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Psychotomimetic Phenylisopropylamines. 5. 4-Alkyl-2,5-dimethoxyphenylisopropylamines†

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A homologous series of 4-alkyl-2,5-dimethoxyphenylisopropylamines (alkyl = H through n-C_5H_{11} and t-C_4H_9) was synthesized and compared with mescaline as serotonin agonists in a sheep umbilical preparation. The three-carbon homolog **6d** was found to be the most potent of the straight-chain series in accordance with its observed psychotomimetic effectiveness in man.

Following the early observations that the 3-carbon isopropylamine side chain on a substituted aromatic ring was optimum to induce hallucinogenic or psychotomimetic intoxication in man,[1] most studies have been concerned with ring-substitution variations. Three aromatic ether substituents[2] arranged in a 2,4,5-orientation pattern[3] appear to provide maximum potency. The replacement of two adjacent methoxy groups with a methylenedioxy ring generally increases potency;[4] but the addition of further methylene groups, either as a dioxane ring[4a] or as an ethoxy substituent,[5] generally decreases CNS effectiveness. These relations between structure and human response have been reviewed.[6]

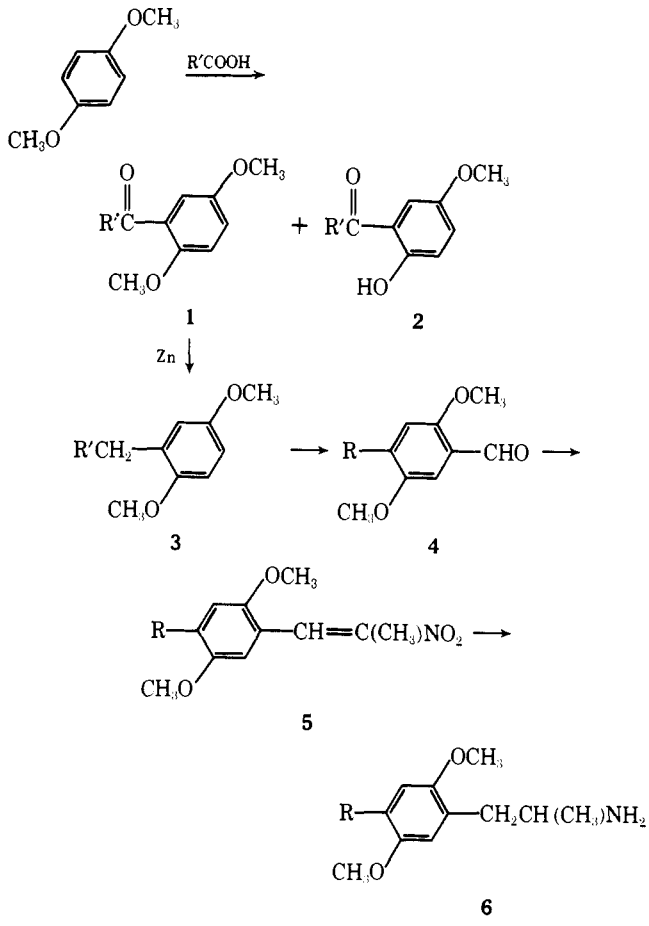
Within this optimum 2,4,5-substitution pattern it was found[7] that the replacement of the 4-methoxyl group with a methyl group led to a base with greatly increased potency and prolonged action. This compound, DOM (**6b**), serves as a starting point in the present study, which concerns various alkyl variations at the 4 position. The straight-chain homologous series from C_0 to C_5 as well as the 4-*tert*-butyl analog **6g** have been prepared and have been quantitatively evaluated, both as serotonin agonists in in vitro preparations (employing sheep umbilical strip preparations[8]) and as psychotomimetics in vivo in man (utilizing the double-conscious technique of assay[1b,6]).

