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Technical Note

Phosphorus–Nitrogen Compounds. 31. *N*-Phosphinylamino-1,2,5,6-tetrahydropyridines: Analgesic Activity and Effect on Blood Glucose[1]

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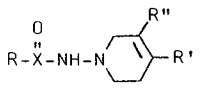
INTRODUCTION

This study is part of a continuing investigation to determine if phosphinyl agents possess properties similar to their carbonyl counterparts. The title compounds are representatives of a new type of chemical entity recently synthesized by the reduction of phosphinyliminopyridinium inner salts (phosphaminimides) (1). They are also phosphorus analogues of *N*-carbonylamino-1,2,5,6-tetrahydropyridines[5] in which a phosphinyl (P=O) moiety replaces a carbonyl (C=O) group.



Ia R = $(C_2H_5O)_2$, X = P, R' & R" = H
IIa R = C_2H_5O, X = C, R' & R" = H
Ib R = $(C_6H_5)_2$, X = P, R' + $CH_3C(O)$, R" = H
IIb R = C_6H_5, X = C, R' = $CH_3C(O)$, R" = H
Ic R = $(C_6H_5)_2$, X = P, R' = H, R" = CH_3
IIc R = C_6H_5, X = C, R' = H, R" = CH_3

Scheme I

The latter agents have been reported to possess antiinflammatory (2), analgesic (2), hyperglycemic, and hypoglycemic (2,3) properties.

The present research describes the preparation of an additional phosphinyl compound (Ib) and the results from testing it, and two previously reported agents of this nature (Ia and (Ic), for analgesic, hypoglycemic, and hyperglycemic properties. For purposes of comparison, three analogous carbonyl compounds (IIa–IIc), which were reported to have these activities (2,3), were resynthesized and similarly tested.

MATERIALS AND METHODS

The ^{1}H-NMR spectra were determined on a Nicolet NT-300 or a GE QE-300 spectrometer using tetramethylsilane as the internal standard and deuterated chloroform as the solvent. Chemical shifts are reported as δppm units, and coupling constants as Hz. The ir (potassium bromide) spectra were recorded on a Perkin–Elmer 283 spectrophotometer and absorptions are reported as cm^{-1}. Melting points were taken on a Thomas–Hoover apparatus and are corrected to reference standards. Ultraviolet spectra were determined on a Perkin–Elmer 200 and Bausch–Lomb Spectronic 20 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Norcross, Ga. Silica gel 60 (70–230 mesh) and neutral alumina (Brockman activity 1, 80–200 mesh) were used for column chromatography, with monitoring of eluants and the reaction mixture by the use of silica gel UV_{254} (Brinkmann Polygram) tlc plates.

4-Acetylethylene Ketal of *N*-[(Diphenylphosphinyl)imino]pyridinium Inner Salt (Id)

A solution of *O*-(mesitylenesulfonyl)hydroxylamine (4) (2.0 g, 9.3 mmol) in methylene chloride (20 ml) was added dropwise to a 0–5°C solution of 4-(1-ethylenedioxoethyl)pyridine (5) (1.53 g, 9.3 mmol) in methylene chloride (10 ml). After slowly warming to 20°C over 3 hr the reaction mixture gave a pale yellow solution which was diluted with methylene chloride (80 ml). Diphenylphosphinic chloride (3.5 g, 15 mmol) in methylene chloride (25 ml) and then triethylamine (2.5 g, 24.5 mmol) were added at 5–10°C with stirring. The reaction mixture was stirred at 20°C for 18 hr and the solvent removed under reduced pressure to yield a yellow mass. This material was chromatographed on silica gel using 2 and 5% methanol in chloroform and then rechromatographed on

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[5] The 1,2,5,6 numbering of the tetrahydropyridines, which gives the ring double bond the lowest number, is considered more correct than the 1,2,3,6 sequence previously assigned in Ref. 2.

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neutral alumina using 1% methanol in chloroform as the eluants to yield **Id**, which was triturated with ether to form a white solid. M.P., 133–134°C (dec.). Yield 1.7 g (48%). *Anal.* Found: C, 66.36; H, 5.60; N, 7.32 for $C_{21}H_{21}N_2O_3P$ requires C, 66.29; H, 5.57; N, 7.36. IR: 1620 (C=C), 1170, 1210 (P=O). NMR: 1.56 (s,3H,CH_3), 3.71 (m,2H,CH_2O), 4.03 (M,2H,CH_2O), 7.40 (m,8H,2Ph, C_3–H, C_5–H pyridinium), 7.92 (m,4H,2Ph), 8.68 (d,J=6.41,2H,C_2–H,C_6–H pyridinium).

