Notes

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

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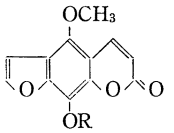
It was reported[2] that dialkylphosphate and dialkylthiophosphate esters of hydroxycoumarins have insecticidal properties. In connection with this, Mustafa, *et al.*[3] prepared dialkylphosphate and dialkylthiophosphate esters by heating xanthotoxol, 4-hydroxybergapten, and 4-hydroxyisopimpinellin with 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 condensaion of the hydroxycoumarin with several phosphoryl chlorides including substituted phosphodiamidic 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_2N_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=$PO(N\langle\rangle O)_2$
VI: R=$PO(OH)_2$
VII: R=H
VIII: R=$CH_2CH{-}C(CH_3)_2$ (O)

Chart 1

Experimental[6]

5-Methoxy-8-hydroxypsoralen Dimethylphosphate (I)——A mixture of 5-methoxy-8-hydroxypsoralen[4] (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, Weiheim 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-S_2 or EPI-G3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on Varian A-60 spectrophotometer with Me_2Si (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_2CO_3 (g)	Reflux time (hr)	Recrystn. solvent	Yield (g)	Yield (%)	mp (°C)
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_6H_6-ligroin	1.2	49	147—149
V	3	6[e]	140	7	8	iso-PrOH	3.4	58	215—216.5

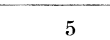
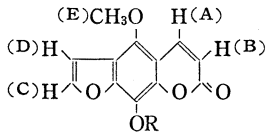
a) $(CH_3O)_2POCl$,[7] b) $(CH_3CH_2O)_2POCl$,[8] c) $(CH_3CH_2O)_2PSCl$,[9] d) $[(CH_3)_2N]_2POCl$,[10] e)  [5]

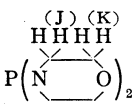
Table II. IR and Analytical Data of Esters (I—V)

Compound	IR cm^{-1} (KBr) $\nu_{P=O}$	IR cm^{-1} (KBr) $\nu_{C=O}$	Formula	Analysis (%) Calcd. C	H	P	N	S	Found C	H	P	N	S
I	1290	1725	$C_{14}H_{13}O_8P$	49.43	3.85	9.11			49.17	3.80	9.07		
II	1290	1730	$C_{16}H_{17}O_8P$	52.18	4.65	8.64			52.27	4.75	8.64		
III	1310	1735	$C_{16}H_{17}O_7PS$	51.51	4.31	7.82		8.10	51.46	4.39	8.04		8.33
IV	1300	1720	$C_{16}H_{19}O_6N_2P$	52.46	5.23	8.46	7.65		52.51	5.33	8.77	7.56	
V	1300	1730	$C_{29}H_{23}O_8N_2P$	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



$P(OCH_3)_2$ (F) $P(OCH_2CH_3)_2$ (G)(H) $P[N(CH_3)_2]_2$ (I)



Compd.	Assignment A	B	C	D	E	F	G	H	I	J	K	J value (cps) 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 $CDCl_3$ for compounds I—V, and in D_2O for compound VI, respectively. Superscripts s, d, t, q, and m stand for singlt, 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* bellw 45°. The residual powder was crystallized from EtOH to give yellow needles (1.0 g, mp 225—233°). Yield 76%. IR cm^{-1} (KBr): $\nu_{P=O}$ 1310, $\nu_{C=O}$ 1700. Calcd. for $C_{12}H_8O_8P$: 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 deprssion was seen in admixture test with I prepared from VII and $(CH_3O)_2POCl$. 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.

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Tetrahydronaphthylamines and Related Compounds. II.[1] Synthesis of 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-phenyl-2-naphthylamine[2]

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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 reaction[5] to give the corresponding amino nitrile (III) in about 50% yield. The intramolecular cyclization of III was achieved in concentrated sulfuric acid[6] 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).