Methoxyphosphonium Ions: Intermediates in the Arbuzov Reaction

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Compounds of the form ABR'P$^+$OR X$^-$ (I) are believed to be intermediates in the Arbuzov reaction. Several compounds of this sort, with X = $^-O_3SCF_3$ and R = R' = CH_3, have now been isolated. Evidence is presented for the phosphonium salt structure. The compound $CH_3P^+(OCH_3)_3$ is a rapid methylating agent; it reacts quantitatively and too fast to measure with water, and with I$^-$ with a second-order constant of 900 M^{-1} s^{-1} at 0 °C in acetone. Various compounds of type I with A and B = CH_3O, aryl, aryloxy, and alkyl have been isolated and characterized.

When trimethyl phosphite is treated with methyl iodide, the first detectable product is dimethyl methylphosphonate, and the methyl iodide is recovered. This example of the Arbuzov reaction is believed[1-3] to go through the intermediate iodide salt of the methyltrimethoxyphosphonium ion 1 (eq 1 with X = I)

$$P(OCH_3)_3 + CH_3X \rightarrow \underset{1}{CH_3P^+(OCH_3)_3} + X^- \quad (1)$$

which rapidly decomposes yielding the phosphonate and methyl iodide (eq 2).

$$\underset{1}{X^-} + \underset{1}{CH_3P^+(OCH_3)_3} \rightarrow XCH_3 + \underset{3}{OP(CH_3)(OCH_3)_2} \quad (2)$$

This plausible intermediate has not been isolated, and the reaction has not been adequately studied in dilute solution by modern kinetic methods. Nevertheless, the failure to observe the postulated intermediate requires that the attack of I$^-$ on 1 must be very fast. The mechanism is rendered more plausible by the isolation of salts of the form **2**, $CH_3P(OAr)_3^+$ X$^-$, where the presumed second step becomes the very unfavorable nucleophilic attack on aryl carbon.[4] Similarly, the compound $CH_3P^+[OCH_2C(CH_3)_3]_3$ I$^-$ has been reported.[5] Recently methyltriphenoxyphosphonium trifluoromethanesulfonate has been prepared[6] and has been shown to be a strong electrolyte in acetonitrile, although the compound with X = I has been reported[7,8] to be a weak electrolyte because the reaction with silver nitrate is slow.[4] There is a report of the isolation of Et_2MeP^+OMe I$^-$ as a reasonably stable crystalline material.[7] Other workers have been able to isolate trialkoxyphosphonium fluoroborates obtained by interaction of $Et_3O^+BF_4^-$ or $Ph_3C^+BF_4^-$ with phosphites.[9]

Because the presumed reaction of the intermediate is a nucleophilic substitution reaction, we guessed that if we could provide a methylating agent with a very weakly nucleophilic leaving group, the phosphonium salt might be isolable even with the most reactive examples. This has proved to be the case using the reaction of methyl trifluoromethanesulfonate with trimethyl phosphite. In hexane or ether, a white crystalline product is rapidly precipitated to which we assign the structure 1 triflate. The compound is not highly stable and is contaminated with a small amount of the Arbuzov product **3**, but it is adequately characterized by the proton NMR in $CDCl_3$ (PCH_3, δ 2.18, doublet, J_{PH} = 17 Hz, area 1.0; OCH_3, δ 4.05, doublet, J_{PH} = 11 Hz, area = 3.0), the ^{31}P NMR (proton decoupled, δ +53.1 from H_3PO_4, the new convention[10] for the sign of the chemical shift is used throughout), and the yield of acid produced very rapidly on hydrolysis (97%, based on $C_6H_{12}O_6PSF_3$). Since it was not easily obtained in a much purer state, it was not characterized by elemental analysis.

The salt showed three fast reactions: hydrolysis, yielding triflic acid, dimethyl methylphosphonate, and (presumably) methanol; a reaction with sodium iodide in acetone, yielding methyl iodide and the phosphonate ester; and a reaction with trimethyl phosphite, also yielding the phosphonate ester. We did not attempt to measure the hydrolysis rate.

The reaction with sodium iodide in acetone was very fast and exothermic. The rate was followed in quite dilute solutions by the change of temperature with time, with the data treated as described by Bell.[11] The rate constant for iodide ion attack so obtained at 0 °C (with a temperature rise of about 0.1 °C) is 9×10^2 M^{-1} s^{-1}. This rate constant is quite large enough to account for the failure to detect an intermediate in the methyl iodide catalyzed rearrangement of trimethyl phosphite.

