. 115°/0.2 mm Hg. Phenyl-diethoxyphosphoryl methane is a colorless oil with a geranium-like odour. Refractive index $n_D^{25} = 1.4960$. (Found: C 57.8; H 7.52. Calc. for $C_{11}H_{17}O_3P$ (228.2): C 57.8; H 7.52). Yield 80 %.

Phenyl-diethoxyphosphoryl acetaldehyde. 1.0 moles of sodium were allowed to react with 2 moles of methyl formate in 200 ml ether, in a round bottomed flask with reflux condenser. 1 mole of phenyl-diethoxyphosphoryl methane, together with 250 ml of ether, was added when all sodium had been consumed. The mixture was boiled for 4 h and then stirred at room temperature for 24 h, after which the ether solution was extracted with 2 × 200 ml of water. pH of this extract was adjusted to $\sim$10 and the solution extracted with 3 × 100 ml of ether, the ether extracts being discarded. The aqueous solution was acidified with sulfuric acid to pH $\sim$3 and percolated with ether for 12 h. The ether extract thus obtained was evaporated, giving a viscous residue. The residue was dissolved in benzene and the benzene evaporated; this operation was repeated. Finally, the product was distilled at 110°/0.2 mm Hg, the first 5 ml of distillate being discarded. A few brown drops remained in the distillation flask. The phenyl-diethoxyphosphoryl acetaldehyde preparation thus obtained is an oil with a roselike odour. Refractive index is $n_D^{25} = 1.5195$ immediately after distillation, but increases with time and after a week becomes constant at $n_D^{25} = 1.5320$. After a few days of storage at $n_D^{25} = 1.5320$ the compound solidifies to crystals (m.p. 58°C). (Found C 56.3; H 6.61. Calc. for $C_{12}H_{17}O_4P$ (256.2): C 56.3; H 6.68). Yield: 50 %.

2-Phenyl-2-diethoxyphosphoryl ethanol. Phenyl-diethoxyphosphoryl acetaldehyde in ethanol solution was hydrogenated with hydrogen at 50 atm and 70°C for five days, using Adams platinum catalyst. The alcohol was purified by fractional distillation (b.p. 130°C/0.1 mm Hg), and is a liquid with $n_D^{25} = 1.5040$. (Found: C 55.3 H 7.5 Calc. for $C_{12}H_{19}O_4P$ (258.2): C 55.8; H 7.37). Yield 90 %.

Verification of purity and chemical structure

Phenyl-diethoxyphosphoryl acetaldehyde (51 mg + 1 ml C_2H_5OH + 39 ml 0.1 M KCl) was titrated with 0.1 M NaOH. The sodium hydroxide was added in 0.1 ml portions every third minute.

One drop of 5 % $FeCl_3$ solution was added to 5 ml 1 % aqueous solution of the aldehyde.

Infrared spectra of the aldehyde and ethanol were recorded with a Perkin and Elmer Mod 21 spectrophotometer. 0.2 M solutions in carbon tetrachloride were used. The spectrophotometer was used with a sodium chloride prism, resolution 927, response 2 : 1170, gain 5.7, speed 5, suppression 3, and scale 5 cm/μ. The thickness of the cell was about 0.1 mm.

RESULTS

Phenyl-diethoxyphosphoryl methane, phenyl-diethoxyphosphoryl acetaldehyde and phenyl-diethoxyphosphoryl ethanol have been prepared.

Sodium dissolves in phenyl-diethoxyphosphoryl methane in 10 % ether solution under formation of hydrogen and a white precipitate.

Phenyl-diethoxyphosphoryl acetaldehyde in aqueous solution reacts as an acid, and can thus be determined titrimetrically with sodium hydroxide. 95 % of the actual preparation reacted as acid ($pk_a \sim 7$). In aqueous solution, the aldehyde also forms a brilliant violet complex with iron (III) ions. On extraction with chloroform, the chloroform becomes purple.

The infrared spectrum of phenyl-diethoxyphosphoryl acetaldehyde exhibited the following characteristic features: Absorption bands at 2 800—2 600 cm^{-1} indicating a hydrogen bonded hydroxyl group, at 1 725 cm^{-1} indicating a carbonyl group, at 1 630 cm^{-1} indicating a carbon-carbon double bond, and at 1 200 cm^{-1} indicating a strongly hydrogen bonded phosphoryl group.

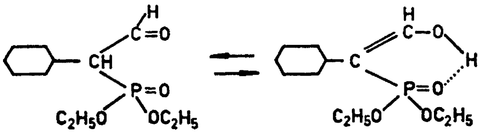
The infrared spectrum of the 2-phenyl-2-diethoxyphosphoryl ethanol showed the following characteristic features: Absorption bands at 3 500—3 200 cm^{-1} indicating a hydroxyl group with weak hydrogen bond, at 1 250 cm^{-1} indicating a normal phosphoryl group, but no bands at 1 725 cm^{-1} or 1 630 cm^{-1} which indicates that the aldehyde has been hydrogenated. Infrared spectra and a more thorough interpretation of them are given in part 2 of this investigation[2].

DISCUSSION

Phenyl-diethoxyphosphoryl methane apparently contains a reactive hydrogen atom, presumably situated in the methane residue. The structure of the condensation product from phenyl-diethoxyphosphoryl methane and methylformate is of major importance for the confirmation of the structure of the corresponding ethanol.

The first problem was to obtain the phenyl-diethoxyphosphoryl acetaldehyde sufficiently pure for identification. Distillation at 110°C and 0.2 mm Hg is a poor method for fractionation, and the carbon-hydrogen content a poor indicator of purity if, which is reasonable, phenyl-diethoxyphosphoryl methane is the main impurity. However, the protolytic titration method employed solved this problem.

Refractive index of the aldehyde increased with time after distillation. Simultaneously, an increase in the absorption band of hydroxyl in the infrared spectrum was observed [2]. This, together with the other results, strongly suggests that the aldehyde shows keto-enol tautomerism. Moreover, the infrared spectrum indicates a strong hydrogen bond between the enol hydroxyl group and the phosphoryl group, which suggests a sixmembered chelate ring with conjugated double bonds. The only structure which fits all these facts is the following, which is also analogous to the intermediate product in the syntheses of tropic acid.



Simpler hydrogenation methods for the aldehyde than the catalytic hydrogenation used in preparation of the phenyl-diethoxyphosphoryl ethanol may exist. However, it was felt that a simple addition of hydrogen is the best way to establish the structure of the ethanol. The infrared spectrum of the ethanol supports the view that in total a hydroxymethylene group has been introduced at the carbon atom between the phenyl and phosphoryl groups.

Our sincere thanks are due to the Director of this Institute, Professor G. Ljunggren, for his kind interest in this work.

REFERENCES

1. Tammelin, L. E. *Svensk Kem. Tidskr.* **70** (1958) 157.
2. Larsson, L. and Tammelin, L. E. *Acta Chem. Scand. In press.*
3. Tammelin, L. E. and Fagerlind, L. *Acta Chem. Scand. In press.*
4. Müller, E. *Ber.* **51** (1918) 254.
5. Kinnear, A. M. and Perren, E. A. *J. Chem. Soc.* **1952** 3437.

Received March 17, 1960.