4-Acetylethylene Ketal of *N*-[(Diphenylphosphinyl)amino]-1,2,5,6-tetrahydropyridine (Ie)

A precooled (0°C) solution of **Id** (0.92 g, 2.4 mmol) in ethanol (20 ml) was added dropwise to a solution of sodium borohydride (0.45 g, 12 mmol) in ethanol (10 ml). The mixture was stirred at 0°C for 10 hr, water (50 ml) was added, and the temperature was slowly increased to 20°C. Extraction with methylene chloride (4 × 50 ml), drying with sodium sulfate, and then evaporation of solvent under reduced pressure gave a pale yellow solid. This material was chromatographed twice on silica gel by eluting with chloroform and 1% methanol in chloroform to give a white solid which was recrystallized from methylene chloride/ether to yield **Ie**. M.P. 148–150°C (dec.). Yield 0.6 g (65%). *Anal.* Found: C, 62.86; H, 6.64; N, 6.93 for $C_{21}H_{25}O_3N_2P.H_2O$ requires C, 62.65; H, 6.76; N, 6.96. IR: 3530, 3340 (OH), 3130 (NH), 1590 (C=C), 1190 (P=O). NMR: 1.40 (s,3H,CH_3), 1.90 (s,2H,H_2O), 2.18 (m,2H,C_5–H), 2.98 (t,2H,C_6–H), 3.45 (d,J=2.84,C_2–H), 3.77 (m,2H,CH_2O), 3.91 (m,2H,CH_2O), 4.14 (d,J=17.89,1H,NH), 5.69 (m,1H,C_3–H), 7.47 (m,6H,2Ph), 7.92 (m,4H,2Ph).

N-[(Diphenylphosphinyl)amino]-4-acetyl-1,2,5,6-tetrahydropyridine (Ib)

A solution of **Ie** (0.6 g, 1.56 mmol) in a mixture of water (2 ml) and acetone (30 ml) containing pyridinium *p*-toluenesulfonate (0.12 g, 0.5 mmol) was refluxed for 4 hr. The solvent was removed under reduced pressure, chloroform (100 ml) was added, and the mixture was washed with a saturated solution of sodium bicarbonate (20 ml) and sodium chloride (20 ml). The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was washed with ether and dried under reduced pressure to yield **Ib** as a pale yellow solid. The product was confirmed as consisting of pure **Ib** by tlc. M.P. 194–196°C (dec.). Yield 0.47 g, (88%). IR: 3060 (NH), 1665, 1590 (C=O), 1185, 1205 (P=O). NMR: 2.24 (s,3H,CH_3), 2.37 (m,2H,C_5–H), 2.99 (t,2H,C_6–H), 3.68 (d,J=2.82,C_2–H), 4.24 (d,J=17.27,1H,NH), 6.64 (m,1H,C_3–H), 7.47 (m,6H,2Ph), 7.93 (m,4H,2Ph).

Biological Testing

Analgesic Activity

The writhing test of Collier *et al.* (6) was employed using a 0.03% solution of phenyl-*p*-benzoquinone (PBQ) in 5% ethanol as the irritant. Five male Swiss albino mice (21–24 g) were used in each control (0.2 ml of vehicle only) and test group. The test compounds were ultrasonically suspended in a vehicle consisting of physiological saline and Tween 80 surfactant and administered at a dose of 3 and 30 mg/kg subcutaneously in a volume of about 0.2 ml to the test group. Thirty minutes later about 0.2 ml of PBQ solution was injected intraperitoneally into each mouse in the control and test groups. The total number of writhes exhibited by animals in the test groups was recorded during 10 and 30 min. The percentage change between the test groups and the control group (displaying 78 and 142 writhes after 10 and 30 min, respectively), similarly counted, were calculated.