The reaction of the salt with trimethyl phosphite is extremely exothermic, and we were unable to measure a rate constant by Bell's method in our simple apparatus. The rate constant is apparently greater than that for iodide attack. The reaction is the simple methyl transfer, reaction 3.

$$\underset{1}{CH_3P^+(OCH_3)_3} + P(OCH_3)_3 \rightarrow CH_3\overset{\overset{O}{\|}}{P}(OCH_3)_2 + \underset{1}{CH_3P^+(OCH_3)_3} \quad (3)$$

The high but unknown rate of this reaction suggests that it may play an important role in the Arbuzov rearrangement of trimethyl phosphite catalyzed by methyl iodide, since the rate constant for (3) is higher than for iodide attack, and the nucleophile is present at higher concentration. Reaction 3 has been previously described as a part of the "autocatalytic mechanism."[3,12] It is the high rate of (3) which accounts for the contamination of 1 triflate by **3**.

The low reactivity of 1 triflate can either be attributed to the low rate of nucleophilic attack of the triflate ion on 1 (reaction 4)

$$1 + OTf^- \rightleftarrows 3 + MeOTf \quad (4)$$

or to a possibly unfavorable equilibrium for this reaction. The latter is certainly true, for we were able to synthesize 1 triflate by treatment of **3** with methyl triflate, a synthesis about as convenient as that from trimethyl phosphite although not as conspicuously exothermic. Indeed, the facility of the reverse reaction 4, together with that of reaction 3, suggests that in the synthesis of 1 triflate, **3** may be an intermediate. Since we hope to generalize this reaction to some of preparative value, it is important that the general reaction 5

$$ABPOR + CH_3OTf \rightarrow ABP^+CH_3(OR) + OTf^- \quad (5)$$

goes directly rather than via an Arbuzov product, OPABR, which would give an *O*-methyl compound, $ABP^+R(OCH_3)$, rather than an OR compound. We have therefore treated triethyl phosphite with methyl triflate and find only the direct product, $(CH_3CH_2O)_3P^+CH_3$ OTf^-, not contaminated at the level of the proton NMR spectrum with P-ethylated or O-methylated material.

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Table I. $MeP^+(OMe)AB^-OSO_2CF_3$

Registry no.	A	B	^1H NMR δ[a]	^1H NMR Multiplicity	^1H NMR J, Hz	^{31}P NMR,[b] δ	Mp, °C
64294-66-2	OMe	OMe	4.05	d	11	+53.1	28–32
			2.18	d	17		
64294-67-3	OMe	Ph	7.6	m		+78.5	Oil
			4.0	d	10		
			2.38	d	14		
64294-69-5	Ph	Ph	7.8	m		+74.5	34–37
			4.0	d	13		
			2.8	d	15		
64294-70-8	OPh	OPh	7.0	m		+41.5	Oil
			3.7	d	11		
			2.53	d	17		
64294-72-0	Et	OMe	3.96	d	11	+99.0	~0
			2.12	d	14		
			1.7	m			
64294-74-2	Et	Et	3.95	d	11	+103.5	~0
			2.35	m			
			2.1	d	12		
64315-07-7	o-$C_6H_4O_2$		7.1	m		+49.6	Oil[d]
			3.71	d	12		
			3.22	d	8		
64294-75-3	$(EtO)_3P^+CH_3$[c]		4.4	m	6		
			2.17	d	17		
			1.45	t	6		

[a] Chemical shifts relative to Me_4Si; spectra taken in $CDCl_3$ on a Varian A-56/60. [b] Chemical shifts relative to 85% H_3PO_4; spectra taken in $CDCl_3$ on a Varian XL-100. [c] This compound is not structurally described by the table heading. [d] At times a crystalline compound could be obtained which was a solid at 0 °C.

Several other substances identified as alkoxyphosphonium triflates have been made by the same method. They are presented in Table I, which shows the proton and phosphorus chemical shifts. The major contaminant is the Arbuzov product, shown by both proton and phosphorus NMR. They have not yet been otherwise characterized, but the wide range of compounds suggests that this reaction is both general and practical for the preparation of alkoxyphosphonium triflates.

