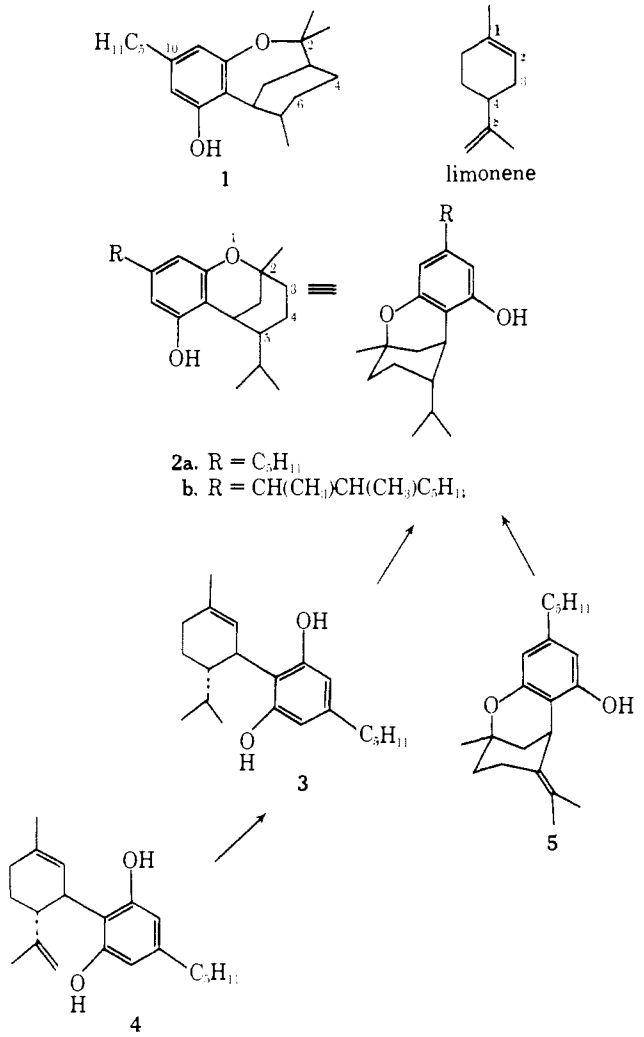
Scheme I



pound **2a** obtained from cannabidiol[2] and from the condensation of olivetol with pinene[1] were shown to be identical by direct comparison of their infrared, NMR, and mass spectra and their thin-layer and gas chromatographic behavior.

The infrared and NMR spectra were superimposable. The NMR assignments are as follows: (CCl_4) δ 0.95 (d, J = 7 Hz, isopropylmethyl), 1.07 (d, J = Hz, isopropylmethyl), 1.30 (peak of C-2 CH_3, situated on top of various other protons), 2.35 (br, m, benzylic), 3.30 (br, C-6 proton), 5.95, 6.12 (aromatic protons).

The above correction applies also to the 1,2-dimethylheptyl homolog (at C-10) **2b** obtained by the condensation of pinene (or limonene) with 5-(1,2-dimethylheptyl)resorcinol. The NMR assignments are as follows: (CCl_4) δ 0.75, 0.90, 1.05, 1.15, 1.20, 1.30 (methyl groups), 3.30 (br, C-6 proton), 5.90, 6.10 (aromatic protons).

Structure **2a** is compatible with the structures assigned to the condensation products of some alkylated hydroquinones with several monoterpenes (including limonene),[5] as well as the products of the related condensation of orcinol with limonene.[6,7]

Acid condensations of phenols with limonene apparently proceed as suggested,[5,6] not solely by attack of the aromatic compound at C-2 of limonene but also at C-3. This is probably due to migration of the double bond in limonene to an endocyclic position.

In the previous publication[1] we suggested that a benzopyran moiety is not an absolute requirement for activity. This suggestion is not supported by the data now reported, as all compounds tested by us actually contain such a moiety.

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(7) The latter reaction has also been independently investigated in our laboratory. Although the reaction conditions employed by us were different than those of Stevens et al.,[6] identical products in essentially identical yields were obtained. Our reactions conditions are those described in our previous publication[1] for the reaction between olivetol and limonene.

Synthesis and Hypoglycemic Activity of Phenacyltriphenylphosphoranes and Phosphonium Salts

Benjamin Blank,* Nicholas W. DiTullio, Linda Deviney, John T. Roberts, and Harry L. Saunders

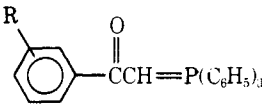
SmithKline Corporation, Division of Research and Development, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received March 6, 1975*

Phenacyltriphenylphosphorane (**1a**) and several analogs substituted in the meta position of the phenacyl group lowered blood glucose levels in 48-hr fasted rats. The corresponding phosphonium salts had comparable hypoglycemic activity. Two compounds (**1a** and **1b**) were also hypoglycemic in fed rats, but hypoglycemia could not be elicited in another species.

