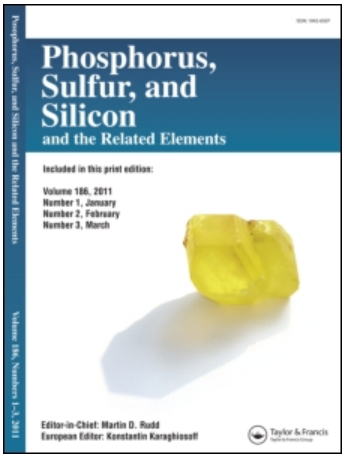

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ORGANOPHOSPHORUS COMPOUNDS. XXXVIII. SYNTHESIS OF DIALKYL PHOSPHATES OF 3-CHLORO-4-HYDROXY CARBOSTYRIL AND 3,4-DIHYDROXY-1-METHYLCARBOSTYRIL AS POTENTIAL ANTICHOLINESTERASES

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ORGANOPHOSPHORUS COMPOUNDS. XXXVIII. SYNTHESIS OF DIALKYL PHOSPHATES OF 3-CHLORO-4-HYDROXYCARBOSTYRIL AND 3,4-DIHYDROXY-1-METHYLCARBOSTYRIL AS POTENTIAL ANTICHOLINESTERASES

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Trialkyl phosphites react with 3,3-dichloro-2,4-dioxocarbostyrils (**1a, b**) and 2,3,4-trioxo-1-methylcarbostyril (**1c**) to give dialkyl phosphates of types (**4**) and (**9**), respectively. Structures of the new products were established by analytical and spectroscopic (IR, ^{1}H NMR, ^{31}P NMR, and MS) results. The anticholinesterase activity of compounds (**4a**), (**4d**), and (**9a**) was tested.

INTRODUCTION

Phosphoric acid esters derived from nitrogen heterocyclics such as pyridines, quinolines, pyrimidines and quinoxalines are known to evoke remarkable anticholinesterase activity.[1-3] Since very little is known regarding phosphoric acid esters of carbostyrils,[4] we have now endeavoured the synthesis of a number of these esters to examine their pharmacological potentialities.

RESULTS AND DISCUSSION

We have found that 3,3-dichloro-2,4-dioxocarbostyril (**1a**) and its 1-methyl analog (**1b**) react with trimethyl-, triethyl-, and triisopropyl phosphites readily, in benzene, at room temperature to give colourless crystalline products assigned the vinyl phosphate structure (**4**) (cf., Scheme 1) for the following reasons: (i) Correct elemental analyses and molecular weight determination (MS) were obtained for all products, (ii) The IR spectrum (in KBr) of compound (**4a**), taken as an example, showed bands at 3200 cm^{-1} (NH), 1655 cm^{-1} (C=O, amide), 1650 cm^{-1} (>C=C<, vinyl ester),[5] 1590, 1500 cm^{-1} (C=C, aromatic), 1230 cm^{-1} (P=O)[6] and at 1040 cm^{-1} (P—O—CH_3).[6] Moreover, the spectrum of (**4a**) revealed the absence of the absorption at 1680 cm^{-1}, recorded for the aryl carbonyl band in the parent compound (**1a**). The ^{1}H NMR spectrum of (**4a**) (in DMSO) showed the presence of the methoxyl-group protons (6 H) as a doublet (J_{HP} = 11.5 Hz) at δ = 3.88, and the