Results and Discussion

Chemistry. The four homologs **6c–f** were prepared according to the Scheme I. *p*-Dimethoxybenzene is acylated with the appropriate carboxylic acid or acid chloride. When the acid chloride is employed in the conventional Friedel–Crafts reaction, a variable amount of the phenol resulting from demethylation adjacent to the position of attack is generated. This phenol **2** is easily removed from the reaction mixture by extraction with alkali and can be completely avoided by acylation with the free carboxylic acid in polyphosphoric acid. The phenol can be readily converted into the diether **1** with methyl iodide. The structural assignment of **2** is based upon its spectral nature (an intrinsic yellow color resulting from a hydrogen-bond system) and by its facile reaction with methyl isocyanate to form the heterocycle **7** (Scheme II). A novel feature of **7** is the olefinic methylene group (a quartet structure in the NMR proton spectrum) that becomes a methyl group (sharp singlet) with the addition of acid.

Clemmenson reduction of the ketone **1** to the hydrocarbon **3** is followed by the preparation of the aldehyde **4** by standard Vilsmeyer techniques. Conversion to the nitrostyrene **5** and reduction to the free base **6** were achieved by conventional techniques. Details are given in the Experimental Section for the 4-amyl homolog **6f**; the other compounds in this study were prepared similarly.

Scheme I



a, R = H
b, R = CH_3
c, R = C_2H_5; R′ = CH_3
d, R = n-C_3H_7; R′ = C_2H_5
e, R = n-C_4H_9; R′ = n-C_3H_7
f, R = n-C_5H_{11}; R′ = n-C_4H_9
g, R = t-C_4H_9

Pharmacology. The seven compounds **6a–g** as well as mescaline have been pharmacologically evaluated. They have been assayed as serotonin agonists on sheep umbilical artery strips and compared both as to dosage required to evoke the response seen for serotonin (at the 25% level, ED_{25}) and as to the percentage of serotonin response seen at maximum effect. These methods have been described in detail.[8] The human hallucinogenic potential of those com-

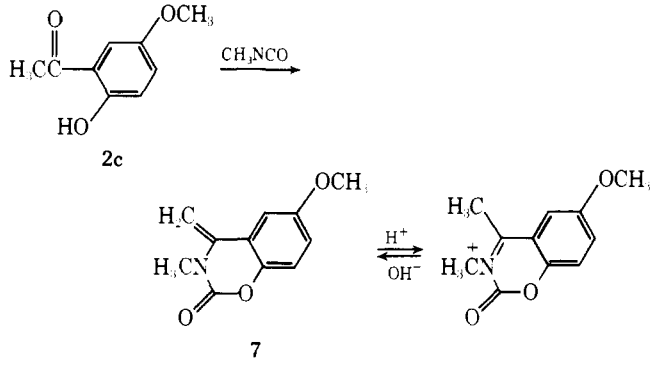
†References 2a, 3, 2b, and 5, respectively, are to be considered papers I–IV of this series.

Table I. Phenylisopropylamine Hydrochlorides 6. Physical and Pharmacological Properties

No.	R	Mp, °C	Recrystn solvent	Yield, %[a]	Formula[b]	Code	$ED_{25} \times 10^{-3}$ M[c]	N[d]	% max con- trn[e]	Hallucn potency[f]
6a	H	107–108[g]	Ac_2O	68	$C_{11}H_{18}ClNO_2$	2,5DMA	1700 (1400–2100)	6	44	8[h]
6b	CH_3	189–190[i]	IPA–Et_2O	91	$C_{12}H_{20}ClNO_2$	DOM	18 (15–22)	7	80	80[h]
6c	C_2H_5	194–195[j]	MeCN	88	$C_{13}H_{22}ClNO_2$	DOET	5.3 (4.2–6.6)	7	79	100[k]
6d	n-C_3H_7	182–183	MeCN	54	$C_{14}H_{24}ClNO_2$	DOPR[l]	2.6 (2.5–2.7)	7	80	80[m]
6e	n-C_4H_9	151–152	MeCN	44	$C_{15}H_{26}ClNO_2$	DOBU	4.3 (3.5–5.3)	7	71	36[m]
6f	n-C_5H_{11}	145–146	MeCN	39	$C_{16}H_{28}ClNO_2$	DOAM	24 (8.6–79)	7	43	10[m]
6g	t-C_4H_9	170–171	Ac_2O	76	$C_{15}H_{26}ClNO_2$	DOTB	7.4 (5.6–9.7)	7	65	*n*
Mescaline							180 (150–270)	5	77	1
Serotonin							71 (57–88)	7	100	*n*

