SYNTHESIS AND STUDY OF THE ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF SOME PHOSPHINIC ACID ESTERS

B. K. Beznosko,[1] V. M. Usanova,[1] L. V. Zhuravleva,[1] V. E. Baulin,[1] A. N. Yarkevich,[1] V. Kh. Syundyukova,[1] and E. N. Tsvetkov[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 31, No. 12, pp. 12 – 14, December, 1997.

Original article submitted October 2, 1995.

As is known, 1,1-dimethyl-3-oxobutylphosphonic acid dimethyl ester (dimephosphon) exhibits antiinflammatory properties, although the mechanism of its action differs from that known in classical nonsteroidal drugs [1]. Recently we have demonstrated that some alkyldiphenylphosphin oxides possess antiinflammatory and/or analgesic properties [2]. The most active of these compounds, isoamyldiphenylphosphin oxide, has rather low toxicity and is comparable in its activity with acetylsalicylic acid. In contrast to the latter acid, this oxide produces no ulcerogenic effect even at a dose of 1/3 LD_{50}. Therefore, it was of interest to continue the search for new antiinflammatory and analgesic agents in the series of phosphoryl-containing compounds.

The purpose of this work was to study the antiinflammatory and analgesic properties and the acute toxicity of some alkyl and acryl esters of diphenylphosphinic (I – XVII) and dibutylphosphinic (XVIII) acids.

Most of the esters of diphenyl- and dibutylphosphinic acids were obtained by interactions of their chloroanhydrides with the corresponding alcohols or phenols in the presence of bases (triethylamine or pyridine) in a benzene medium:

$$R_2P(O)Cl + R'OH \xrightarrow[\text{benzene}]{Et_3N \text{ or pyridine}} R_2P(O)OR'$$

I, III – XIV, XVIII

I: R = Ph, R′ = Me;
III: R = Ph, R′ = Pr;
IV: R = Ph, R′ = *i*-Pr;
V: R = Ph, R′ = Bu;
VI: R = Ph, R′ = C_5H_{11};
VII: R = Ph, R′ = *i*-C_5H_{11};
VIII: R = Ph, R′ = C_6H_{13};
IX: R = Ph, R′ = C_7H_{15};
X: R = Ph, R′ = C_9H_{19};
XI: R = R′ = Ph;
XII: R = Ph, R′ = 4-$MeO_2ClC_6H_4$;
XIII: R = Ph, R′ = 2-$MeO_2ClC_6H_4$;
XIV: R = Ph, R′ = 2-ClC_6H_4;
XVIII: R = R′ = Bu.

[1] Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Moscow Oblast, Russia.

Compound II was obtained by interaction of diphenylphosphinic acid with ethylorthoformate:

$$Ph_2P(O)OH + (EtO)_3CH \longrightarrow Ph_2P(O)OEt$$

II

Phosphinic acid esters XV – XVII were synthesized from di(*p*-tolyl)phosphinic acid without isolation of the corresponding chloroanhydride:

$$(4\text{-}MeC_6H_4)_2P(O)OH \xrightarrow[2.\ R^2OH,\ \text{pyridine}]{1.\ PCl_5} (4\text{-}MeC_6H_4)_2P(O)OR^2$$

XV – XVII

XV: R^2 = Et; XIV: R^2 = Bu; XVII: R^2 = 4-$O_2NC_6H_4$.

EXPERIMENTAL CHEMICAL PART

The syntheses were performed with anhydrous solvents in a dry argon atmosphere. The column chromatography was conducted with a silica gel of the L grade (100 – 160 μm) using chloroform as the eluent. The ^1H and ^{31}P NMR spectra were recorded on a Bruker CXP-200 spectrometer using TMS and 85% phosphoric acid as the internal standards. The melting temperatures were determined on a Boetius PHMK-05 heating stage. The data of elemental analyses coincide with the results of calculations according to the empirical formulas.