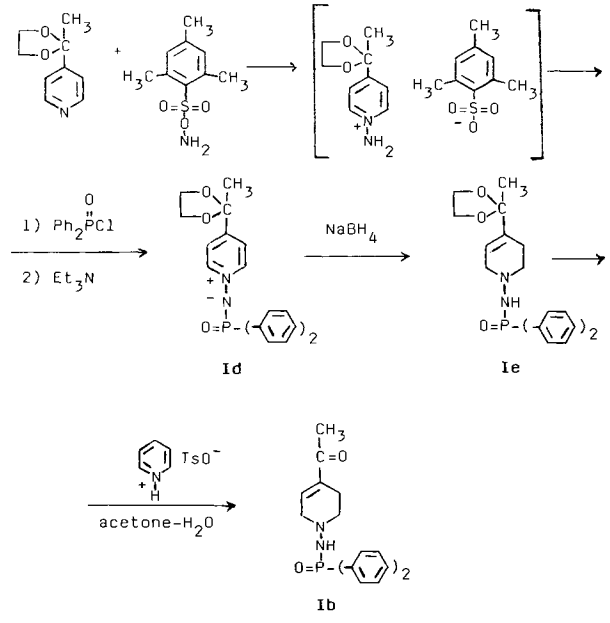
Blood Glucose Determinations

A modification of the method of Raabo and Terkildsen (7) was used whereby a 0.25% solution of *o*-dianisidine dihydrochloride was used as the chromagen. Four male Sprague–Dawley rats (250–270 g) were used per group. The animals were fasted overnight and about 2 ml of the vehicle (1% tragacanth) or 100 mg/kg of test compounds, suspended in the same volume of vehicle, was administered orally. Blood samples were collected from the tail 0, 2, and 4 hr after dosing using measuring capillary tubes and the sera from these were analyzed by measuring at 450 nm the oxidized *o*-dianisidine which is produced enzymatically via an NADH-coupled reaction from glucose.

RESULTS AND DISCUSSION

The compounds investigated in this paper include the *N*-diethoxyphosphinyl (**Ia**) and *N*-ethoxycarbonyl (**IIa**) derivatives of -amino-1,2,5,6-tetrahydropyridine and the *N*-diphenylphosphinyl and *N*-phencarbonyl derivatives of this molecule which possess a 4-acetyl (**Ib** and **IIb**) or a 3-methyl (**Ic** and **IIc**) group, respectively.

Compound **Ib** was synthesized by the following sequence of reactions.



Scheme II

Table I. Analgesic Activity and Blood Glucose Concentration Effects of Ia–Ic and IIa–IIc

	Analgesic activity			Hyperglycemic–hypoglycemic activity[a]	
		Inhibition of writhing (%)		Change in blood glucose concentration (%)	
Compound	Dose (mg/kg sc)	10 min	30 min	2 hr	4 hr
Ia	3	33	20		
	30	96	82		
IIa	3	31	16		
	30	45	32		
Morphine	0.038	46	38		
Ib				−9 ± 4.2	−1 ± 2.0
IIb				+13 ± 11.8	+15 ± 14.7
Ic				−9 ± 4.6	+3 ± 2.9
IIc				+83 ± 20.0*	+15 ± 13.8

[a] Mean value ± SE.
* Statistically significant ($P < 0.05$).

The ethylene ketal of 4-acetylpyridine was reacted with *O*-(mesitylenesulfonyl)hydroxylamine and diphenylphosphinic chloride in the presence of triethylamine to give *N*-[(diphenylphosphinyl)amino]-4-(1-ethylendioxoethyl)pyridinium inner salt (Id). Compound Id was then reduced with sodium borohydride to yield the corresponding 1,2,5,6-tetrahydropyridine compound (Ie), which was cleaved to give Ib.

The three pairs of analogues were concurrently studied in mice and rats for analgesic activity and effect on blood glucose concentrations. Compounds IIa, IIb, and IIc were selected for retesting since they were reported to possess the greatest analgesic, hypoglycemic, and hyperglycemic activities, respectively, of those previously investigated (2,3).

The abilities of Ia and IIa in doses of 3 and 30 mg/kg to reduce phenyl-*p*-benzoquinone-induced writhing in mice 10 and 30 min after administration of the irritant are shown in Table I. The highest analgesic potency was displayed by Ia, which gave 96 and 82% reductions, compared to reductions of only 42 and 32% for IIa, after 10 and 30 min respectively, at 30 mg/kg. Compounds Ia and IIa were equipotent at doses of 3 mg/kg after 30 min. Both agents are weak analgesics with approximately 1/80 the potency of morphine, when comparing effects at a dose of 3 mg/kg, and apparently have a short duration of action.

The effect on the blood glucose concentration of rats receiving 100-mg/kg oral doses of Ib, IIb, Ic, and IIC is summarized in Table I. The hyperglycemic activity of IIc occurring after 2 hr was confirmed with this compound; however, the slight hypoglycemic effect reported for IIb was not found in this study.

This investigation shows that analgesic activity in mice was produced by the diethoxy derivative of *N*-phosphinylamino-1,2,5,6-tetrahydropyridines and the effect was more pronounced than that displayed by its carbonyl analogue. Two diphenyl derivatives of this compound bearing 4-acetyl and 3-methyl groups, however, had no effect on blood glucose concentrations in rats.

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