The phosphorus chemical shifts shown in Table I fall in the range believed to be characteristic of phosphonium salts rather than phosphoranes, but a study of the various compounds used to establish this rule suggests that a structural ambiguity might exist in the original compounds,[13] as well as in ours; thus, the NMR chemical shift is not a totally unequivocal method for structure assignment. In a similarly ambiguous way, the phosphorane in its stable conformation would have one apical and two equatorial methoxyls of presumably different chemical shift. The observed presence of only one methoxy doublet argues compellingly either for the phosphonium structure or for a rapidly pseudorotating pentacovalent system. However, rapid pseudorotation is sufficiently prevalent in phosphoranes so that it cannot be reasonably eliminated. The observation of high electrical conductivity of methyltriphenoxyphosphonium triflate is convincing evidence for the ionic structure;[14] yet, exactly the same cation as the iodide salt was reported to react only slowly with silver ion in ethanol solution,[4] which was widely interpreted as implying a phosphorane structure.[7,8] We have repeated this experiment and find that we can explain the slow iodide precipitation by the following reaction sequence (eq 6–8).

$$MeP^+(OPh)_3 + EtOH \rightarrow PhOH + MeP^+(OPh)_2(OEt) \quad (6)$$

$$MeP^+(OPh)_2(OEt) + I^- \rightarrow OP(Me)(OPh)_2 + EtI \quad (7)$$

$$EtI + Ag^+ \rightarrow AgI \quad (8)$$

The slow reaction with silver nitrate is presumably the reaction with ethyl iodide. Curiously, this series of reactions was well understood by Landauer and Rydon,[4] who proposed making alkyl iodides in this way. The widespread alternate interpretation as evidence for a nonionic phosphorane is apparently a consequence of an initial misreading, followed by numerous quotations[7,8,15–17] of secondary sources. We have not yet studied further the kinetics of this reaction, but a fairly rapid formation of ethyl iodide in this system is readily observable by NMR. Thus there remains no evidence of a stable or slowly equilibrated phosphorane in these systems with reasonably stable counterions. We therefore recommend that the term "quasiphosphonium ion" be abandoned in favor of the unqualified phosphonium ion.

A report of the reaction of methyl diethylphosphinite with methyl iodide to yield a stable methyldiethylmethoxyphosphonium iodide[7] is the only case we have found reported of a true Arbuzov intermediate, except for a few cases where the ester group is a highly branched alkyl.[5,18,19] This report is apparently inconsistent with the very fast reaction of the ion 1 with iodide ion, but it is possible that the substitution of two ethyl groups for two of the methoxy groups inductively decreases the rate so much that the iodide salt is isolable, especially if it is not very soluble. We have therefore repeated this experiment and isolated methyldiethylmethoxyphosphonium iodide at −10 °C but found it quite unstable in our hands. Decomposition to diethylmethylphosphine oxide occurs in about 20 min at room temperature and in about 24 h at −78 °C.

Conclusion

Compounds of the type $ABP^+(OR)(CH_3)^-OSO_2CF_3$ are readily prepared by the reaction of ABPOR with $CH_3O_3SCF_3$. They are ionic, they are powerful alkylating agents, and the cations are both intermediate in and catalytic for the Arbuzov reaction.

Experimental Section

A presumed serious hazard connected with this study is that of the toxicity of methyl trifluoromethanesulfonate. By analogy to the slightly less reactive methyl fluorosulfonate which has been found to be a lethal inhalation hazard,[20] all operations should be carried out in a good hood and with scrupulous care in handling this powerful

methylating agent. It is also now classified as a cancer suspect agent.

Methods. The phosphonium salts are moisture sensitive; therefore, precautions were taken to ensure that all reagents and glassware were thoroughly dried. Commercial anhydrous ethyl ether was used without further purification. In two cases the starting materials for the phosphonium salts (methyl diethylphosphinite and dimethyl ethylphosphonite) were pyrophoric, and all transfers of these compounds were performed in a glovebag purged with nitrogen. ^{31}P NMR spectra were obtained on a Varian XL-100 spectrometer, and chemical shifts are reported relative to 85% phosphoric acid;[10] proton spectra were obtained on a Varian A-56/60 spectrometer at 60 MHz with tetramethylsilane reference. Melting and boiling points are uncorrected.

