Notes

[Chem. Pharm. Bull.,
21(2) 437-439 (1973)]

UDC 547.587.51'722.2.057.09

Preparation of Some Phosphate Esters of 5-Methoxy-8-hydroxypsoralen

KENJI SEMPUKU

Research Laboratory, Nippon Shinyaku Co., Ltd.¹⁾

(Received July 27, 1972)

It was reported²⁾ that dialkylphosphate and dialkylthiophosphate esters of hydroxycoumarins have insecticidal properties. In connection with this, Mustafa, *et al.*³⁾ prepared dialkylphosphate and dialkylthiophosphate esters by heating xanthotoxol, 4-hydroxybergapten, and 4-hydroxyisopimpinellin with dialkyl (or dialkylthio)phosphoryl chlorides in dry acetone in the presence of anhydrous K_2CO_3 .

The author wishes to report the preparation of phosphate esters (I—VI) of 5-methoxy-8-hydroxypsoralen (VII), obtainable by acid hydrolysis of byakangelicol (VIII),⁴⁾ by condensation of the hydroxycoumarin with several phosphoryl chlorides including substituted phosphorodiamidic chlorides.

Montgomery, *et al.*⁵⁾ obtained phosphoric acid monoesters by subjecting the phosphorodimorpholidate esters of several alcohols to mild acid hydrolysis by use of Amberlite IR 120 resin (H^+ form). The author has tried this mild hydrolysis with V and has obtained monoester VI whose ether linkage was intact during the acid treatment. The direct phosphorylation of IV with $POCl_3$ in pyridine followed by hydrolysis has failed. Methylation of VI with CH_3N_2 readily gave I. On heating VI in methanolic HCl, VII was obtained.

- I : $R = PO(OCH_3)_2$
 II : $R = PO(OC_2H_5)_2$
 III : $R = PS(OC_2H_5)_2$
 IV : $R = PO[N(CH_3)_2]_2$
 V : $R = PO\left(\begin{array}{c} \diagup \quad \diagdown \\ N \quad O \end{array}\right)_2$
 VI : $R = PO(OH)_2$
 VII : $R = H$
 VIII : $R = CH_2CH-C(CH_3)_2$
 $\diagdown \quad \diagup$
 O

Chart 1

Experimental⁶⁾

5-Methoxy-8-hydroxypsoralen Dimethylphosphate (I)—A mixture of 5-methoxy-8-hydroxypsoralen⁴⁾ (VII) (0.85 g, 3.66 millimoles), dry acetone (30 ml), and anhydrous K_2CO_3 (1.7 g, 12.3 millimoles) was stirred at room temperature for 2 hr. To this was gradually added $(CH_3O)_2POCl$ ⁷⁾ (1.7 g, 11.8 millimoles). The mixture was refluxed for 5 hr, clarified by filtration while hot, and concentrated *in vacuo*. Addition of ether to the residue gave crystals, which were recrystallized from iso-PrOH to give prisms of I.

Compounds II—V were similarly prepared (Table I). Tables I, II, and III summarize the reaction results and characters of compounds I—V.

Mild Hydrolysis of V to 5-Methoxy-8-hydroxypsoralen Phosphate (VI)—A mixture of V (1.9 g), Amberlite IR 120 (H^+) (250 ml), and H_2O (200 ml) was stirred at 65° for 2 hr. After cooling and addition of

1) Location: Nishioji 8-jo, sagaru, Minami-ku, Kyoto.

2) G. Schrader, "Die Entwicklung neuer insektizider Phosphorsäureester," Verlag Chemie, Weinheim 1963, S. 187—207.

3) A. Mustafa, M.M. Sidky, and M.R. Mahran, *Ann.*, **684**, 187 (1965).4) T. Noguchi and M. Kawanami, *Yakugaku Zasshi*, **58**, 1052 (1938).5) H.A.C. Montgomery and J.H. Turnbull, *J. Chem. Soc.*, **1958**, 1963.6) All the mp were uncorrected. Infrared (IR) measurement was carried out on Hitachi EPI-S₂ or EPI-G3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on Varian A-60 spectrophotometer with Me_4Si (TMS) as internal standard.7) G. Sosnousky and E.H. Zaret, *J. Org. Chem.*, **34**, 968 (1969).

