SOME NEW DERIVATIVES OF PYRIDYL- AND QUINOLYLPHOSPHONIC ACIDS

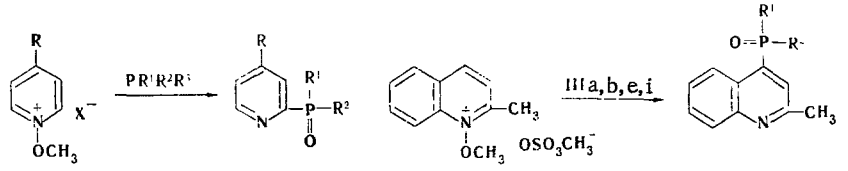
D. A. Predvoditelev, T. G. Chukbar, and É. E. Nifant'ev

UDC 547.241'823'831

Diamides and amido esters were obtained by the reaction of pyridine and quinoline N-oxide salts with phosphorous acid amido esters, and pyridyl- and quinolylphosphonic acid esters were obtained by reaction of the N-oxide salts with sodium dialkylphosphites.

Considering the interest in heterocycles containing C-P-bonded phosphonate fragments [1-5], we synthesized the previously unknown amide and amido esters of pyridyl- and quinolylphosphonic acid (IVa-b and Va-b, Table 1) by reaction of pyridine (Ia, b) and quinaldine (II) N-oxide salts with phosphorus acid ester diamides and diester amides (IIIa-e).

The dimethylsulfate (Ia and II) and methiodide (Ib) salts were used as the starting compounds, and the reaction was carried out under milder conditions in the case of Ib. The individuality of the products was studied from the results of thin-layer chromatography (TLC) and partially from the PMR spectra (Table 1). Substitution proceeds in two directions simultaneously (α and γ), as indicated by two sometimes-almost-indistinguishible triplets of methyl groups in the PMR spectra of IVa, b and Va, and by doubling of the signal of the isopropylidene grouping in the spectrum of ester Va; the isomer ratio depends on the synthetic conditions.



Ia-c IVa-g Va-c

I a R=H, X=OSO_3CH_3; b R=H, X=I; c R=CH_3, X=OSO_3CH_3; III a $R^1=R^2=N(C_2H_5)_2$, $R^3=OC_2H_5$; b $R^1=R^2=N(C_2H_5)_2$, $R^3=OC_3H_7$; c $R^1=R^2=N(C_2H_5)_2$, $R^3=OCH_2CHCH_2OC(CH_3)$; d $R^1=N(C_2H_5)_2$, $R^2=R^3=OC_2H_5$; e $R^1=N(C_2H_5)_2$, $R^2=R^3=OCH_2CHCH_2OC(CH_3)_2$; f $R^1=R^2=OC_2H_5$, $R^3=ONa$; g $R^1=R^2=OC_4H_9$, $R^3=ONa$; h $R^1=R^2=OC_6H_{13}$, $R^3=ONa$; i $R^1=R^2=OCH_2CHCH_2OC(CH_3)_2$, $R^3=ONa$; IV a R=H, $R^1=R^2=N(C_2H_5)_2$; b R=H, $R^1=N(C_2H_5)_2$, $R^2=OC_2H_5$; c R=H, $R^1=R^2=OC_2H_5$; d R=H, $R^1=R^2=OC_4H_9$; e R=H, $R^1=R^2=OC_6H_3$; f R=H, $R^1=R^2=OCH_2CHCH_2OC(CH_3)_2$; g $R=CH_3$, $R^2=R^3=OC_2H_5$; V a $R^1=R^2=N(C_2H_5)_2$; b $R^1=N(C_2H_5)_2$, $R^2=OCH_2CHCH_2OC(CH_3)_2$; c $R^1=R^2=OCH_2CHCH_2OC(CH_3)_2$

We also synthesized a number of esters of pyridyl-, γ-picolyl-, and quinaldylphosphonic acids (IVc-g and Vc, Table 1), by reaction of sodium dialkylphosphites (IIIf-i) with N-oxide salts (Ia-c and III). Ester IVc was previously synthesized by reaction of

V. I. Lenin Moscow State Pedagogical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 377-381, March, 1975. Original article submitted September 28, 1973.