Materials. A general method was employed to make methyl esters of phosphonous and phosphinous acids. This involved the reaction of methanol with a chlorophosphorous compound in the presence of *N,N*-diethylaniline to absorb the hydrochloric acid formed. A typical example of the method is the synthesis of dimethyl phenylphosphonite.

Dimethyl phenylphosphonite was prepared by the dropwise addition of 25.1 g (0.14 mol) of phenyldichlorophosphine (Strem Chemicals) to 8.96 g (0.28 mol) of methanol and 33.94 g (0.28 mol) of *N,N*-diethylaniline in about 100 mL of anhydrous ether. The reaction was conducted in an ice bath and under a nitrogen atmosphere. The mixture was allowed to stir for several hours, and then the *N,N*-diethylaniline hydrochloride was filtered and washed with anhydrous ether. The combined filtrate and washings were distilled under vacuum with a nitrogen bleed. The clear product was collected at 95–97 °C (16 mm) [lit.[21] 94.5 °C (13 mm)]: yield, 53%; ^{31}P NMR ($CDCl_3$) δ +159 (lit.[22] +159).

Methyl diphenylphosphinite was prepared in a similar manner using diphenylchlorophosphine (Strem Chemicals) and 1 equiv each of methanol and *N,N*-diethylaniline: bp 140–143 °C (88 mm) [lit.[23] 151–152 °C (10 mm)]; yield, 85%; proton NMR ($CDCl_3$) δ 3.53 (d, J_{HP} = 15 Hz, $POCH_3$), 7.3 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +155.2 (lit.[24] +115.6).

Diphenylmethyl Phosphite. Methanol (1 equiv) and 1 equiv of *N,N*-diethylaniline and diphenyl phosphorochloridite were used to prepare diphenylmethyl phosphite: bp 158–162 °C (9 mm) [lit.[25] 169.5–170.5 °C (11 mm)]; yield, 75%; proton NMR (CDCl) δ 3.57 (d, J_{HP} = 9 Hz, $POCH_3$), 6.9 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +128. The diphenyl phosphorochloridite was prepared in low yield (30%) by the reaction of 2 equiv of phenol with phosphorus trichloride: bp 102–105 °C (0.5 mm). Diphenyl phosphorochloridite was prepared in an alternate manner from triphenyl phosphite and propionyl chloride:[26] bp 122–123 °C (0.7 mm) [lit.[26] 115 °C (0.5 mm)]; yield, 60%.

Dimethyl Ethylphosphonite. Similarly, dimethyl ethylphosphonite was prepared from methanol, *N,N*-diethylaniline, and dichloroethylphosphine (Strem Chemicals). This compound is pyrophoric and was always handled in a nitrogen atmosphere: bp 103–105 °C (760 mm) [lit.[27] 73.5–74.5 °C (225 mm)]; yield, 34%; proton NMR ($CDCl_3$) δ 1.1 (m, PCH_2CH_3), 3.43 (d, J_{HP} = 11 Hz, $POCH_3$); ^{31}P NMR ($CDCl_3$) δ +190.

Methyl diethylphosphinite was prepared by the reaction of methyl phosphorodichloridite with ethylmagnesium bromide similar to that described for propyl dipropylphosphinite.[28] A purged apparatus was charged with 13.3 g (0.1 mol) of methyl phosphorodichloridite and 34.8 g (0.44 mol) of pyridine in about 150 mL of anhydrous ether. The flask was kept at dry ice–acetone temperatures while 0.22 mol of ethylmagnesium bromide was added dropwise. The mixture was allowed to stir for several hours and then warmed to room temperature. The solution with suspended pyridine salt was filtered and the precipitate washed with ether in a thoroughly purged glovebag. The filtrate and washings were distilled with a nitrogen bleed: bp 48–50 °C (60 mm); yield, 60%.

The above preparation required the difficult separation of pyridine from the desired product so an alternate method was used to prepare methyl diethylphosphinite. Methanol and *N,N*-diethylaniline (1 equiv each) were allowed to react with diethylchlorophosphine (Strem Chemicals) as before. Again all transfers were done in a nitrogen atmosphere: bp 124–126 °C (760 mm); yield, 85%; proton NMR ($CDCl_3$) δ 1.2 (m, PCH_2CH_3), 3.4 (d, J_{HP} = 13 Hz, $POCH_3$); ^{31}P NMR ($CDCl_3$) δ +139.4.