[a]Yield based upon the corresponding nitrostyrene precursor. [b]All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values. [c]Molar concentration effective in producing 25% of the maximum serotonin contraction and the standard error of the geometric mean. [d]Number of replicate assays in tissue responses. [e]Maximum contraction achieved at any concentration, with serotonin defining 100%. [f]Expressed as mescaline units, derived by dividing the effective dose of mescaline by the effective dose of the compound in question, both determined in man (see ref 6). [g]This salt crystallizes poorly, and a range of melting points is reported in the literature: K. Bailey, D. Legualt, and D. Verner, *J. Assoc. Off. Anal. Chem.*, 57, 70 (1974), report mp 105–106°; B. T. Ho, W. M. McIsaac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert, and M. B. Noel, *J. Med. Chem.*, 13, 26 (1970), report mp 111.5–112.5°; R. T. Coutts and J. L. Malicky, *Can. J. Chem.*, 51, 1402 (1973), report mp 114–116°; and R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, 62, 161 (1940), report mp 117.5°; K. Bailey et al. (vide infra) have observed an increase in melting point upon standing in the air, with eventual deliquescence. The oxalate salt is stable. [h]See ref 6. [i]S. B. Matin, P. S. Callery, J. S. Zweig, A. O'Brien, R. Rapoport, and N. Castagnoli, *J. Med. Chem.*, 17, 877 (1974), report mp 185–188°; ref 7b reports mp 189–189.5°. [j]Lit.[7b] mp 195–195.5°. [k]See S. H. Snyder, L. Faillace, and H. Weingartner, *Am. J. Psychiat.*, 125, 113 (1967); S. H. Snyder, S. Unger, R. Blatchley, and C. F. Barfknecht, *Arch. Gen. Psychiat.*, 31, 103 (1974). [l]A potential ambiguity exists with the use of this code. The term DOP has been used [A. S. Kulkarni, *Biol. Psychiat.*, 6, 177 (1973)] in a study involving a compound thought to be the 4-isopropyl analog of **6d**. It is now known that the compound studied was in fact the 4-*n*-propyl isomer described here. Thus both DOP and DOPR refer to **6d**. Very recently the isopropyl analog has been prepared [F. A. B. Aldous, B. C. Barrass, K. Brewster, D. A. Buxton, D. M. Green, R. M. Pinder, P. Rich, M. Skeels, and K. J. Tutt, *J. Med. Chem.*, 17, 1100 (1974)] and appears, in animal assay, to be much reduced in psychotomimetic potency. [m]Value from present study. [n]This compound has not been established as being hallucinogenic.

Scheme II



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pounds not previously reported in the literature has been determined by previously published methods.[6] These results are given in Table I.

Of the six compounds that form a homologous series, it is apparent that all three parameters of biological potency show a maximum at about 2- to 3-carbon chain length, with a clear decrease in effectiveness at the extremes (0- and 5-carbon chain lengths). A semilog plot of these data is given in Figure 1.

Previous studies have reported[8,9] a promising qualitative correlation between activation of serotonin receptors by mescaline and other hallucinogenic compounds representing different structural families (LSD, psilocybin, DOB). The present study indicates that within a close homologous series there is a quantitative correlation between serotonin-like response and psychotropic action. With the more lipophilic drugs this correlation becomes excellent.

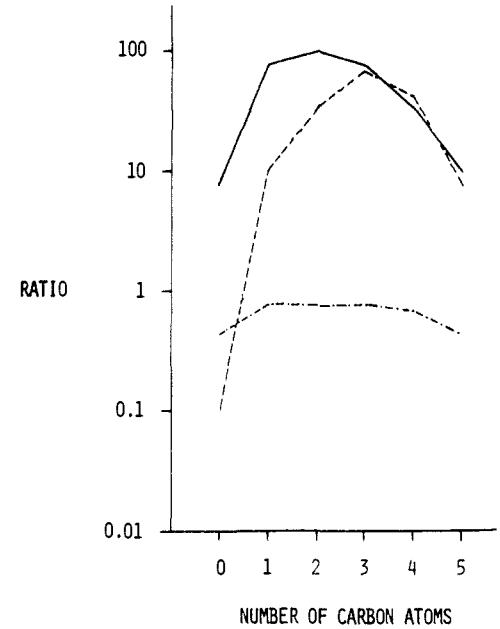

Figure 1. Relative potencies of experimental compounds 6a–f compared to the appropriate reference drug. The ratios are taken to allow a large value to represent a high potency: ——, ED (mescaline)/ED (compound) (human potency, in vivo); - - - -, ED_{25} (mescaline)/ED_{25} (compound) (serotonin agonism, in vitro); —·—·—, maximum contraction of compound/contraction of serotonin (= 100%) (in vitro).