lithium diethylphosphite with the dimethylsulfate salt of pyridine N-oxide [2] and by reaction of 2-nitropyridine N-oxide with triethyl phosphite [4], whereas ester IVg was obtained by reaction of sodium diethylphosphite with the dimethylsulfate salt of 4-methylpyridine N-oxide [2], but they were not characterized in detail. In [2] a comparison of the PMR spectra of esters of pyridylphosphonic acids with methyl groups in various positions of the ring demonstrated convincingly that the phosphorous-containing groups in this reaction enter only the 2 or 6 positions. The individuality of the esters that we obtained was proved by chromatography and the ^{31}P NMR spectra (singlet at −9.3 to 10.3 ppm), whereas their structures were confirmed by PMR and IR spectroscopy.

Let us note that we synthesized not only the simplest esters but also the first representatives of analogs of derivatives of phosphatidic acids Vb and phosphatidylglycerol IVf and Vc, which contain heterocyclic nitrogen-containing bases with a C-P bond [6], by reaction of amido esters and salts of phosphorous acid with pyridine and quinaldine N-oxide salts.

EXPERIMENTAL

All of the experiments were carried out in a dry argon atmosphere. The products were chromatographed in a loose layer of activity II aluminum oxide. The following solvent systems were used: dioxane (A), ether—hexane—acetonitrile (4:4:1) (B), dioxane—hexane (1:1) (C), and benzene—dioxane (3:1) (D). The chromatograms were developed with iodine vapors. The IR spectra of solutions of the compounds in carbon tetrachloride were recorded with a UR-10 spectrometer. The PMR spectra of carbon tetrachloride solutions were recorded with a JNM-C-60 HA spectrometer with hexamethyldisiloxane as the standard. The ^{31}P NMR spectra were recorded without a solvent with a JNM-4H-100 spectrometer (40.5 MHz) with 85%) phosphoric acid as the external standard.

Pyridine N-oxide and 4-methylpyridine N-oxide were obtained by the method in [7], 2-methylquinoline N-oxide was obtained by the method in [8], pyridine N-oxide methiodide was obtained by the method in [9], and the dimethylsulfate salts of pyridine and 4-methylpyridine N-oxides were obtained in toluene solutions by the method in [2, 10].

2-Methylquinoline N-Oxide Dimethylsulfate Salt (II). A 2.21-g (17.5 mmole) sample of dimethyl sulfate was added to a solution of 2.79 g (17.5 mmole) of 2-methylquinoline N-oxide in 20 ml of dioxane, after which the reaction mixture was held at room temperature for 12 h. The resulting heavy oil was separated and crystallized on standing. The salt was recrystallized twice from acetone to give 4.25 g (85%) of a product with mp 107-108°. Found: C 50.3; H 5.3; N 4.7%. $C_{12}H_{15}NO_5S$. Calculated: C 50.6; H 5.3; N 4.9%.

Reaction of Amido Esters of Phosphorous Acid with Pyridine and Quinaldine N-Oxide Salts. The heterocyclic N-oxide salt in dimethylformamide (DMFA) was added dropwise with stirring to a solution of the appropriate amido ester of phosphorus acid in DMFA, and the mixture was heated at 145° for 4 h. The reagent ratio was equimolecular. In the case of the preparation of IVa by reaction of salt Ia with amido esters IIIa-c, the DMFA was removed from the reaction mixture by distillation, and the residue was dissolved in an equal volume of water and extracted with chloroform. The reaction product was extracted from the chloroform with 4 N HCl, and the extract was treated with 10% NaOH to pH 9, and the mixture was again extracted with chloroform. The chloroform extract was dried with magnesium sulfate, the chloroform was removed by distillation, and the residue was distilled; in the case of the preparation of IVa from salt to Ic and ester IIIa the reaction was carried out at 100° for 1.5 h. In the synthesis of IVb, the DMFA was removed from the reaction mixture by distillation, the residue was distilled in an equal volume of water, and the aqueous solution was treated with NaOH to pH 10 and extracted with chloroform. The chloroform extract was dried with magnesium sulfate, the chloroform was removed by distillation, and the residue was distilled; in the case of the preparation of Va by the action of esters IIIa, b the reaction was carried out at 135° for 4 h, after which the DMFA was removed by distillation, and the residue was distilled. In the synthesis of Vb, the reaction mixture was held at 125° for 4 h, and the mixture was worked up as in the case of the preparation of IVb by treatment of the aqueous solution with an alcohol solution of KOH.