Methyl *o*-phenylene phosphite was prepared following the method of Crofts et al.:[29] bp 80–82 °C (17 mm); yield, 90%; proton NMR ($CDCl_3$) δ 3.22 (d, J_{HP} = 10 Hz, $POCH_3$), 7.0 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ +128.

Trimethyl phosphite obtained commercially was distilled under nitrogen: bp 109–110 °C; ^{31}P NMR ($CDCl_3$) δ +140 (lit.[22] 140).

Preparation of Phosphonium Salts. A typical preparation of a methylphosphonium triflate is described. Methyl triflate (Aldrich, 5 g, 0.03 mol) was placed in a flask thoroughly purged with nitrogen in 25 mL of anhydrous ether. The reaction vessel was cooled to 0 °C. Trimethyl phosphite (3.7 g, 0.03 mol) was added dropwise. The mixture was allowed to stir for about 1 h. A fine white precipitate was present. The mixture was filtered rapidly under a nitrogen stream, and the solid was stored in a vacuum desiccator at 0 °C.

All of the phosphonium salts were prepared in a similar manner, the only difference being the nature of the product. In some cases, the phosphonium salt was an oil which resisted crystallization. Where the product was an oil, the solvent was removed at 0 °C using a vacuum pump with a nitrogen bleed. All of the phosphonium salts prepared were sensitive compounds and had limited lifetimes shown by liquefaction of the crystals; methyltrimethoxyphosphonium triflate would last for about 1 week, while diethylmethoxymethylphosphonium triflate only lasted for several hours at −10 °C. In particular, 2-methoxy-2-methyl-1,3,2-benzodioxaphospholium triflate and diphenoxymethoxymethylphosphonium triflate showed a tendency to undergo further reaction to the Arbuzov product (i.e., loss of the *O*-methyl group) unless the temperature was maintained at 0 °C during reaction. Furthermore, longer reaction time (overnight stirring) is necessary in these two cases involving methyl *o*-phenylene phosphite and diphenylmethyl phosphite.

Measurement of Rates of Reactions. The method employed to determine the rate of reaction of methyltrimethoxyphosphonium triflate with iodide was similar to that of Bell.[11] The methyltrimethoxyphosphonium triflate (0.029 g, 0.0001 mol) in 30 mL of dried spectroqualilty acetone was placed in a test tube shaped glass container equipped with a sealed stirrer, an inert gas inlet, and a sealed thin-walled bulb containing sodium iodide (0.015 g, 0.0001 mol) in 2 mL of acetone on the end of a movable glass rod located over a spike in the bottom of the tube. A glass sealed thermistor was also in the solution for measuring temperature. The solution was purged by passing nitrogen through, and the whole apparatus was placed in an ice–water bath. When temperature equilibrium was obtained, as shown by the thermistor resistance, the glass bulb was broken on the spike. The temperature rise was observed on a potentiometric recorder attached to the thermistor via a Wheatstone bridge circuit. This reaction showed a temperature rise of about 0.1 °C attained in approximately 12–18 s. The method was limited by the time constants of the thermistor and the recorder.

When the reaction was done in a more concentrated solution, the NMR spectrum corresponded to that of an approximately 1:1 mixture of methyl iodide and dimethyl methylphosphonate.

A similar method was used to follow the reaction of methyltrimethoxyphosphonium triflate with trimethyl phosphite. This reaction proved to be too fast to follow in this manner. The product was again identified by both the proton and phosphorus NMR spectra.

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Registry No.—Dimethyl phenylphosphonite, 2946-61-4; methyl diphenylphosphinite, 4020-99-9; diphenylchlorophosphine, 1079-66-9; diphenylmethyl phosphite, 3577-87-5; diphenyl phosphorochloridite, 5382-00-3; dimethyl ethylphosphonite, 15715-42-1; dichloroethylphosphine, 1498-40-4; methyl diethylphosphinite, 13506-71-3; methyl phosphorodichloridite, 3279-26-3; ethyl bromide, 74-96-4; methyl *o*-phenylene phosphite, 20570-25-6; trimethyl phosphite, 121-45-9; methyl triflate, 333-27-7.