TABLE I. Preparation of Phosphate Esters (I—V) of 5-Methoxy-8-hydroxypsoralen (VII)

Compound	VII (g)	Chloride (g)	Dry acetone (ml)	Anhyd. K ₂ CO ₃ (g)	Reflux time (hr)	Recrystn. solvent	Yield		mp (°C)
							(g)	(%)	
I	0.85	1.7 ^{a)}	30	1.7	5	iso-PrOH	0.36	29	156—157.5
II	2	4.5 ^{b)}	70	4.5	5	MeOH	1.7	54	164—166
III	0.3	0.6 ^{c)}	10	0.5	10	EtOH	0.14	28	190—191
IV	1.55	3.3 ^{d)}	60	3.5	2	C ₆ H ₆ -ligroin	1.2	49	147—149
V	3	6 ^{e)}	140	7	8	iso-PrOH	3.4	58	215—216.5

a) (CH₃O)₃POCl₂,⁷⁾ b) (CH₃CH₂O)₂POCl₂,⁸⁾ c) (CH₃CH₂O)₂PSCl,⁹⁾ d) [(CH₃)₂N]₂POCl₂,¹⁰⁾ e) (O—N)₂POCl₂¹¹⁾

TABLE II. IR and Analytical Data of Esters (I—V)

Compound	IR cm ⁻¹ (KBr)		Formula	Analysis (%)										
	$\nu_{\text{P=O}}$	$\nu_{\text{C=O}}$		Calcd.					Found					
				C	H	P	N	S	C	H	P	N	S	
I	1290	1725	C ₁₄ H ₁₃ O ₈ P	49.43	3.85	9.11				49.17	3.80	9.07		
II	1290	1730	C ₁₆ H ₁₇ O ₈ P	52.18	4.65	8.64				52.27	4.75	8.64		
III	1310	1735	C ₁₆ H ₁₇ O ₇ PS	51.51	4.31	7.82		8.10		51.46	4.39	8.04		8.33
IV	1300	1720	C ₁₆ H ₁₉ O ₆ N ₂ P	52.46	5.23	8.46	7.65			52.51	5.33	8.77	7.56	
V	1300	1730	C ₂₉ H ₂₃ O ₈ N ₂ P	53.33	5.15	6.88	6.22			53.22	5.24	6.85	6.03	

TABLE III. NMR Data of Esters (I—VI) Showing Positions of Proton Assignment

Compd.	Assignment											J value (cps)		
	A	B	C	D	E	F	G	H	I	J	K	J _{AB}	J _{CD}	J _{GH}
I	1.90 ^d	3.74 ^d	2.37 ^d	2.97 ^d	5.81 ^d	5.81 ^s 5.99 ^s						10	2.5	
II	1.91 ^d	3.73 ^d	2.37 ^d	2.98 ^d	5.82 ^s		5.45 ^q 5.87 ^q	8.53 ^t 8.55 ^t				10	2.5	7.2
III	1.87 ^d	3.73 ^d	2.36 ^d	2.95 ^d	5.77 ^s		5.42 ^q 5.57 ^q	8.51 ^t 8.53 ^t				10	2.5	7.2
IV	1.90 ^d	3.74 ^d	2.39 ^d	3.02 ^d	5.84 ^s				7.01 ^s 7.19 ^s			10	2.5	
V	1.90 ^d	3.73 ^d	2.35 ^d	2.98 ^d	5.82 ^s					6.4— 6.8 ^m	6.1— 6.4 ^m	10	2.5	
VI	1.84 ^d	3.73 ^d	2.22 ^d	2.84 ^d	5.82 ^s							10	2.5	

Values with reference to TMS (τ=10). The NMR measurement was taken in CDCl₃ for compounds I—V, and in D₂O for compound VI, respectively. Superscripts s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet, respectively. Relative intensity of all the protons was well corresponding to the given structures.

8) F.R. Atherton, H.T. Howard, and A.R. Todd, *J. Chem. Soc.*, **1948**, 1106.

9) T.W. Mastin, G.R. Norman, and E.A. Weilmuenster, *J. Am. Chem. Soc.*, **67**, 1662 (1945).