In a continuing search for hypoglycemic agents which act by novel mechanisms, a variety of chemical structures was screened for hypoglycemic activity in the 48-hr fasted rat. A result of this practice was the finding that 2-triphenylphosphoranylideneacetophenone (phenacyltriphenylphosphorane, **1a**) and the phosphonium salt precursor **2a** induced significant hypoglycemia in the 48-hr fasted rat. Several additional analogs were prepared and studied in the 48-hr fasted rat to determine what structural features were needed to evoke this hypoglycemic response.

The compounds were prepared according to the method of Aksnes[1] (Tables I and II). The phenacyl bromides used

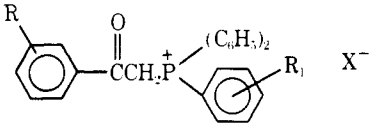
Table I. Phosphoranes



No.	R	Mp, °C	Recrystn solvent[a]	% yield	Formula	Hypoglycemic act. in 48-hr fasted rat[b] 1 hr	2 hr	4 hr
1a	H	175	A–B	92	$C_{26}H_{21}OP$	−16[c]	−24[d]	−24[e]
1b	*m*-CF_3	140–141	A–C	60	$C_{27}H_{20}F_3OP$	−15[c]	−20[d]	−22[d]
1c	*o*-CF_3	170	A–C	77	$C_{27}H_{20}F_3OP$	−1	−2	−12
1d	*p*-CF_3	195	A–C	80	$C_{27}H_{20}F_3OP$	5	1	−4
1e	*m*-CH_3	152	A–C	72	$C_{27}H_{23}OP$	−24[c]	−28[c]	−30[c]
1f	*p*-CH_3	179–181	A–C	91	$C_{27}H_{23}OP$	1	−1	−2
1g	*m*-OCH_3	164	A–C	92	$C_{27}H_{23}O_2P$	−36[c]	−38[c]	−42[c]
1h	*p*-OCH_3	140	A–C	50	$C_{27}H_{23}O_2P$	−9	−1	−4
1i	*m*-Cl	151	A–C	57	$C_{26}H_{20}ClOP$	−4	−39[c]	−42[c]
1j	*p*-Cl	195–197	A–C	84	$C_{26}H_{20}ClOP$	−2	−13[d]	−21[c]
1k	*p*-CO_2Me	180–182	D	20	$C_{28}H_{23}O_3P$	−3	−1	−8[c]
1l	*p*-CO_2H	164–166	E–F	38	$C_{27}H_{21}O_3P$	−1	−7	−8
1m	3,4-Cl_2	178–180	A–C	76	$C_{26}H_{19}Cl_2OP$	4	0	2
3		165[f]				−3	−4	4
4		157–159[g]				1	0	2
5		227–229[h]				3	9	−4

[a] The abbreviations have the following meanings: A, C_6H_6; B, Et_2O; C, ligroine (bp 40–60°); D, MeCN; E, MeOH; F, H_2O. [b] Results are expressed as the percent difference between the mean change in control and treated groups after a drug dose of 100 mg/kg po. [c] $p \leq 0.001$. [d] $p \leq 0.01$. [e] $p \leq 0.05$. [f] Lit.[11] mp 171°. [g] Lit.[10b] mp 156–158°. [h] Lit.[11] mp 205°.

