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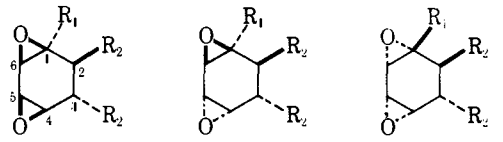
Synthesis of (±)-Crotepoxide, (±)-Epicrotepoxide, and (±)-Isocrotepoxide

Sir:

Crotepoxide (**1**), also known as futoxide, was isolated by Kupchan et al.[1] from *Croton macrostachys* and has been found to possess significant inhibitory activity against Lewis lung carcinoma and Walker intramuscular carcinoma. The structure of **1**,[2] confirmed by an x-ray crystallographic analysis,[3] reveals it to be a member of the small but pharmacologically interesting family of naturally occurring 1,3-diepoxides.[4] We wish to report the total synthesis of (±)-crotepoxide (**1**), its 4,5-epimer **2** (epicrotepoxide), and the 1,6;4,5-bis epi compound **3** (isocrotepoxide).[5]

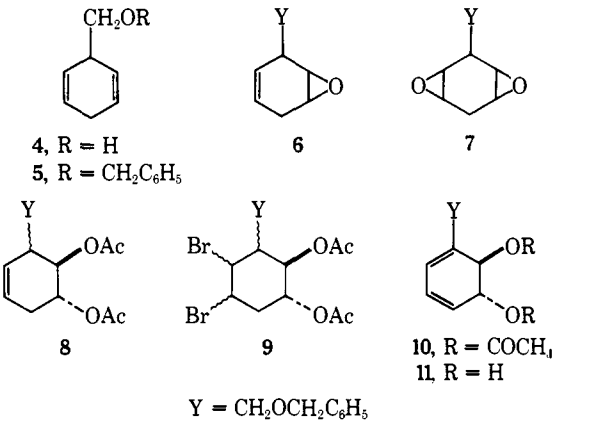


1 **2** **3**

R_1 = $CH_2OCOC_6H_5$, R_2 = $OCOCH_3$

1,4-Dihydrobenzyl benzyl ether (**5**), prepared from **4**[6] (NaH, benzyl bromide, glyme, 0 °C, 77%), underwent epoxidation upon treatment with *m*-chloroperbenzoic acid (MCPA) in CH_2Cl_2 (36 h, room temperature) to give **6** (79%) and only a trace of diepoxide **7**.[7] Exposure of **6** to acetic anhydride (HOAc, 36 h, reflux) produced trans diacetate **8** (79%) as a mixture of two diastereomers. This mixture was brominated (CH_2Cl_2) in the presence of pyridine yielding stereoisomeric dibromides **9** (93%) which, without separation, were dehydrohalogenated (LiCl, Li_2CO_3, HMPA, 105 °C, 16 h) to give a 90% yield of a single diene **10** (δ^{CDCl_3} 1.98 (3 H, s), 2.02 (3 H, s), 4.06 (2 H, s), 4.50 (2 H, s), 5.44 (1 H, t, J = 5 Hz), 5.74 (1 H, d, J = 5 Hz), 5.8-6.2 (3 H, broad m), 7.32 (5 H, s)). Reduction of **10** ($LiAlH_4$, ether, 0 °C) afforded diol **11** (84%). The efficient preparation of the relatively stable diene **10** (32% overall from benzoic acid) and corresponding diol **11** permitted a detailed study of their behavior under oxygenation ($^1\Delta_g$ O_2) and epoxidation conditions, and they therefore became the focal intermediates in the synthesis of crotepoxide and its stereoisomers.

Epoxidation of **10** (MCPA, CH_2Cl_2) at 25 °C gave monoepoxides **12** and **13** exclusively in a 1:1 ratio. Configuration was assigned to these stereoisomers on the basis of a comparison of the chemical shift of H_6 (**12**, δ 3.60; **13**, δ 3.47) with the corresponding proton (δ 3.44) in senepoxide (**14**),[8] and also from the observation that epoxidation of **11** proceeded stereospecifically[9] to give **15** which, upon acetylation (Ac_2O, pyridine, 6 h, room temperature), yielded **12.** The difficulty associated with epoxidation of the 4,5 double bond of **10** was overcome by invoking the forcing conditions devised by Kishi.[10] Thus, treatment of **10** with MCPA in 1,2-dichloroethane in the presence of 2,6-di-*tert*-butyl-*p*-cresol (90 °C, 2 h) afforded in 55% yield a readily separable mixture of trans diepoxide **16** and cis diepoxide **17** in the ratio 8:1. Hydrogenolysis of **16** and **17** (10% Pd/C, EtOH) gave the corresponding primary alcohols **18** and **19** in quantitative yield, and subsequent benzoylation (C_6H_5COCl, $CHCl_3$) furnished (70% in each case) (±)-4,5-epicrotepoxide (**2**, mp 119-121 °C) and (±)-crotepoxide (**1**).[11] The stereochemistry of epicrotepoxide is revealed most convincingly by the chemical shift of H_2 (δ 5.74, d, J = 8 Hz; cf. δ 5.73 in **1**) and of H_4 (δ 3.39, d, J = 4 Hz; cf. δ 3.10 in **1**).