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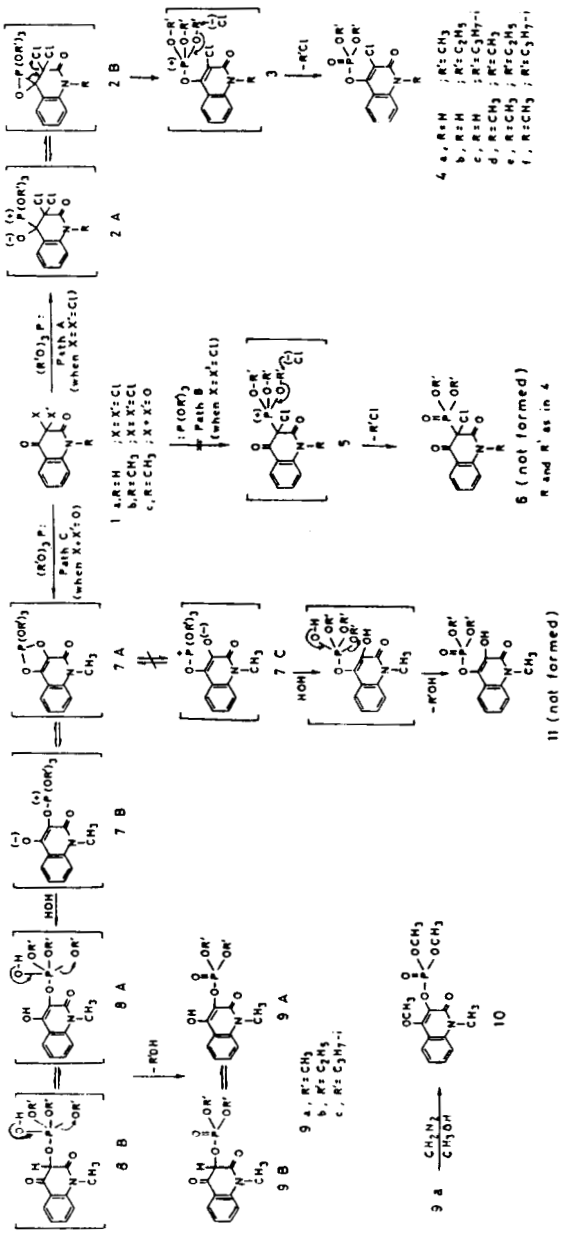
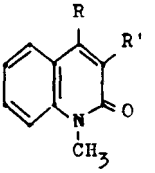
aromatic protons (4 H) as a multiplet at δ = 7.66–7.10 ppm. The ^{31}P NMR shift (vs. H_3PO_4) recorded for (**4a**) was $\delta = -7.78$ ppm which corresponds to a vinyl phosphate.[7,8] A possible explanation for the course of the reaction of trialkyl phosphites with (**1a, b**) is shown in Scheme 1. This involves attack by the phosphite phosphorus on the carbonyl carbon at position 4 in compound (**1**) to give the *C*-phosphonium adduct (**2A**), existing probably in equilibrium with the cyclic form (**2B**) (path A). This latter then suffers rearrangement of the phosphorus moiety to oxygen, yielding the enol phosphonium halide (**3**); a process which is favoured by P_π–d_π interaction.[9] Structure (3) readily affords the vinyl phosphate (4) by removal of R′Cl. This last step is accomplished via cleavage of the alkoxy group by a halide ion.[10,11] From the above results, it could be seen that the reaction of trialkyl phosphite with 3.3-dichloro-2,4-dioxocarbostyril (**1a, b**) proceeds according to the Perkow reaction mechanism yielding vinyl phosphates (**4a–f**) and not according to the Michaelis–Arbuzov reaction[12,13] which would afford phosphonate esters of type (**6**) (cf., path B in Scheme 1).

Further, this study was extended to include the reaction of 2,3,4-trioxo-1-methylcarbostyril (**1c**) with the same phosphite reagents to determine which carbonyl group of the trioxo system of (**1c**) would be attacked preferentially by phosphorus. We have now observed that compound (**1c**) reacts with trimethyl-, triethyl-, and triisopropyl phosphites at room temperature to give colourless crystalline products (**9**) which respond positively to the ferric chloride reaction and dissolve freely in 10% aqueous alkali. The hydroxy phosphate structure (**9**) (Scheme 1) was inferred from the following: (i) Correct elemental analysis and molecular weight determination (MS) were obtained for all products, (ii) The IR spectrum (in KBr) of compound (**9a**), taken as an example, showed bands at 3400 cm^{-1} (OH, broad), 1655 cm^{-1} (C=O, amide), 1250 cm^{-1} (P=O)[6] and 1040 cm^{-1} (P—O—CH_3),[6] (iii) Its ^1H NMR spectrum (in DMSO) showed the —OH proton, which is exchangeable with D_2O, as a broad singlet at δ = 11.75 and the methoxyl protons (6 H) appeared as a doublet at δ = 3.88 due to coupling with phosphorus (J_{HP} = 11.5 Hz). The aforementioned IR and ^1H NMR spectral data of (**9a**) rule out an alternative structure like (**9B**) which would predict a doublet (J_{HP} = 11.5 Hz), attributable to the methine proton. (iv) The ^{31}P NMR shift ($\delta = -6.68$, vs. 85% H_3PO_4) recorded for (**9a**) is also compatible with a phosphate structure.[7,8] (v) The fact that compounds (**9a–c**) respond positively to the ferric chloride colour reaction and are freely soluble in 10% NaOH solution are in favour of the hydroxyphosphate structure (**9A**) rather than the possible alternative form (**9B**), (vi) Further, treatment of compound (**9a**) with ethereal diazomethane solution in the presence of methanol resulted in the formation of the methyl ether (**10**) in a 75% yield. The lack of absorption band around 3400 cm^{-1} (OH) in the IR spectrum of (**10**) and presence of singlet at δ = 3.46 (OCH_3) in its ^1H NMR spectrum were distinguishing features of compound (**10**). When compound (**10**) was subjected to alkaline hydrolysis, it yielded a hydroxy compound (**12a**) which showed reactions characteristic for compounds where the —OH group is chelated owing to a neighboring carbonyl function.[14–16] Thus, compound (**12a**) gives a yellow precipitate with 0.1% aqueous uranyl acetate solution[15] and it develops a green colour reaction with alcoholic ferric chloride solution. Moreover, compound (**12a**) is recovered practically unchanged upon treatment with ethereal diazomethane



SCHEME 1

solution. These results favour structure (**12a**), and hence the precursor structure (**9A**), rather than the alternative structure (**12b**).