Experimental Section

Infrared spectra were determined as films or as Nujol mulls on a Beckman IR-18. Ultraviolet spectra were obtained on a Beckman Acta III. All gas-chromatographic separations were achieved on OV-17 on Chromosorb W; the analytical system 3%, 6 ft × ⅛ in., glass column, with FID, and the preparative system 10%, 10 ft × ⅜ in., aluminum column, with thermal detector. NMR analyses were conducted on a Varian A-60. Melting points were taken in open

capillaries on a Mel-Temp block and are uncorrected. Elemental analyses are represented by the symbols of the elements analyzed for; if any element falls more than 0.4% from the theoretical value, the analysis is given in full.

4-Methyl-2,5-dimethoxyphenylisopropylamine (**6b**) and 4-*tert*-butyl-2,5-dimethoxyphenylisopropylamine (**6g**) were prepared from the corresponding hydroquinones as described.[7b] 2,5-Dimethoxyphenylisopropylamine (**6a**) was prepared by conventional means from commercial 2,5-dimethoxybenzaldehyde.[3]

2,5-Dimethoxyphenyl *n*-Butyl Ketone (1f). a. Employing Polyphosphoric Acid. A solution of *p*-dimethoxybenzene (110 g, 0.80 mol) and valeric acid (102 g, 1.0 mol) in polyphosphoric acid (168 g) was heated on the steam bath for 3 hr. The resulting deep red homogeneous solution was poured into water (1 l.) and extracted with methylene chloride (3 × 200 ml). The organic extracts were pooled and washed with 150-ml portions of 5% NaOH until the aqueous phase remained basic and once with dilute hydrochloric acid. The solvent was removed in vacuo and the residue allowed to crystallize. After removing unreacted dimethoxybenzene by filtration the mother liquors were distilled in vacuo to yield the product as an amber oil: bp 188–192° (20 mm); 53.0 g (yield 30%, efficiency 71% based upon recovered starting material). Anal. ($C_{13}H_{18}O_3$) C, H.

b. Employing Aluminum Chloride. To a suspension of anhydrous $AlCl_3$ (116 g) in CH_2Cl_2 (350 ml) there was added with stirring valeroyl chloride (94.6 g, 0.78 mol). This mixture was added slowly and with vigorous stirring to a solution of *p*-dimethoxybenzene (92 g, 0.67 mol) in CH_2Cl_2 (300 ml). This was allowed to stir at ambient temperature for 1 hr during which time the color changed from the initial red to a deep yellow-green. The reaction was quenched in water (2 l.), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were combined and washed repeatedly with 5% NaOH. Following one wash with dilute HCl, the organic phase was flash evaporated and vacuum distilled. The fraction with bp 140–200° (45.1 g) was dissolved in hexane (250 ml) and extracted with a solution of KOH (12 g) in methanol (60 ml). (In the lower homologs this step is unnecessary in that the phenol by-product was removed by the aqueous base extraction step.) The methanol solution was washed once with hexane; the hexane fractions were pooled and flash evaporated to yield a pale amber oil, phenol-free by infrared and identical with the product obtained from the PPA run above. The yield was 30%. Attempts to replace the CH_2Cl_2 solvent with CS_2 led to a reduced yield of the desired dimethoxyphenone product and did not circumvent the formation of the related phenol **2**. Essentially the same procedure was employed for the following intermediates. **1c**: bp 147–150° (20 mm); yield 77%. Anal. ($C_{10}H_{12}O_3$) C, H. **1d**: bp 130–137° (4 mm); yield 88% (with CS_2, 40%). Anal. ($C_{11}H_{14}O_3$) C, H. **1e**: bp 170–178° (20 mm); yield 70% (with CS_2, 61%). Anal. ($C_{12}H_{16}O_3$) C; H: calcd, 7.74; found, 6.93.