10) *Inorg. Syntheses*, **7**, 71.

EtOH (400 ml), the reaction mixture was clarified by suction filtration, the cake was washed with 65% aq. EtOH (200 ml), and the combined filtrate and washing were concentrated *in vacuo* below 45°. The residual powder was crystallized from EtOH to give yellow needles (1.0 g, mp 225–233°). Yield 76%. IR cm^{-1} (KBr): $\nu_{\text{P=O}}$ 1310, $\nu_{\text{C=O}}$ 1700. Calcd. for $\text{C}_{12}\text{H}_8\text{O}_8\text{P}$: C, 46.17; H, 2.88; P, 9.98. Found: C, 46.23; H, 3.00; P, 9.74. The NMR data are shown in Table III.

Preparation of I by Methylation of VI with CH_2N_2 —A CH_2N_2 -saturated ether solution (5 ml) was added to VI (90 mg) dissolved in MeOH (3 ml). On addition, vigorous generation of N_2 was observed. The mixture was allowed to stand at room temperature for 1 hr, concentrated, and the crystalline residue was recrystallized from iso-PrOH to give prisms (60 mg, mp 155–156°). Yield 73%. No mp depression was seen in admixture test with I prepared from VII and $(\text{CH}_3\text{O})_2\text{POCl}$. The IR and NMR spectral patterns were identical with those of I from VII.

Hydrolysis of VI to VII—A mixture of VI (0.55 g), concentrated HCl (2 ml), and MeOH (6 ml) was refluxed for 4 hr, concentrated to dryness *in vacuo*, and the residue was recrystallized from 70% aq. EtOH to give crystals (0.33 g, mp 208–210°). Yield 81%. The IR spectral pattern was identical with that of VII prepared from VIII.

[Chem. Pharm. Bull.
21(2) 439–443 (1973)]

UDC 547.654.1.04

Tetrahydronaphthylamines and Related Compounds. II.¹⁾ Synthesis of 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-phenyl- 2-naphthylamine²⁾

KEIICHI NOMURA, JUN ADACHI, MICHIO HANAI,
and KEMMOTSU MITSUHASHI

Faculty of Pharmaceutical Sciences, University of Toyama³⁾

(Received August 3, 1972)

In our synthetic studies on analgetics, we attempted to prepare several compounds which have a bulky substituent at the 2-position of 1,2,3,4-tetrahydro-2-naphthylamine, because it is considered that their conformation will be similar to that of morphine and benzomorphan. The present paper describes the synthesis of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-phenyl-2-naphthylamine (I) and an interesting observation on stereochemistry of an amino alcohol in the course of this synthesis.

3-(3,4-Dimethoxyphenyl)-propiophenone (II)⁴⁾ was submitted to a modified Strecker reaction⁵⁾ to give the corresponding amino nitrile (III) in about 50% yield. The intramolecular cyclization of III was achieved in concentrated sulfuric acid⁶⁾ to afford 2-amino-3,4-dihydro-6,7-dimethoxy-2-phenyl-1(2H)-naphthalenone (IVa), which was methylated to give the corresponding 2-dimethylamino derivative (IVb). Attempts to reduce directly the amino ketones (IVa and IVb), *i.e.*, Wolff–Kishner reduction, Clemmensen reduction and catalytic hydrogenation, were unsuccessful. Reduction of IVa with sodium borohydride in ethanol

- 1) a) Part I: K. Mitsuhashi, J. Adachi, N. Shimizu, K. Nomura, and S. Shiotani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1321 (1972); b) This paper forms Part XVI of "Studies on Structure-Activity Relationship of Analgetics," Part XV: S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1980 (1972).
- 2) This work was presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, Apr. 1972.
- 3) Location: *Gofuku 3190, Toyama*.
- 4) J. Koo, *J. Am. Chem. Soc.*, **75**, 2000 (1953).
- 5) R.E. Steiger, *Org. Syn.*, Coll. Vol. **III**, 586 (1955).
- 6) C.K. Bradsher, E.D. Little, and D.J. Beavers, *J. Am. Chem. Soc.*, **78**, 2153 (1956).