TABLE 1. Characteristics of the Compounds Obtained

Compound	bp, °C (mm)	n_D^{20}	Empirical formula	Found, % N	Found, % P	Calc., % N	Calc., % P	R_f (system)	IR spectra, cm^{-1}	PMR spectrum, δ, ppm*	Yield, %
IVa	135—137 ($2 \cdot 10^{-3}$)	1,5032	$C_{13}H_{24}N_3OP$	15,5	11,4	15,6	11,5	0,86 (A), 0,45 (B)	1230 (P=O), 1300 (C—N), 1430 (P—Ar), 1190, 1210 (P—N<C C>)[11], 710[12], 3050 (CH pyridine), 1580, 1470 (ring vibrations)	Two t* 1,33 (CH_3), m 3,34 (CH_2), m 7,83 (C=5), 8,37 (C=3 and C=4), 8,9 (C=6) (pyridine)[2]	28—40
IVb	70—75 (bath) $1 \cdot 10^{-2}$	1,4500	$C_{11}H_{19}N_2OP$	12,5	13,1	12,4	12,8	(A), 0,71 (A), 0,35 (B)	—	m 1,5 (CH_3), m 3 (CH_3CH_2—N), m 4,25 (CH_3CH_2—N), m 7,4—9,14 (pyridine)	20
IVc	100—105 (bath) $1 \cdot 10^{-4}$	1,4955	$C_9H_{14}NO_3P$	6,4	14,3	6,5	14,4	0,75 (A), 0,37 (B)	—	t 1,33 (CH_3), m 4,26 (CH_2), m 7,6 (C=5), 8,04 (C=3 and C=4), 8,83 (C=6) (pyridine)	24
IVd	122—124 ($1 \cdot 10^{-2}$)	1,4835	$C_{13}H_{22}NO_3P$	5,1	11,3	5,2	11,5	0,76 (A), 0,47 (B)	1260 (P=O), 1430 (P—Ar), 3055 (CH pyridine), 1580, 1470 (ring vibrations)	t 0,9 (CH_3), m 1,8 ($CH_3CH_2CH_2$—), m 4,26 (—CH_2O), m 7,58 (C=5), 8 (C=3 and C=4), 8,83 (C=6) (pyridine)	10—38
IVe	132—134 ($1 \cdot 10^{-4}$)	1,4700	$C_{17}H_{30}NO_3P$	4,4	9,2	4,3	9,5	0,78 (A), 0,49 (B)	1260 (P=O), 1430 (P—Ar), 3060 (CH pyridine), 1585, 1475 (ring vibrations)	—	36
IVf	165—170 (bath) $7 \cdot 10^{-3}$	1,4805	$C_{17}H_{26}NO_7P$	3,6	8	3,6	8,1	0,85 (A), 0,6 (D)	1225 (P=O), 1380 [$(CH_3)_2C$<], 1425 (P—Ar), 3040 (CH pyridine), 1465 (ring vibration)	Two lines 1,3 [$(CH_3)_2C$<], m 4,17 (CH_2CHCH_2), m 7,6 (C=5), 8 (C=3 and C=4), 8,9 (C=6) (pyridine)	30
IVg	100—105 (bath) $7 \cdot 10^{-3}$	1,4962	$C_{16}H_{16}NO_3P$	6,3	13,7	6,1	13,5	0,76 (A), 0,38 (B)	—	—	37
Va	118—122 ($3 \cdot 10^{-4}$)	‡ 1,4822	$C_{18}H_{28}N_3OP$	13,1	9,2	12,7	9,4	0,78 (C)	—	t 1,34 (CH_3CH_2—N), m 3,2 (CH_3CH_2—N), s 2,57 (CH_3 quinaldine)[3], m 7,25—9,85 (quinoline)	13—34
Vb	185—190 (bath) $1 \cdot 10^{-4}$	1,5206	$C_{20}H_{29}N_2O_4P$	7	7,7	7,1	7,9	0,56 (D)	1220 (P=O), 1375 [$(CH_3)_2C$<], 1430 (P—Ar), 3050 (CH quinoline) 1580, 1505, 1460 (ring vibrations)	Two lines 1,2 [$(CH_3)_2C$<], s 2,6 (CH_3 quinaldine), t 1,07 (CH_3CH_2N), m 3,26 (CH_3CH_2N), m 4 (CH_2CHCH_2), m 7—8,8 (quinoline)	21
Vc	190—195 (bath) $1 \cdot 10^{-4}$	1,4699	$C_{22}H_{30}NO_7P$	3,7	6,5	3,1	6,9	0,66 (D)	1220 (P=O), 1380 [$(CH_3)_2C$<], 1430 (P—Ar), 3050 (CH quinoline), 1575, 1505, 1460 (ring vibrations)	Two lines 1,23 [$(CH_3)_2C$<], s 2,6 (CH_3 quinaldine), m 4,1 (CH_2CHCH_2), m 6,83—8,8 (quinoline)	22