2-Hydroxy-5-methoxyphenyl *n*-Butyl Ketone (2f). The basic methanolic solution from procedure b above was added to water, acidified with HCl, and extracted with CH_2Cl_2. The extracts were pooled and the solvent was removed in vacuo yielding an oil (18.9 g) which crystallized spontaneously. This was triturated under 10 ml of cold methanol and filtered free of solvent, and the residual solids were recrystallized from 30 ml of boiling methanol. The product, mp 62–62.5°, yield 12.2 g, showed a near-ultraviolet absorption maximum at 355 nm in methanol shifting to 381 nm with KOH. This property was common to all the phenolic phenones of this series. Using a similar synthetic procedure the following phenols were prepared. **2c**: mp 49–49.5°; yield 16%. Anal. ($C_9H_{10}O_3$) C, H. **2d**: mp 47–48°; yield 0.5%. Anal. ($C_{10}H_{12}O_3$) C, H. **2e**: oil; yield 0.4%.

4-Methenyl-6-methoxy-3-methylbenzoxazin-1,3(2)-one (7). A solution of **2c** (51.0 g, 0.31 mol) in CH_3NCO (120 ml) was cooled to about 10° and treated with triethylamine (4 drops). After standing 24 hr the solid which had formed was filtered and slurried for 1 hr in water (1 l.). After filtering and drying there was obtained 53.5 g of **7**, mp 111–113°. Anal. ($C_{11}H_{11}NO_3$) C; H: calcd, 5.40; found, 5.01. N: calcd, 6.83; found, 6.30. The methenyl group showed two well-resolved doublets in the NMR (with integration of two hydrogens) centered at 4.53 and 5.00 ppm in acetic acid and at 4.53 and 5.12 ppm in Me_2SO (relative to Me_4Si). These were completely eradicated by the addition of trifluoroacetic acid.

2-Amyl-1,4-dimethoxybenzene (3f). Mossy zinc (360 g) was allowed to stand in a solution of $HgCl_2$ (7.2 g) in hot water (200 ml) for 2 hr. The water was drained and replaced with concentrated HCl (200 ml). A solution of **1f** (53.0 g, 0.24 mol) in ethanol (107 ml) and concentrated HCl (30 ml) was added dropwise over the course of 4 hr. Over this same period an additional 330 ml of concentrated HCl was added in small increments. The final mixture was held at reflux for 12 hr, cooled, diluted with water (1 l.), and extracted with CH_2Cl_2. The extracts were pooled and washed successively with water, 5% NaOH, and water. After removal of the solvent the residual oil was distilled in vacuo (20 mm). The desired product **3f** (19.9 g, yield 38%) was contained primarily (>90%) in the fraction with bp 152–170°. Using this procedure the following intermediates were prepared. **3c**: bp 90–93° (2 mm); yield 38%. **3d**: bp 137–145° (20 mm); yield 45%. **3e**: bp 141–145°(20 mm); yield 62%.

4-Amyl-2,5-dimethoxybenzaldehyde (4f). A mixture of $POCl_3$ (36.3 g) and *N*-methylformanilide (40.9 g) was allowed to incubate for 30 min. Then **3f** (18.9 g, 0.09 mol) was added and the resulting solution heated on the steam bath for 2 hr. The resulting product was added to water (1 l.), stirred several hours, and extracted with CH_2Cl_2. The extracts were pooled and evaporated to a dark residue which was leached several times with boiling hexane. After removal of the hexane the resulting amber oil was distilled, providing the desired product [bp 201–205° (20 mm)] as a crystalline solid (12.5 g, yield 58%). An analytical sample from methanol had mp 25–26°. Anal. ($C_{14}H_{20}O_3$) H; C: calcd, 71.16; found, 71.92. Using this procedure the following intermediates were prepared. **4c**: mp 46–47°; yield 73%. Anal. ($C_{11}H_{14}O_3$) C, H. **4d**: oil; yield 60%. **4e**: mp 47–48°; yield 22%. Anal. ($C_{13}H_{18}O_3$) C, H. The product **4d** was about 90% pure by GLC and was converted to **5d** without further purification.

