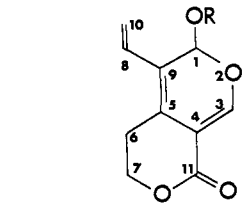
In previous studies on the biosynthesis of gentiopicroside[3] and a related compound, swertiamarin,[4] label from acetate-1-^{14}C was incorporated into these glucosides, but its location was not disclosed. The mevalonoid origin of both these nontryptophan-derived segments of the indole alkaloids[5,6] and the iridoid compounds[7] has been established. Furthermore, there is evidence that the cyclopentanoid monoterpene loganin is a precursor of the C_{10} units of certain alkaloids.[8] On the basis of its structural resemblance to these compounds, gentiopicroside has been postulated to be on this common biogenetic pathway,[9] and we wish to present evidence supporting this concept.

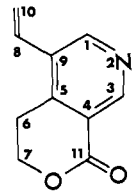
Gentiopicroside was found in relative abundance (2.5%) in the roots of *Swertia caroliniensis* (Walt) Kuntze. Ethyl acetate extraction afforded a mixture of predominantly polar compounds from which a hydrated amorphous gentiopicroside, mp 118–121°, could be isolated by silica gel chromatography with ethyl acetate–methanol (9:1) as eluent. Recrystallization from ethyl acetate–benzene–methanol (9:9:2) gave anhydrous crystals of gentiopicroside,[10] mp 181°, exhibiting the following spectral properties: λ_{max}^{EtOH} 247 (sh), 255 (sh), and 270 mμ (log ε 3.84, 3.93, and 3.97, respectively); $[\alpha]D$ −217.6° (*c* 1, MeOH); λ_{max}^{Nujol} 2.90, 5.85, and 6.20 μ. Acetylation[1] of the hydrous or anhydrous forms of **1** yields gentiopicroside tetraacetate (**2**), mp 140°; optical rotation, $[\alpha]D$ −159.5° (*c* 1, chloroform); ultraviolet: λ_{max}^{EtOH} 248 (sh), 254 (sh), and 270 mμ (log ε 3.86, 3.89, and 3.94, respectively); infrared: $\lambda_{max}^{CHCl_3}$ 5.70, 5.80, and 6.18 μ; nmr:[11] δ 7.48 (singlet, 3 H).[2] Upon treatment of the tetraacetate **2** with methanolic ammonium hydroxide, followed by acid hydrolysis,[12] glucose is removed and the oxygen of the dihydropyran ring is replaced with nitrogen, affording gentianine (**3**), mp 81°; ultraviolet: λ_{max}^{EtOH} 218, 245 (sh), and 285 (sh) mμ (log ε 4.42, 3.93, and 3.18, respectively); infrared: $\lambda_{max}^{CHCl_3}$ 5.80, 6.30, 6.35, and 6.75 μ; nmr: δ 3.10 (triplet, 6 H), 4.58 (triplet, 7 H), 5.5–6.0 (octet, 10 H, AB of ABX system), 6.6–7.0 (quartet, 8 H, X of ABX system), 8.91 (singlet, 3 H), and 9.23 (singlet, 1 H).[13]

Administration of DL-mevalonate-2-^{14}C (97.6 μcuries, 2.5 mg) by means of a cotton wick inserted through the stem of an intact *Swertia* plant resulted in the labeling of gentiopicroside (**1**) (0.04% incorporation). Crude gentiopicroside isolated as described above was converted directly to its tetraacetate (**2**) which was recrystallized to constant specific activity (0.13 μcurie/mmole). Conversion to gentianine (**3**) (0.13 μcurie/mmole) revealed that all of the radioactivity was present in the aglucone. Decarboxylation of the calcium salt[14] of gentianine afforded carbon dioxide representing the C-11 carbon. Measurements as $BaCO_3$ (0.026 μcurie/mmole) indicated it contained 20% of the total activity in gentianine (**3**).