Diphenylphosphinic acid methyl ester (I). To a solution of 0.032 mole of diphenylphosphinic acid chloroanhydride [3] in 50 ml benzene were sequentially added dropwise 0.034 mole of absolute methanol and 0.034 mole of triethylamine. The reaction mixture was boiled with stirring for 2 h and cooled to room temperature. Then 75 ml of water was added and the mixture was acidified to pH 2 with concentrated hydrochloric acid. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated in vacuum. The residue was chromatographed on a column filled with silica gel. Yield of ester I, 76%; m.p., 55 – 57°C (ether – pentane); reported b.p., 178°C/2 Torr [4]. Esters

0091-150X/97/3112-0638$18.00

III – XIV and XVIII were obtained using analogous procedures.

Diphenylphosphinic acid ethyl ester (II). To 0.01 mole of diphenylphosphinic acid were added 25 ml of ethylorthoformate; the reaction mixture was boiled for 4 h, and the 75 – 100°C fraction was distilled off and evaporated in vacuum. The residue was chromatographed on a column filled with silica gel. Yield of ester II, 78%; m.p., 39 – 41°C (pentane); reported b.p., 173 – 175°C/1.5 Torr [5].

Diphenylphosphinic acid propyl ester (III). Yield, 71%; m.p., 89 – 91°C (benzene – hexane); reported m.p., 89.5 – 91°C [6].

Diphenylphosphinic acid propyl ester (IV). Yield, 74%; m.p., 98 – 99°C (benzene – hexane); reported m.p., 97 – 99°C [4].

Diphenylphosphinic acid butyl ester (V). Yield, 69%; m.p., 91 – 93°C (benzene – heptane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.90 (m, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 4.00 (m, 2H, OCH_2), 7.48 (m, 6H, $H_{arom.}$), 7.88 (m, 4H, H_{arom}); ^{31}P NMR spectrum $CDCl_3$ (δ, ppm): 30.05.

Diphenylphosphinic acid amyl ester (VI). Yield, 60% (oil); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.90 (m, 3H, CH_3), 1.30 (m, 4H, $2CH_2$), 1.68 (m, 2H, CH_2), 4.00 (m, 2H, OCH_2), 7.48 (m, 6H, $H_{arom.}$), 7.88 (m, 4H, H_{arom}); ^{31}P NMR spectrum $2CDCl_3$ (δ, ppm): 29.97.

Diphenylphosphinic acid isoamyl ester (VII). Yield, 67%; m.p., 43 – 45°C (hexane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 1.00 (m, 6H, $2CH_3$), 1.70 (m, 2H, CH_2), 1.8 (m, 1H, CH), 4.04 (m, 2H, OCH_2), 7.54 (m, 6H, $H_{arom.}$), 7.92 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum $CDCl_3$ (δ, ppm): 29.87.

Diphenylphosphinic acid hexyl ester (VIII). Yield, 64% (oil); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.90 (m, 3H, CH_3), 1.40 (m, 6H, $3CH_2$), 1.80 (m, 2H, CH_2), 4.08 (m, 2H, OCH_2), 7.58 (m, 6H, $H_{arom.}$), 7.96 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum $2CDCl_3$ (δ, ppm): 29.93.

Diphenylphosphinic acid heptyl ester (IX). Yield, 70% (oil); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.92 (m, 3H, CH_3), 1.35 (m, 8H, $4CH_2$), 1.74 (m, 2H, $2CH_2$), 4.04 (m, 2H, OCH_2), 7.54 (m, 6H, $H_{arom.}$), 7.92 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum $2CDCl_3$ (δ, ppm): 29.87.

Diphenylphosphinic acid nonyl ester (X). Yield, 76% (oil); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.90 (m, 3H, CH_3), 1.36 (m, 12H, $6CH_2$), 1.76 (m, 4H, CH_2), 4.08 (m, 2H, OCH_2), 7.52 (m, 6H, $H_{arom.}$), 8.00 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum $CDCl_3$ (δ, ppm): 30.01.

Diphenylphosphinic acid phenyl ester (XI). Compound XI was obtained from diphenylphosphinic acid chloroanhydride and phenol. Yield, 76%; m.p., 134 – 136°C (benzene – hexane); reported m.p., 135 – 136°C [4].

Diphenylphosphinic acid (4-methoxycarbonyl)phenyl ester (XII). Yield, 71%; m.p., 129 – 131°C (benzene – hexane).