1-(2,5-Dimethoxy-4-amylphenyl)-2-nitropropene (5f). A solution of **4f** (12.3 g, 0.05 mol), ammonium acetate (4 g), and nitroethane (12 ml) in acetic acid (50 ml) was refluxed on the steam bath for 4 hr. The mixture was added to water (250 ml) and extracted with CH_2Cl_2. The extracts were pooled and washed with water, and the solvent was removed. The resulting red oil was seeded with a sample of **5f** obtained by preparative GLC and recrystallized from methanol: yield 88% of orange crystals. An analytical sample had mp 43–44°. Anal. ($C_{16}H_{23}NO_4$) C, H, N. Essentially the same procedure was employed for the preparation of the following intermediates. **5c**: mp 67–68°; yield 26%. Anal. ($C_{13}H_{17}NO_4$) C, H, N. **5d**: mp 94–96°; yield 34%. Anal. ($C_{14}H_{19}NO_4$) C, H, N. **5e**: mp 55–56°; yield 71%. Anal. ($C_{15}H_{21}NO_4$) C, H, N. In the preparation of **5e** and **5f** the crude product was reduced directly to the final amine without recrystallization, accounting for the high apparent yields of the nitrostyrenes and the low apparent yields of the final amines. The reduction of the nitrostyrenes **5c** and **5d** was performed on the purified intermediate. All analytical samples were prepared by recrystallization from methanol.

2,5-Dimethoxy-4-amylphenylisopropylamine (6f, DOAM). The nitrostyrene **5f** (13.2 g, 0.045 mol) was leached from a Soxhlet thimble into a suspension of $LiAlH_4$ (10 g) in anhydrous ether (500 ml). The mixture is stirred at reflux for 18 hr and at room temperature for an additional 48 hr. With external cooling, dilute sulfuric acid (1 l. of 8%) was added dropwise until hydrogen evolution ceased, then as rapidly as the formed solids could be dispersed. The ether layer was separated and the acidic aqueous phase washed with additional ether. Sodium potassium tartrate (250 g) was added to the aqueous phase which was made basic (with 5% NaOH) and extracted with CH_2Cl_2. After removal of the CH_2Cl_2 the residue (6.2 g) was dissolved in anhydrous ether (200 ml) and the solution saturated with anhydrous HCl. After filtration the product (**6f**) was recrystallized from acetonitrile to give mp 145–146° and yield 39%. The melting points, yields, and recrystallization solvents of the other final amine hydrochlorides, prepared by this procedure, are given in Table I.

References and Notes

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Novel Phosphate Anthelmintics. 3. Alkyl and Aryl 1-Methyleneallyl Phosphates, Phosphonates, and Phosphinates

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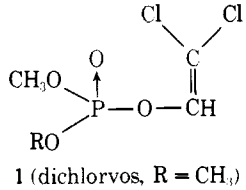
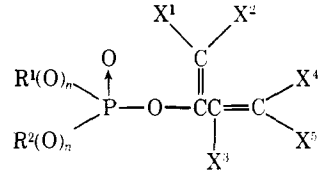
A series of new highly chlorinated 1-methyleneallyl ("butadienyl") dialkyl phosphates and related phosphonates and phosphinates has been synthesized and assessed for anthelmintic activity in mice against the tapeworm *Hymenolepis nana* and the pinworm *Syphacia obvelata*. Highest activity was observed with diethyl 2,3,3-trichloro-1-dichloromethyleneallyl ("perchlorobutadienyl") phosphate (**14**), while replacement of both ethoxy groups by methoxy and larger alkoxy or phenyl groups gave less efficacious compounds. In general, chlorine depletion of the 1,3-butadien-2-yl moiety or saturation of one double bond reduced anthelmintic responses.

Scores of 2,2-dichlorovinyl phosphates have been synthesized and many were found effective anthelmintics[1,2] since the discovery of the broad anthelmintic[3] properties of dichlorvos, 2,2-dichlorovinyl dimethyl phosphate (1, R = CH_3). Generally, a variety of alkyl, aralkyl, and aralkenyl groups have been used as substituents, R, to modify the biological activity of dichlorvos. It was of interest to determine the anthelmintic properties arising from 1 by the formal attachment of an unsaturated, highly chlorinated, group to the α-carbon atom of the β,β-dichlorvinyl moiety. 1-Methyleneallyl esters of general structure **2** were chosen for study since the influence on activity of both methylene groups could be studied independently in relation to their degree of chlorination. This study was facilitated by the development in these laboratories of general methods for the preparation of a series of highly chlorinated butenones.