The similarity of the mevalonate-2-^{14}C labeling of gentiopicroside with that of the iridoid and indole alkaloid C_{10} moieties lends further support to a common pathway *via* a cyclopentanoid monoterpene **5**, possibly loganin,[8] as illustrated below. A compound having the skeleton of **6** may then serve as a precursor for either gentiopicroside and related glucosides or the above-mentioned indole alkaloids. Randomization of the original terminal dimethyl groups is characteristic of these monoterpenes.[5–7]



1. R = glucose
2. R = glucose tetraacetate



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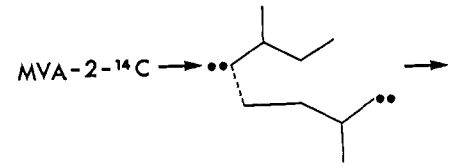

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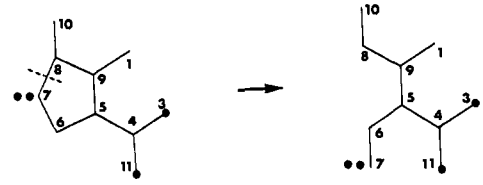

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Acknowledgment. We are indebted to Professor John Dwyer for valuable assistance and advice in obtaining plant material. This work was supported by National Institutes of Health General Support Grant No. 104 and the National Science Foundation under Grant No. GB 4815.

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(5) H. Goeggel and D. Arigoni, *Chem. Commun.*, 538 (1965).
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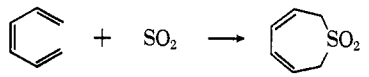
The Addition of Sulfur Dioxide to *cis*-Hexatriene. Thiepin 1,1-Dioxide

Sir:

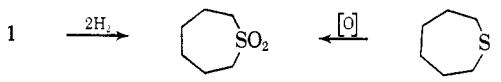
The nature of the conjugating properties of sulfones and the requirements for aromaticity in heterocycles render the properties of thiepin 1,1-dioxide of interest. We have prepared this compound by a reaction sequence utilizing the novel 1,6 addition of sulfur dioxide to *cis*-hexatriene.

A 1:1 adduct is formed when an ethereal solution of *cis*-hexatriene[1] and sulfur dioxide is allowed to stand at room temperature. The structure of the new substance, mp 107–108°, is indicated to be 2,7-dihydrothiepin 1,1-dioxide (**1**) by chemical and spectroscopic



1

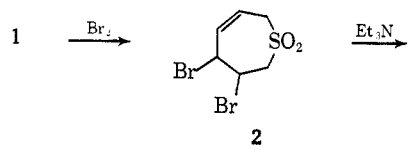
means.[2] Catalytic hydrogenation over palladium on charcoal resulted in the uptake of 2 molar equiv of hydrogen and afforded hexahydrothiepin 1,1-dioxide, mp 70–71°, identical with authentic material[3] produced by peracid oxidation of hexamethylene sulfide. The ultraviolet spectrum of the adduct, λ_{max}^{EtOH} 227



mμ (ε 5850), is characteristic for a medium-ring conjugated diene. A mass spectral molecular weight of 144 was obtained. The nmr spectrum conclusively confirms the assigned structure; the four aliphatic hydrogens appear as a doublet at τ 6.32 (splitting 7 cps with further fine coupling) and an equivalent number of ethylenic hydrogens appear as a complex multiplet between τ 3.3 and 4.2. The adduct dissociates cleanly in the melt at 150–160° to regenerate *cis*-hexatriene and less than 1% *trans*-hexatriene or 1,3-cyclohexadiene.[4]

Heretofore only benzothiepin 1,1-dioxides have been available for investigation.[5] Results of studies of these substances, which have suggested a lack of benzenoid character in the heterocyclic ring, are obscured by the bond-fixing effect of the annelated benzene ring. A synthesis of the parent heterocycle, thiepin 1,1-dioxide, appeared feasible from the hexatriene–sulfur dioxide adduct.

With excess bromine in chloroform 2,7-dihydrothiepin 1,1-dioxide formed a dibromide, mp 128–129°. On the basis of its nmr spectrum it is provisionally formulated as *cis*- or *trans*-3,4-dibromo-2,3,4,7-tetrahydrothiepin 1,1-dioxide (**2**).[2]



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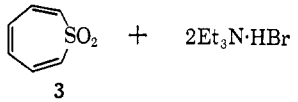

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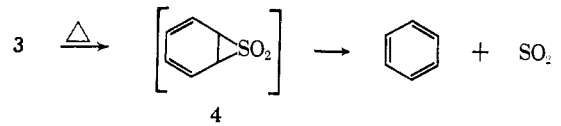
Treatment of the dibromide with 2 equiv of triethylamine in benzene solution at 25° resulted in rapid precipitation of triethylamine hydrobromide and, after chromatography of the benzene-soluble products, thiepin 1,1-dioxide (**3**), mp 117–118°, was isolated.[2] The structural assignment is supported by the spectral and chemical properties of this material. The nmr spectrum exhibits only multiple ethylenic hydrogen absorption at τ 2.8–3.5. Medium-to-strong infrared absorption occurs at 3030, 1530, 1440, 1370, 1300, 1170, 1120, 920, 792, 737, 670, and 650 cm^{-1} in potassium bromide. A mass spectral molecular weight of 142 was obtained.