*The following singlets (δ, ppm) are present in the ^{31}P NMR spectra: −9.4 (IVc), −9.35 (IVd), −10.3 (IVf). Specific gravity (d_4^{20}): 1.1464 (IVc), 1.0621 (IVd), 0.9952 (IVe), 1.1677 (IVf), and 1.1271 (IVg). Molar reactivities (MR_D; the found value is given first and is followed by the calculated value): 54.68, 54.89 (IVc); 72.46, 73.36 (IVd); 91.31. 91.83 (IVe), 94.15, 94.0 (IVf); 59.35, 59.5 (IVg).

†Abbreviations: s is singlet, t is triplet, and m is multiplet.

††This is the n_D^{26} value.

Preparation of Diethyl 2-Pyridyl- (IVc-e), 2-(4-Methyl)pyridyl- (IVg), and 4-(2-Methyl)quinolylphosphonates (Vc). The appropriate dialkyl phosphite was added to finely granulated sodium in toluene. After the sodium had dissolved completely (sometimes heating was required), the toluene was removed by distillation, and a solution of the heterocyclic N-oxide salt (Ia-c or II) in DMFA was added dropwise with stirring and cooling from −5 to −10° to a solution of the salt in DMFA. The reagent ratio was equimolecular. The reaction mixture was held at room temperature for 10 h, after which it was worked up as in the synthesis of IVa. In the preparation of IVd from salt Ia and IVe the reaction was carried out in toluene, whereas the reaction was carried out in benzene in the case of IVg. In the case of the synthesis of IVd from salt Ib the reaction was carried out at 100° for 1.5 h, and the mixture was worked up as in the synthesis of IVb. In the preparation of IVf and Vc the reaction was carried out in benzene, after which the solvent was removed by distillation, and the residue was distilled.

LITERATURE CITED

1. D. Redmore, Chem. Rev., 71, 315 (1971).
2. D. Redmore, J. Org. Chem., 35, 4115 (1970).
3. D. Redmore, J. Org. Chem., 34, 1420 (1969).
4. I. G. Gadogan, D. J. Sears, and D. M. Smith, J. Chem. Soc., C, 1314 (1969).
5. A. K. Sheikman, G. V. Samoilenko, and S. N. Baranov, Zh. Obshch. Khim., 40, 700 (1970).
6. D. A. Predvoditelev, G. A. Urvantseva, and É. E. Nifant'ev, Ah. Obshch. Khim., 43 1801 (1973).
7. E. Ochiai, Aromatic Amine Oxides, Elsevier, New York (1967), p. 24; Organic Syntheses, ed. by H. Baumgarten, Vol. 5, Wiley—Interscience.
8. J. Pachter, J. Amer. Chem. Soc., 75, 3026 (1953).
9. Okamoto Toshiniko and Tani Hideo, Chem. and Pharm. Bull., 7, 825 (1959).
10. A. R. Katritzky and E. Zunt, Tetrahedron, 25, 4291 (1969).
11. I. V. Komlev, A. I. Zavalishina, I. P. Chernikevich, D. A. Predvoditelev, and É. E. Nifant'ev, Zh. Obshch. Khim., 42, 802 (1972).
12. G. I. Drozd, M. A. Sokal'skii, O. G. Strukov, and S. Z. Ivin, Zh. Obshch. Khim., 40, 2404 (1970).