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Studies on Vitamin D (Calciferol) and Its Analogues. 13. 3-Deoxy-3α-methyl-1α-hydroxyvitamin D_3, 3-Deoxy-3α-methyl-1α,25-dihydroxyvitamin D_3, and 1α-Hydroxy-3-epivitamin D_3. Analogues with Conformationally Biased A Rings[1,2]

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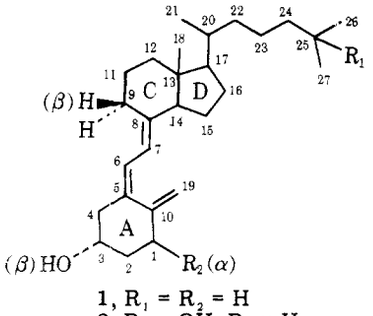
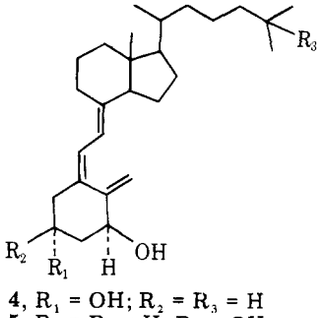
Lithium dimethylcuprate reacts with high stereoselectivity from the α face at C_3 of each of the three steroids: the 3β-tosylate (**10b**) of 1α-hydroxycholesterol (**10a**) to give inversion product **11a**; cholesta-2,5-dien-1-one (**14**) or its presumed equivalent **13** (3β-benzoyloxycholest-5-en-1-one) to afford the 1,4-addition product **12a**; and 1α-acetoxycholesta-3,5-dien-7-one (**23**) to produce mainly the 1,6-addition compound **24a**. The diol **10a** was also epimerized stereoselectivity at the 3 position to afford **26a**. The alcohol **11a**, its 25-hydroxy counterpart **11c**, and **26a** were converted by conventional methods to 3-deoxy-3α-methyl-1α-hydroxyvitamin D_3 (**7**), 3-deoxy-3α-methyl-1α,25-dihydroxyvitamin D_3 (**8**), and 1α-hydroxy-3-epivitamin D_3 (**9**). The intermediates **12a** and **24a** could also be utilized for preparing intermediates leading to **7**, and the 3α-methyl configuration for the various intermediates was rigorously established by chemical and spectral correlations. High-resolution ^1H NMR studies at 300 MHz revealed that the A ring of **7** is locked into a single chair conformer with both 1α-hydroxyl and 3α-methyl equatorially oriented. By contrast, **9**, which differs from **7** only in the replacement of the 3α-methyl by hydroxyl, exists predominantly (~70%) in the opposite chair conformer. All three analogues, **7**, **8**, and **9**, possess an ability to elicit in vivo intestinal calcium absorption and bone calcium mobilization in the chick.

Before vitamin D_3 (**1**) elicits its physiological action (calcium transport), it must be metabolized to 25-hydroxyvitamin D_3 (**2**) and then to 1α,25-dihydroxyvitamin D_3 (**3**). The latter (**3**), the most biologically potent calciferol known, is now considered to be a steroid hormone both from a structural as well as a functional point of view. Its metabolic precursors **1** and **2** can be defined as prohormones.[4] Unlike the classical steroid hormones[5] such as estradiol, aldosterone, and dihydrotestosterone, which possess the fully intact cyclopentanoperhydrophenanthrene nucleus, vitamin D is unique inasmuch as it lacks the B ring. Recent ^1H NMR studies have shown that the A ring of **3**,[6a-c] as well as that of other related calciferols,[6] is partitioned between two rapidly equilibrating chairlike conformations.[7] We have considered the interesting possibility that one of the two unique chair forms of vitamin D might be involved in selective binding to various receptor



1, $R_1 = R_2 = H$
2, $R_1 = OH$; $R_2 = H$
3, $R_1 = R_2 = OH$



4, $R_1 = OH$; $R_2 = R_3 = H$
5, $R_1 = R_2 = H$; $R_3 = OH$
6, $R_1 = R_2 = R_3 = H$
7, $R_1 = R_3 = H$; $R_2 = CH_3$
8, $R_1 = H$; $R_2 = CH_3$; $R_3 = OH$
9, $R_1 = R_3 = H$; $R_2 = OH$

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