Upon low-pressure catalytic hydrogenation (palladium on carbon in ethyl acetate) thiepin 1,1-dioxide rapidly absorbed 3 molar equiv of hydrogen and yielded hexahydrothiepin 1,1-dioxide, previously characterized. The substance decomposes above its melting point; at 100° in deuteriochloroform it has a half-life of approximately 3 hr. The exclusive products in the latter case are benzene and sulfur dioxide, determined by gas chromatographic, infrared, nmr, and odor comparison with authentic materials. The episulfone **4** is a probable intermediate in this decomposition



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but could not be detected when the reaction was followed by nmr spectroscopy. Thiepin 1,1-dioxide may be sublimed at 100° (1 mm) with only slight loss, however.

The properties so far observed are consistent with thiepin 1,1-dioxide being a nonplanar triene with no special effect attributable to the inclusion of a sulfonyl group between the terminals of the conjugated system. Thiepin 1,1-dioxide absorbs in the ultraviolet: λ_{max}^{EtOH} 262 mμ (ε 4610), λ_{min}^{EtOH} 232 mμ (ε 2070), plus end absorption at λ^{EtOH} 215 mμ (ε 13,000). This spectrum matches that of cycloheptatriene,[6] λ_{max} 266 mμ (ε 4170), and is unlike that of tropone,[7] $\lambda_{max}^{H_2O}$ 225 (ε 21,200) 228 (22,100), 231.5 (22,100), 239 (12,700), 304 infl (8000), and 312.5 mμ (8400). In the infrared region the sulfur–oxygen stretching frequencies (1300 and 1120 cm^{-1}) are at typical values and are unshifted from that of other compounds in this series. The chemical shift of the hydrogens in the nmr spectrum does not indicate a substantial diamagnetic ring current[8] in this case; some deshielding is expected from the sulfonyl group, and the general position of the vinylic absorption in thiepin dioxide (τ 2.8–3.5) corresponds to that of the dihydro compound (**1**) (τ 3.3–4.2).[9] In addition, the ready hydrogenation and thermal instability suggest a lack of benzenoid character in the system.

Examination of molecular models indicates a dihedral angle of 50° between the planes of adjacent double bonds in the minimally strained boat conforma-

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(9) Compare, however, tropone[10] (τ *ca.* 3.0) with 3,5-cycloheptadienone[11] (τ 3.5–4.4, vinyl).

(10) D. J. Bertelli, C. Golino, and D. L. Dreyer, *J. Am. Chem. Soc.*, **86**, 3329 (1964).

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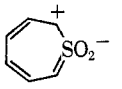
tion. The aforementioned properties suggest the resonance energy (if any) acquirable from charge-separated canonical forms (*e.g.*, **3a**, presumably involving d-orbital participation) is insufficient to compensate for the angle strain required to form a planar conjugated system. Final conclusions must await



3a

study of the reactions of thiepin 1,1-dioxide and its derivatives.

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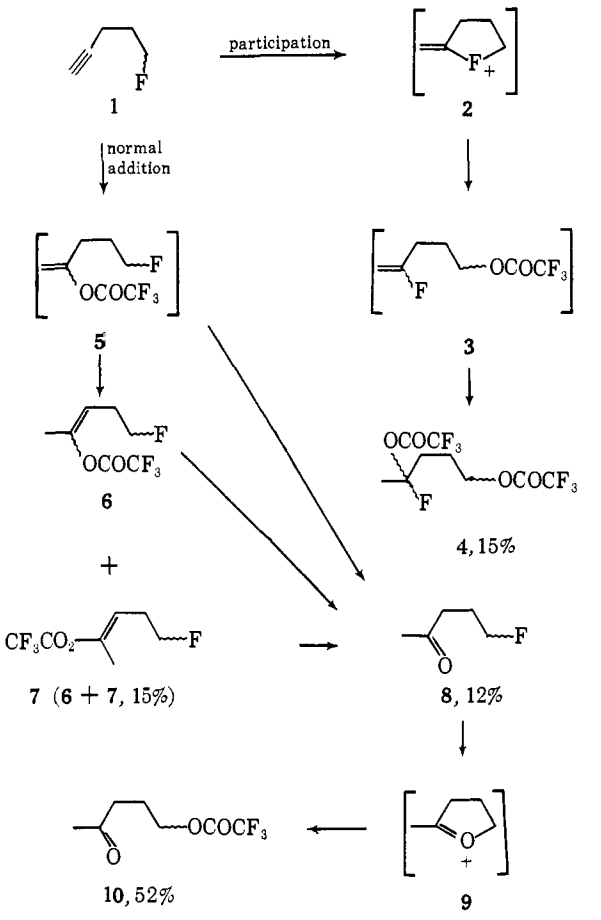
Possible Fluoronium Ion Intermediates in the Reaction of Trifluoroacetic Acid with 5-Fluoro-1-pentyne and 5-Fluoro-2-pentyl Tosylate[1]