Diphenylphosphinic acid (2-methoxycarbonyl)phenyl-ester (XIII). Yield, 61%; m.p., 91 – 92°C (benzene – hexane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 3.85 (s, 3H, CH_3), 7.22 – 8.00 (m, 14H, $H_{arom.}$); ^{31}P NMR spectrum, $CDCl_3$ (δ, ppm): 31.80.

Diphenylphosphinic acid (2-chloro)phenyl ester (XIV). Yield, 69%; m.p., 101 – 103°C (benzene – hexane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 2.40 (s, 6H, $2CH_3$), 7.24 (m, 6H, $H_{arom.}$); 7.78 (m, 4H, $H_{arom.}$); 7.34 (m, 2H, $H_{arom.}$); 8.14 (m, 2H, $H_{arom.}$); ^{31}P NMR spectrum $CDCl_3$ (δ, ppm): 34.34.

Di(4-tolyl)phosphinic acid ethyl ester (XV). To a suspension of 0.01 mole of di(4-tolyl)phosphinic acid [7] in 20 ml of benzene were added in portions with stirring 0.011 mole PCl_5, and the mixture was boiled for 30 min to complete the reaction. Then the solvent and $POCl_3$ were distilled off in vacuum. To the oily residue dissolved in 20 ml of benzene was added with stirring and cooling (5 – 10°C) a mixture of 0.01 mole of pyridine and 0.012 mole of absolute ethyl alcohol in 5 ml of dry benzene. The reaction mixture was allowed to stand for 2 h and evaporated in vacuum. The residue was dissolved in 30 ml of chloroform, washed with water (2 × 20 ml), concentrated to a small volume, and chromatographed on a column. Yield of ester XV, 84%; m.p., 63 – 65°C (hexane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 1.34 (t, 3H, CH_3), 2.34 (s, 6H, $2CH_3$), 4.08 (q, 2H, CH_2O), 7.24 (m, 4H, $H_{arom.}$), 7.70 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum, $CDCl_3$ (δ, ppm): 30.72.

Di(4-tolyl)phosphinic acid butyl ester (XVI). Obtained similarly to compound XV. Yield of ester XVI, 58% (oil); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 0.91 (mt, 3H, CH_3), 1.44 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 2.37 (s, 6H, $2CH_3$), 4.02 (m, 2H, CH_2O), 7.24 (m, 4H, $H_{arom.}$), 7.70 (m, 4H, $H_{arom.}$); ^{31}P NMR spectrum, $CDCl_3$ (δ, ppm): 32.52.

Di(4-tolyl)phosphinic acid 4-nitropenyl ester (XVII). Obtained similarly to compound XV. Yield of ester XVII, 80%; m.p., 136 – 137°C (benzene – heptane); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 2.40 (s, 6H, $2CH_3$), 7.24 (m, 6H, $H_{arom.}$), 7.78 (m, 4H, $H_{arom.}$), 7.34 (m, 2H, $H_{arom.}$), 8.14 (m, 2H, $H_{arom.}$); ^{31}P NMR spectrum, $CDCl_3$ (δ, ppm): 34.34.

Dibutylphosphinic acid butyl ester (XVIII). Compound XVIII was obtained from dibutylphosphinic acid chloroanhydride [3] and butanol. Yield, 65%; m.p., 91 – 93°C (benzene – hexane); reported b.p., 125 – 126°C/1 Torr [8].

EXPERIMENTAL PHARMACOLOGICAL PART

The acute toxicity of the synthesized compounds was determined by single intraperitoneal injections to white male mongrel mice weighing 20 – 24 g. The animals were observed during 14 days and the LD_{50} values were calculated according to the Litchfield – Wilcoxon method [9] using a Nord-10 computer. The acute toxicity of compounds XIV, XV, and XVII was only assessed by injecting them at a dose of 2500 mg/kg.

