Table I. Constants Used for Deriving Eq 4

No.	X	Log 1/C Obsd	Log 1/C Calcd[a]	Δ log 1/C	Log P[b]
1	4-OMe	1.70	1.67	0.03	−0.63
2	H	1.70	1.68	0.02	−0.61
3	4-F	1.74	1.75	0.01	−0.47
4	4-Me	1.82	1.98	0.16	−0.05
5	2-Me	1.92	1.98	0.06	−0.05
6	4-Cl	1.92	2.06	0.14	0.10
7	3-Me	2.05	1.98	0.07	−0.05
8	3-Cl	2.22	2.06	0.16	0.10
9	4-Br	2.22	2.14	0.08	0.25

[a]Calculated using eq 4. [b]The value of compound **2** was determined and the others were calculated from **2** using the π constant; see C. Hansch, A. Leo, S. Unger, K. H. Kim, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973). In the determination, 0.1 *N* NaOH was used as the aqueous phase and the experimental values obtained were extrapolated to infinite dilution.

tives of a parent anion can be made and tested to find log $1/C$ in the hanging clot test; by well chosen, it is meant that a range of 2–3 units in log P should be present. Also, since it is understood that log $1/C$ will be parabolically dependent on log P in the most general sense,[8] log P should be in the range −2.0 to +2.0 for the initial study. Equations 1–4 indicate that one can expect linearity between log P and log $1/C$ in this range in the standard hanging clot test. Since log P values can generally be estimated within an absolute value of ±0.5, it would not be necessary to measure log P values in the preliminary phases of the work; one might measure that of each parent molecule. One could obtain the slope and intercept for each set of congeners from the plot of log $1/C$ vs. log P. Only those cases with intercepts significantly higher than that of eq 3 would merit in-depth study.

Equation 2 indicates that steric effects can be significant in fibrinolytic activity and no doubt further study will show how electronic effects are important. Indeed, it is the stereoelectronic character of the *N*-phenylanthranilate moiety which gives it a higher activity than the salicylates. Without much more experimental effort it would be pointless at this time to speculate on what the ideal stereoelectronic characteristics of the fibrinolytic anions are. This is also true of their mechanism of action; at present it can only be said that the activity is highly dependent on lipophilic character as operationally defined by log P and that it is rather insensitive to steric and electronic changes in the parent structure.

Acknowledgment. We wish to thank Drs. Y. Kishida and T. Hiraoka of the Sankyo Co. for the helpful discussions on the synthesis of the cyclopropanecarboxylic acids.

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Benzoxocin and Benzoxonin Derivatives. Novel Groups of Terpenophenols with Central Nervous System Activity. A Correction

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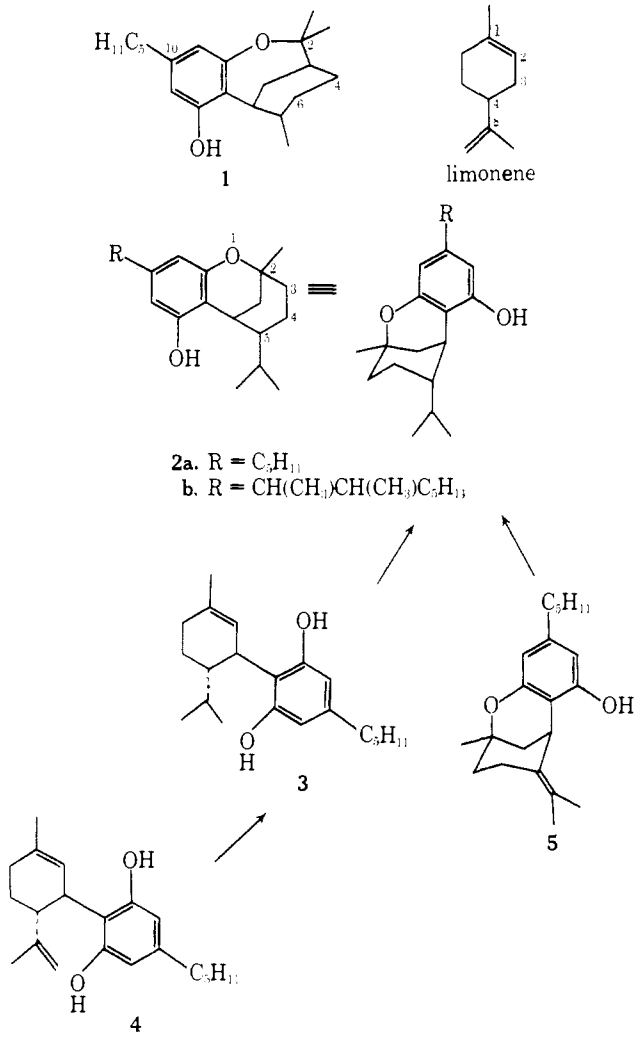
Received November 18, 1974

The structure of a compound previously reported as 2,3,4,5,6,7-hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (**1**) is shown to be actually 3,4,5,6-tetrahydro-7-hydroxy-2-methyl-5-isopropyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (**2a**).

In a recent publication[1] we reported the synthesis of a series of terpenophenols with central nervous system activity. One of the compounds obtained on condensation of olivetol with pinene (or limonene) was assigned the tentative structure 2,3,4,5,6,7-hexahydro-2,2-dimethyl-8-hydroxy-6-methyl-10-pentyl-3,7-methano-1-benzoxonin (**1**) (compound **15a** in the previous paper). On reexamination of the spectral data we concluded that they were more consistent with the structure 3,4,5,6-tetrahydro-7-hydroxy-2-methyl-5-isopropyl-9-pentyl-2,6-methano-2*H*-1-benzoxocin (**2a**), a cannabinoid whose synthesis by another route has been reported[2] (see Scheme I).

In the earlier publication[2] the structure was unequivocally shown to be **2a** by several chemical correlations. Thus dihydrocannabidiol (**3**), obtained on hydrogenation of cannabidiol (**4**), was cyclized with ease to **2a**; it was also obtained as one of the isomers in the hydrogenation of the isocannabinoid **5**, which was the product of three different cyclization sequences. The isocannabinoid **5** has also been obtained by Crombie[3] and by Razdan.[4] Samples of com-

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

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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