Table II. Phosphonium Salts

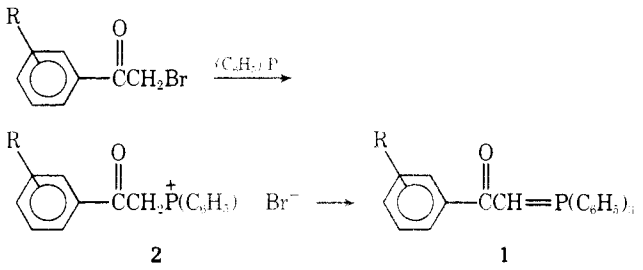


No.	R	R^1	X	Mp, °C	Recrystn solvent[a]	% yield	Formula	Hypoglycemic act. in 48-hr fasted rat[b] 1 hr	2 hr	4 hr
2a	H	H	Br	290	A–B	63	$C_{26}H_{22}BrOP$	−9[c]	−22[d]	−24[d]
2b	*m*-CF_3	H	Br	115[e]	C–D	76	$C_{27}H_{21}BrF_3OP$[f]	−18[d]	−30[g]	−30[g]
2c	*o*-CF_3	H	Br	188	A–B	33	$C_{27}H_{21}BrF_3OP$	3	2	1
2d	*p*-CF_3	H	Br	136	C–D	80	$C_{27}H_{21}BrF_3OP$[f]	3	−5	−9
2e	*m*-CH_3	H	Br	278	A–B	50	$C_{27}H_{24}BrOP$	−25[d]	−26[g]	−29[g]
2f	*p*-CH_3	H	Br	277–278	A–B	63	$C_{27}H_{24}BrOP$	−5	−7	−4
2g	*m*-OCH_3	H	Br	178	C–D	99	$C_{27}H_{24}BrO_2P$	−30[g]	−45[g]	−47[g]
2h	*p*-OCH_3	H	Br	240	A–B	48	$C_{27}H_{24}BrO_2P$	−9.5	0	+12
2i	*m*-Cl	H	Br	222	A–B	50	$C_{26}H_{21}BrClOP$	−37[g]	−36[g]	−42[g]
2j	*p*-Cl	H	Br	264–266	A–B	87	$C_{26}H_{21}BrClOP$[h]	−2	−7	−16[c]
2k	*p*-CO_2Me	H	Br	198–199[c]	A–B	20	$C_{28}H_{24}BrO_3P$	4	−1	−14[d]
2l	3,4-Cl_2	H	Br	283–284	E	88	$C_{26}H_{20}BrCl_2OP$	11	−14	−22[c]
2m	*p*-F	H	Cl	295[i]			$C_{26}H_{21}ClFOP$	−4	−17[d]	−11
2n	*p*-OH	H	Cl	303–305[c]	A–D	55	$C_{26}H_{22}ClO_2P$	−4	2	−2
2o	3,4-$(OH)_2$	H	Cl	277–279	F	50	$C_{26}H_{22}ClO_3P$[j]	−10	−11[c]	−8
2p	H	*m*-OCH_3	Br	127–129	A–D	92	$C_{27}H_{24}BrO_2P$[j]	−6	−11[d]	−12
2q	H	*p*-OCH_3	Br	130	F–D	80	$C_{27}H_{24}BrO_2P$[h]	−4	−17[d]	−33[g]
2r	H	*m*-OH	Br	275–277	A–D	74	$C_{26}H_{22}BrO_2P$[k]	6	0	−8
2s	H	*p*-OH	Br	260–262	A–D	70	$C_{26}H_{22}BrO_2P$[k]	4	0	−2

[a] The abbreviations have the following meanings: A, MeOH; B, H_2O; C, $CHCl_3$; D, Et_2O; E, absolute EtOH; F, MeCN. [b] Results are expressed as the percent difference between the mean change in control and treated groups after a drug dose of 100 mg/kg po except for 2n-s which were administered at a dose of 150 mg/kg po. [c] $p \leq 0.05$. [d] $p \leq 0.01$. [e] With decomposition. [f] Hydrate. [g] $p \leq 0.001$. [h] Hemihydrate. [i] Purchased from NEW-CHEM Co., ref 8. [j] H_2O, 0.75 mol. [k] H_2O, 0.25 mol.

in these syntheses were prepared as described by Cowper and Davidson[2] and were used directly without extensive purification.

An α-methyl (**3**) and α-chloro (**4**) analog of **1a** were prepared together with a vinylog of **3** (**5**). Two possible metabolites of **2a** (**2r** and **2s**) were synthesized from diphenyl-*m*-



2 1

and -*p*-methoxyphenylphosphine[3,4] and phenacyl bromide. The intermediate methyl ethers **2p** and **2q** were cleaved with hydrobromic acid in acetic acid to give **2r** and **2s**.

3. X = CH_3
4. X = Cl

5

Discussion

From the results shown in Tables I and II it can be seen that **1a**, its meta-substituted analogs, and the corresponding phosphonium salts have hypoglycemic activity in the 48-hr fasted rat. While only a limited number of compounds have been synthesized, this has produced a series of compounds in which substituents (both electron releasing and electron withdrawing) have been placed in ortho, meta, and para positions of the phenacyl portion of **1**. Simple changes in the nature of the substituent had no effect on hypoglycemic activity. Compounds wih meta substituents (of any nature) were active while ortho- and para-substituted compounds were inactive. Replacement of the hydrogen on the carbon atom adjacent to phosphorus in **1a** with a methyl or chloro group (3 and 4) gave inactive compounds. The disubstituted analogs **1m**, **2l**, and **2o** were also inactive as was the vinylog of 3 (**5**).