The antiinflammatory properties were studied on white male mongrel rats weighing 110 – 140 g. A model of acute edema was induced by subplantar 0.1 ml injections of 1%

TABLE 1. Antiinflammatory and Analgesic Activity of Phosphinic Acid Esters

Compound	LD_{50}, mg/kg	Effective dose ED_{50}, mg/kg			
		inhibition of agar-induced edema	reduction of convulsions induced by		increasing stay on hot plate
			acetic acid	acetylcholine	
I	675	n/a	30	130	52
II	931	n/a	16.5	220	210
III	–	n/a	350	n/a	n/a
IV	2343	n/a	n/a	190	270
V	1922	n/a	105	n/a	125
VI	2667	n/a	n/a	n/a	330
VII	–	n/a	n/a	130	280
VIII	–	n/a	n/a	n/a	n/a
IX	–	n/a	n/a	n/a	n/a
X	–	n/a	n/a	n/a	n/a
XI	5000	n/a	66	n/a	n/a
XII	–	n/a	n/a	n/a	n/a
XIII	–	n/a	n/a	n/a	n/a
XIV	>2500	350	135	n/a	210
XV	>2500	n/a	64	n/a	n/a
XVI	–	n/a	470	n/a	290
XVII	>2500	360	64	n/a	190
XVIII	1175	n/a	22	160	130
Analgin	3391	165	42	230	21

Notes: – not characterized for acute toxicity; (n/a) not active.

agar solution into hind paws. The edema growth was determined oncometrically as the difference between the paw volumes immediately before and 4 h after the agar injection.

The analgesic activity was determined on white male mongrel mice weighing 20 – 24 g using a model of convulsions induced by 0.2 ml injections of 0.75% acetic acid solution or acetylcholine (4 mg/kg) and a "hot-plate" model.

The test compounds were injected intraperitoneally with 1% starch jelly 1 h before the irritant injection or the pain induction.

The antiinflammatory and analgesic activity of the synthesized compounds was evaluated as ED_{50}, that is, the doses inhibiting the inflammation reaction, decreasing the amount of convulsions, or increasing the latent period (hot-plate test) by 50% with respect to the control level. Each dose was studied in a group of 6 – 10 animals. The ED_{50} values were determined graphically upon plotting the data obtained for 3 – 5 drug doses. The reference drug was represented by analgin.

The results of our experiments showed that all the synthesized compounds exhibited low toxicity, with the LD_{50} values exceeding 500 mg/kg [10]. Most of the compounds studied exhibited no antiinflammatory activity, except for XIV and XVII showing a weak effect.

As for the analgesic action with respect to the model of convulsions induced by acetic acid and the hot-plate test, compounds I, II, and XVIII were slightly superior to analgin. However, the latter reference drug showed a higher activity on the model of acetylcholine-induced convulsions (Table 1).

Thus, the class of phosphinic acid esters may have good prospects in the search for the new substances possessing analgesic activity.

REFERENCES

1. L. E. Ziganshina, I. A. Studentsova, and I. V. Zaikonnikova, *Farmakol. Toksikol.*, **1**, 58 – 60 (1990).
2. B. K. Beznosko, V. M. Usanova, L. V. Zhuravleva, et al., *Khim.-Farm. Zh.*, **24**(4), 22 – 23 (1990).
3. M. I. Kabachnik and E. N. Tsvetkov, *Dokl. Akad. Nauk SSSR*, **135**, 323 – 326 (1960).
4. K. D. Berlin, T. N. Austin, and M. Nagadhushanam, *J. Org. Chem.*, **30**(4), 1267 – 1268 (1965).
5. G. M. Kosolapoff and W. F. Huber, *J. Am. Chem. Soc.*, **69**(8), 2020 – 2021 (1947).
6. K. D. Berlin and R. U. Pagilagan, *J. Org. Chem.*, **31**(1), 129 – 131 (1967).
7. G. M. Kosolapoff and J. S. Powell, *J. Chem. Soc.*, 3535 – 3539 (1950).
8. G. M. Kosolapoff and J. F. McCullougt, *J. Am. Chem. Soc.*, **73**(11), 5392 – 5393 (1951).
9. M. L. Belen'kii, *Methods of Quantitative Assessment of the Pharmacological Effect* [in Russian], Medgiz, Leningrad (1963).
10. K. K. Sidorov, in: *Toxicology of New Commercial Chemicals* [in Russian], Issue 13, Meditsina, Leningrad (1973), pp. 47 – 51.