1 (dichlorvos, R = CH_3)



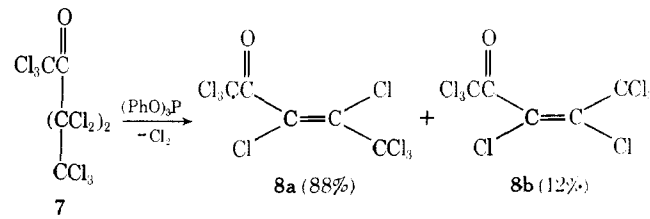
2. R^1, R^2 = alkyl, aryl; $n = 0, 1$; X^1–X^5 = H, Cl, CCl_3

The first reported synthesis of dialkyl 1-methyleneallyl phosphates highly chlorinated in the methyleneallyl moiety was from these laboratories.[4] In 1967,[5] we reported on the potent insecticidal activity for a number of these highly chlorinated dialkyl 1-methyleneallyl phosphates and related phosphonates. Insecticidal activity is largely due to the presence of the 1-methyleneallyl group and we have found it to be highly dependent upon the degree of chlorination. We now wish to describe the synthetic procedures used to prepare these compounds and to relate other details of their properties. Throughout this paper, the term "chlorobutadienyl" refers to chlorination in the 1-methyleneallyl group.

Chemistry. Phosphites, Phosphonites, and Phosphinites. Trialkyl phosphites were purchased from commercial sources or were prepared by the reaction of phosphorus trichloride and the appropriate alcohol in ether in the presence of pyridine or *N,N*-diethylaniline.[6] The latter approach was also used to prepare dimethyl ethylphosphonite[7] and diethyl ethylphosphonite[7] from ethyldichlorophosphine and methanol and ethanol, respectively. Dimethyl phenylphosphonite,[8] diethyl phenylphosphonite,[8] and diisopropyl phenylphosphonite[9] were prepared analogously by the reaction of phenyldichlorophosphine[10] with the respective alcohol. This procedure was also used to prepare methyl diphenylphosphinite[11] from diphenylchlorophosphine[12] and methanol.

Chloro Ketones (Table I). 1,1,4,4,4-Pentachloro-1-buten-3-one (**3**) was readily prepared by the ferric chloride catalyzed fragmentation of β,β-bis(trichloromethyl)-β-propiolactone.[13] An alternate process in which **3** is obtained by treatment of vinylidene chloride with trichloroacetyl chloride in the presence of anhydrous aluminum chloride containing 1% of ferric chloride has recently been described.[14] Addition of chlorine to the double bond of **3** afforded 1,1,1,3,4,4,4-heptachlorobutan-2-one (**4**) which was readily dehydrochlorinated with triethylamine in ether to give 1,1,2,4,4,4-hexachloro-1-buten-3-one[13] (**5**). Compound **5** was also readily prepared by the dechlorination of octachlorobutanone,[15] (**6**). The dechlorination has also been effected using triphenyl phosphite, triphenylphosphine, or a trialkyl phosphite[16] (Scheme I).

Decachloro-2-pentanone (**7**) reacted analogously with triphenyl phosphite to give a mixture of the two geometrically isomeric 1,1,1,2,3,5,5,5-octachloro-2-penten-4-ones[16] (**8a** and **8b**).



7 **8a** (88%) **8b** (12%)

The facile acid-catalyzed thermolysis of the phosphates **15**, **28**, and **42** leading to 1,1,2,4,4-pentachloro-1-buten-3-one (**9**), 1,1,4,4-tetrachloro-1-buten-3-one (**10**), and 1,1,2,4-tetrachloro-1-buten-3-one (**11**) has been described.[17] This technique, which is outlined in Scheme II, represents a valuable preparative method for the selective mono-α-dechlorination of α-chlorocarbonyl compounds originally used in the preparation of the vinyl phosphates