Two possible metabolites of **2a**, **2r** and **2s**, were inactive but the precursor methoxy compounds **2p** and **2q** had hypoglycemic activity comparable to **2a**.

1a was hypoglycemic when tested in fed and alloxan-diabetic rats. However, it did not lower glucose levels when tested in fed guinea pigs. **1b** was also hypoglycemic in fed rats but was inactive when given to fed rabbits or fasted dogs.[5]

It is difficult to explain the differences noted with comparable meta- and para-substituted analogs in these series. Simple steric effects do not seem to account for the differences. If the size of the para substituent is a prime determinant of hypoglycemic activity, then the *p*-fluoro analog **2m** and the unsubstituted compound **2a** would be expected to have comparable activity since the atomic sizes of these atoms are similar (bioisosteric).[6] However, this is not the case.

From the available data we are forced to assume that the "active site" in the affected biological system must have very specific steric requirements. The observations reported here are comparable to previous findings in which 3-mercaptopicolinic acid, alone of many closely related compounds, displayed significant hypoglycemic activity in the 48-hr fasted rat after oral administration.[7]

Experimental Section

Commercially available phenacyl halides were examined spectrally and were used without further purification. Methyl *p*-bromoacetylbenzoate was prepared by bromination of methyl *p*-acetylbenzoate in $CHCl_3$-Et_2O in the usual way.[2] **2m** was purchased from NEW-CHEM Co.;[8] **3–5** were prepared on a custom basis by Orgmet, Inc.,[9] using published procedures.[10,11]

Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical and Physical Chemistry Department of Smith Kline & French Laboratories. The structures of the compounds listed in Tables I and II are supported by elemental analyses and ir and NMR spectral data. Analyses (C and H) for compounds reported in this paper were within ±0.4% of the theoretical values.

The procedures presented below are representative of all the syntheses.

***p*-Carbomethoxyphenacyltriphenylphosphonium Bromide.** To a stirred solution of triphenylphosphine in dry C_6H_6 (100 ml, 0.1 mol) was added an equimolar solution of the phenacyl halide in C_6H_6. The mixture was stirred 45 min under reflux and cooled to 10°, and the solid was filtered, washed with C_6H_6, dried, and recrystallized.

2-Triphenylphosphoranylidene-*p*-carboxyacetophenone. To a solution of 4 mmol of the above salt in 25 ml of MeOH was added 10 ml of cold 40% NaOH. The cloudy solution was stirred 1 hr at room temperature and the MeOH was removed in vacuo. The aqueous residue was acidified with HCl and the mixture was extracted with $CHCl_3$. The $CHCl_3$ phases were washed with H_2O, dried, and concentrated. The residue was triturated and/or recrystallized.

2-Triphenylphosphoranylidene-*p*-carbomethoxyacetophenone. The above phosphonium salt was dissolved in MeOH and made basic by the portionwise addition of NaOMe (NaBr precipitated). The mixture was stirred for 15 min at room temperature and the solvent was evaporated. The residue was dissolved in a mixture of $CHCl_3$ and H_2O and the layers were separated. The aqueous phase was extracted with $CHCl_3$ and the combined organic phases were washed with H_2O until neutral, dried, and evaporated. The residue was triturated with Et_2O, filtered, washed with Et_2O, and recrystallized.

Hydroxyphenyldiphenylphenacylphosphonium Bromides (2r and 2s). **2p** (and **2q**) was stirred under reflux with a 1:1 mixture of 48% HBr and HOAc (10 ml/g of methoxy compound) for 20 hr. The solution was cooled and concentrated and the residue was filtered and recrystallized.

Biochemistry. Hypoglycemic activity was measured in 48-hr fasted male rats weighing ~200 g. On the morning of the test day, a zero-time tail-vein sample was obtained, followed by the oral administration of the test compound suspended in 0.5% tragacanth at a dose of 100 mg/kg. A similar group of animals receiving only the vehicle served as controls. Tail-vein samples were obtained at 1, 2, and 4 hr after drug administration. Glucose determinations and the significance of the values reported in Tables I and II have been described previously.[7,12] Tolbutamide, after an oral dose of 200 mg/kg, lowered blood glucose levels in this test system 28% at 1 hr, 47% at 2 hr, and 48% at 4 hr after treatment. These values were significant at the $p \leq 0.001$ level.

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