12a, R = OCH_3; R′ = OH

b, R = OH; R′ = OCH_3

A possible explanation for the course of the reaction of trialkyl phosphites with trione (**1c**) is shown in Scheme 1. This involves attack by the phosphite phosphorus on the most reactive[17] middle carbonyl group of the trioxo system of trione (**1c**) to give the dipolar structure (**7B**); existing probably in equilibrium with the unsaturated 5-membered cyclic oxyphosphorane (**7A**). Addition of elements of water* (unavoidable moisture) to adduct (**7**) produces a transient intermediate (**8A**) with pentacovalent phosphorus.[8,19-20] This then collapses to give the observed products (**9A**).

From the results of the present investigation, it could be concluded that trialkyl phosphites attack the carbonyl function at position 4 in 3,3-dichloro-2,4-dioxocarbostyrils (**1a, b**); whereas the same phosphite esters react with the trioxo system (**1c**) preferentially at the carbonyl group at position 3. In both cases, however, dialkyl phosphate esters (cf., **4** and **9**) are obtained (Scheme 1).

Preliminary pharmacological tests showed that compounds (**4a**), (**4d**), and (**9a**), as representative examples, exhibit, *in vitro*, remarkable anticholinesterase activity. Further work is in progress and will be published elsewhere.

EXPERIMENTAL*

All mp's were uncorrected. The benzene (thiophene-free) used was dried (Na). Trialkyl phosphites[21,22] were purified by treatment with Na followed by fractional distillation and dialkyl phosphites[23,24] were freshly distilled. The IR spectra were recorded, in KBr, with Perkin-Elmer Infracord Model 137 and Beckman Infracord Model 4220. The ^1H NMR spectra were run on Varian Spectrophotometers at 60 MHz and/or 90 MHz, using TMS as an internal reference. The mass spectra were recorded at 70 eV with a Varian MAT 112 Mass Spectrometer.

3-Chloro-4-hydroxycarbostyril, Dialkyl Phosphates (**4a–c**) *and 3-Chloro-4-hydroxy-1-methylcarbostyril, Dialkyl Phosphates* (**4d–f**)

General Procedure. A mixture of 0.01 mole of **1a**[25] (or **1b**)[26] and the trialkyl phosphite (0.012 mole) in dry benzene (25 ml) was kept at room temperature for 12 hr or refluxed for 6 hr (in case of **1b**). After removal of the volatile materials under reduced pressure, the oily residue was washed several times with petroleum ether (b.r. 40–60°C). The solid product thus obtained was crystallized from an appropriate solvent. Yields, physical and analytical data of compounds (**4a–f**) are given in Table I.

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*cf., the easy formation of triketone monohydrates from their anhydrous triones.[18]

*The names of the compounds described in this work are in line with the IUPAC rules of organic nomenclature.