Sir:

Fluoronium ion intermediates have not been postulated. However, in one very recent study an unsymmetrical, cyclic, donor–acceptor complex was observed by nmr spectroscopy of succinyl fluoride in a 1,1,2-trifluorotrichloroethane–SbF_5 solution.[2a] Fluorocarbonium ions, having a partial positive charge on fluorine, are under active investigation.[2b] We wish to report evidence for fluorine participation and a fluoronium ion intermediate or transition state in the reaction of 5-fluoro-1-pentyne with trifluoroacetic acid. The reaction products and their percentages are given in Scheme I.[3]

Since the reaction of 5-chloro-1-pentyne with trifluoroacetic acid leads to ~85% of a stable vinyl chloride[4] analogous to **3**, our original expectation was that any fluorine shift in the reaction of 5-fluoro-1-pentyne would lead to **3**. When **4**, but no detectable **3**, was found as a reaction product, we realized that the participation pathway of Scheme I would be tenable only if the secondary reaction **3** → **4** was markedly more facile than the analogous reaction involving the vinyl chloride. Independent evidence supporting the postulated reactivity difference was provided by a determination of the rates of reaction of 2-halopropenes with trifluoroacetic acid to give 2-halo-2-propyl trifluoroacetates (*cf.* Table I). The 200-fold greater reactivity of fluoropropene, compared to chloropropene, provides strong assurance that **4**, not **3**, is the *expected* ultimate

Scheme I. Reaction of 5-Fluoro-1-pentyne with Trifluoroacetic Acid



product of 1,4-fluorine shift in the reaction of 5-fluoro-1-pentyne. Furthermore, the relative rates in Table I provide a striking illustration of the effectiveness of 2p–2p overlap in stabilizing the 2-fluoropropyl cation. These data suggest that fluorine may stabilize a carbonium ion in solution, compared to hydrogen. Previously this thermodynamic stability order has been strongly indicated only in gas-phase mass spectroscopic studies.[5]

Table I. First-Order Rate Constants for Reaction of Trifluoroacetic Acid with Propenes at 25.0°

Compound	10^5k, sec^{-1}	k_X/k_H
	4.81	1
	340	71
	1.70	0.35
	0.395	0.082

Turning our attention to the proposed normal addition pathway (Scheme I), we note that reactions of 1-hexyne and/or 5-chloro-1-pentyne with trifluoroacetic acid[4a] provide analogies for the formation of all of the observed products including the, at first sight, surprising major product, 5-trifluoroacetoxy-2-penta-

(1) (a) This work was supported in part by National Science Foundation Grant GP 2917. Award of a NASA traineeship is gratefully acknowledged by R. J. Bopp. (b) Reported in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 12–16, 1966, Organic Abstracts, paper 3.

(2) (a) G. A. Olah and M. B. Comisarow, *J. Am. Chem. Soc.*, **88**, 3313 (1966); (b) G. A. Olah, C. A. Cupas, and M. B. Comisarow, *ibid.*, **88**, 362 (1966).

(3) Percentages are based on areas of gas chromatographic peaks (flame detector) of a flash distillate. Analysis by nmr gave closely similar results. Identification of preparative gas chromatographic fractions was accomplished by nmr analysis. Identifications of **8** and **10** were confirmed by comparison with authentic samples. The structure of **4** was confirmed by carbon and hydrogen analysis, by prolonged solvolysis to give **10**, and by the close correspondence of the nmr spectrum with that of 2-fluoro-2-trifluoroacetoxypropane, CH_3 doublet at δ 1.90, J_{HF} = 18 cps.

(4) (a) P. E. Peterson and J. E. Duddey, *J. Am. Chem. Soc.*, **88**, 4990 (1966). (b) The chloride undergoes slow further reaction with trifluoroacetic acid.

(5) R. H. Martin, F. W. Lampe, and R. W. Taft, *J. Am. Chem. Soc.*, **88**, 1353 (1966).