TABLE I

Product	Yield, %	M.P., °C	Molecular form. (Mol. wt.)	Calc./Found*, % C	H	N	P	Cl	I.R. (cm^{-1})	M.S. m/ε (relative intensity %)	^1H NMR (in DMSO) δ, (ppm)
4a	75	185[a]	$C_{11}H_{11}NO_5PCl$	43.51	3.65	4.61	10.20	11.68	3000, 1640, 1605,	253(12), 303(16),	3.95 (d, 6 H), J = 11.5 Hz;
			(303.638)	43.21	3.7	4.58	10.1	11.63	1300, 1050	268(78), 109(100)	7.5 (m, 4 H); 12.5 (s, NH)
4b	80	155[b]	$C_{13}H_{15}NO_5PCl$	47.16	4.75	3.98	9.35	10.56	3000, 1655, 1610,	331(12), 296(20),	1.3 (t, 6 H); 4.25 (q, 4 H);
			(331.690)	47.01	4.5	4.22	9.3	10.8	1285, 1040	195 (58), 240(100)	7.55 (m, 4 H); 12.95 (s, NH)
4c	85	270[c]	$C_{15}H_{19}NO_5PCl$	50.23	5.11	3.75	8.65	9.91	3000, 1640, 1610,	302(5), 359(10),	1.2 (d, 12 H; J_{HH} = 7 Hz);
			(359.742)	50.1	5.32	3.8	8.7	9.7	1270, 1040	195(90), 120(100)	3.4 (m, 2 H); 7.5 (m, 4H); 11.7 (s, NH)
4d	80	97[a]	$C_{12}H_{13}NO_5PCl$	45.12	4.01	4.21	9.82	11.20	1655, 1600,	251(5), 267(10),	3.9 (d, 6 H), J = 12 Hz;
			(317.664)	45.37	4.13	4.41	9.75	11.5	1290, 1050	317(40), 282(100	3.7 (s, 3 H); 7.5 (m, 4 H)
4e	85	115[a]	$C_{14}H_{17}NO_5PCl$	48.7	4.92	4.10	8.97	10.30	1650, 1600,	310(10), 345(20),	1.35 (t, 6 H); 3.75 (s, 3 H)
			(345.716)	48.5	4.7	4.2	8.9	10.2	1280, 1020	316(25), 288(100	4.16 (q, 4 H); 7.55 (m, 4 H)
4f	87	120[a]	$C_{16}H_{21}NO_5PCl$	51.1	5.7	3.8	8.30	9.32	1650, 1600,	338(1), 373(28),	1.25 (d, 12 H, J_{HH} = 7 Hz);
			(373.768)	51.4	5.6	3.7	8.29	9.49	1270, 1020	209(40), 254(100	3.4 (m, 2 H); 3.75 (s, 3 H); 7.52 (m, 4 H)
9a	70	185[d]	$C_{12}H_{14}NO_6P$	48.20	4.70	4.68	10.37	—	1655, 3400	299(1), 162 (18),	3.88 (d, 6 H, J = 11.5 Hz);
			(299.244)	48.1	4.6	4.7	10.5			106(58), 191(100)	3.7(s, 3 H); 7.55 (m, 4 H)
9b	72	160[d]	$C_{14}H_{18}NO_6P$	51.49	5.60	4.30	9.20	—	1645, 3420	337(2), 162(9),	1.35 (t, 6 H); 4.35(q, 4 H);
			(327.298)	51.3	5.3	4.2	9.4			191(100)	3.6 (s, 3 H); 7.3 (m, 4 H)
9c	75	260[c]	$C_{16}H_{22}NO_6P$	54.2	6.19	3.89	8.80	—	1650, 3390	355(5), 162(15),	1.4 (d, 12 H); 4.85 (m, 2 H);
			(355.352)	54.1	6.3	3.9	8.6			191(100)	7.66 (m, 4 H)
10	70	250	$C_{13}H_{16}NO_6P$	49.84	5.11	4.47	9.90	—	1650		3.46 (s, 3 H, OCH_3);
			(313.271)	49.47	4.92	4.2	9.50				3.30 (s, 3 H, NCH_3)

*Microanalysis has been carried out in "Mikroanalytischen Laboratorium, Bonn, W. Germany and NRC, Cairo, Egypt.
[a]Crystallized from benzene/pet. ether (b.r. 40–60°C).
[b]Ethanol was used as solvent for crystallization.
[c]Acetone was used as solvent for crystallization.
[d]Chloroform/pet. ether (b.r. 40–60°C). P^{31} Shift for compounds **4a** and **4e** are $\delta = -7.78$ and $\delta = -7.57$, respectively.

3,4-Dihydroxy-1-methylcarbostyril, 3-Dialkyl Phosphates (**9a–c**)

General Procedure. A mixture of compound **1c** (0.01 mole)[26] and the trialkyl phosphite (0.12 mole) in dry benzene (20 ml) was kept at room temperature for 12 hr under good stirring. After removing the volatile materials, *in vacuo*, the residual substance was recrystallized from the suitable solvent. Identification of each adduct was based on comparison of its melting point and IR spectrum with the corresponding compound prepared by the reaction of (1c) with the appropriate dialkyl phosphite in boiling benzene for 12 hr. For physical and analytical data of compounds (**9a–c**) cf., Table I.

3-Hydroxy-4-methoxy-1-methylcarbostyril, Dimethyl Phosphate (**10**). To a suspension of compound (**9a**) (0.5 g) in methanol (2 ml) was added an ethereal diazomethane solution (from 5 g *N*-nitrosomethylurea) and the mixture kept for 24 hr at 10°C. The precipitated material was filtered, recrystallized from tetrahydrofuran-benzene to give the monomethyl ether (**10**) as colourless crystals. Melting point, IR, MS and ^{1}H NMR spectral data are given in Table I.

Alkali hydrolysis of compound (**10**). A mixture of compound (**10**) (0.5 g) and aqueous sodium hydroxide (20 ml; 10%) was warmed for 2 hr. After cooling and addition of acetic acid (10%), the residue was collected (0.4 g, 85%) and recrystallized from acetone to give (**12a**) as colourless crystals, mp. 290°C. Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.45; H, 5.53; N, 6.85%.

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