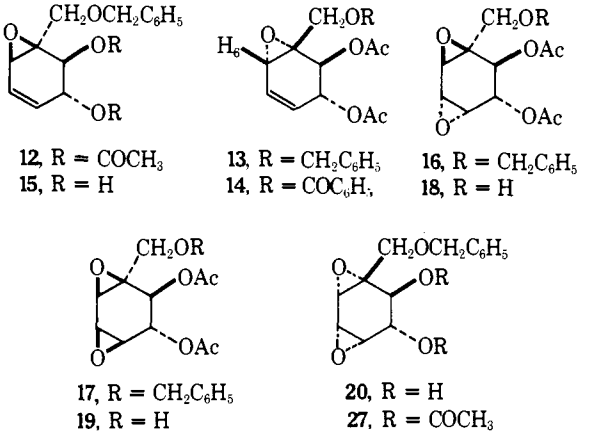
4, R = H
5, R = $CH_2C_6H_5$

6 **7**

8 **9**

10, R = $COCH_3$
11, R = H

Y = $CH_2OCH_2C_6H_5$



12, R = $COCH_3$
15, R = H

13, R = $CH_2C_6H_5$
14, R = COC_6H_5

16, R = $CH_2C_6H_5$
18, R = H

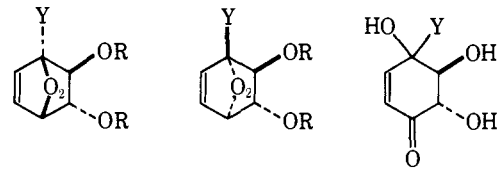
17, R = $CH_2C_6H_5$
19, R = H

20, R = H
27, R = $COCH_3$

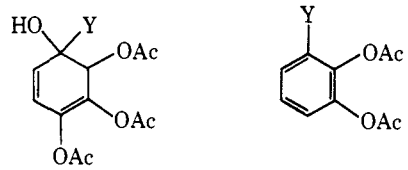
Attempts to effect a direct bisepoxidation of **11** using the hydroxyl groups as controllers were unsuccessful with peracid oxidants. However, the reaction of **11** with *tert*-butyl hydroperoxide (2 equiv, benzene, reflux, 12 h) in the presence of $VO(acac)_2$ as catalyst[12] led stereospecifically to cis diepoxide **20** (15%). Acetylation followed by hydrogenolysis and benzoylation as for crotepoxide gave (±)-isocrotepoxide (**3**) as an oil (δ^{CDCl_3} 2.10 (3 H, s), 2.15 (3 H, s), 3.28 (1 H, m), 3.59 (1 H, m), 3.65 (1 H, m), 4.14 (1 H, d, J = 12 Hz), 4.72 (1 H, d, J = 12 Hz), 5.19 (1 H, t, J = 3 Hz), 5.43 (1 H, bs), 7.54-8.12 (5 H, m)). Formation of **20** exclusively can be rationalized assuming complexation of the vanadium oxidant with the more accessible C-3 hydroxyl of **11.** These epoxidations are known to be highly stereoselective in the case of allylic alcohols,[13] and based on the dimensions of a molecular model, should be likewise for homoallylic alcohols.[14]

Since endoperoxides derived from the reaction of singlet

oxygen with cyclic 1,3-dienes[15] afford cis 1,3-diepoxides by rearrangement under both thermal[16] and photochemical[17] conditions, oxygenation of **10** or **11** appeared to offer an attractive route to crotepoxide and/or its isomer **3**. Diacetate **10** proved to be totally unreactive towards singlet oxygen under all conditions but **11**, upon irradiation (25 °C) in pyridine in the presence of oxygen with hematoporphyrin as sensitizer, gave a mixture of unstable epidioxides **21** and **22** (52%, 1:1; δ^{CDCl_3} 3.3 (2 H, broad, exchanged with D_2O), 3.56 and 3.74 (1 H, m), 3.79 (2 H, s), 3.94 and 4.00 (1 H, m), 4.58 (2 H, s), 4.63 (1 H, broad s), 7.35 (1 H, d, J = 9 Hz), 7.67 (1 H, t, J = 9 Hz), 7.30 (5 H, s)). Prolonged irradiation or heating in pyridine resulted in the conversion of **21** and **22** to the cyclohexenone **23**, characterized as its triacetate **24.** However, the reverse sequence, in which **21**/**22** was acetylated under mild conditions (Ac_2O, Na_2CO_3) and the mixture of endoperoxide diacetates **25** and **26** subjected to refluxing 1,2-dichloroethane in the presence of 2,6-di-*tert*-butyl-*p*-cresol, afforded **17** (24% based on **11**) with no indication of an epimeric diepoxide (**27**). Endoperoxide **26** appears to give mainly an aromatized product tentatively assigned structure **28** and attributed to a facile elimination resulting from the trans disposition of the C-3 proton and peroxide bridge. Endoperoxide rearrangement thus provides an alternate route to **1**.[18]



21, R = H **22**, R = H **23**
25, R = $COCH_3$ **26**, R = $COCH_3$



24 **28**

Y = $CH_2OCH_2C_6H_5$

Epoxidation or oxygenation of suitably functionalized 1,3-cyclohexadienes not only affords feasible pathways to crotepoxide (**1**) and its stereoisomers **2** and **3** but should also be applicable to other members of this important group of natural products, including the highly active antileukemic compound triptolide[4a,19] and the antibiotic LL-Z1220.[4c,20]

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Photosensitized Oxygenation of N^b-Methoxycarbonyltryptophan Methyl Ester and N^b-Methoxycarbonyltryptamine. Isolation and Novel Transformations of a 3a-Hydroperoxypyrroloindole

Sir:

There has been considerable recent interest in the reaction of singlet oxygen with the enamine system.[1] In our recent studies,[2] we have shown that N^b-methyltryptamine reacts with singlet oxygen to give **1** as the primary intermediate[2b] which undergoes either intramolecular oxidation to give **3** or **2a** under the reaction conditions. The *o*-formylaminoacetophenone type compound which has been widely known as the normal product of photooxygenation of tryptophan[3] and indoles,[4] however, was not isolated. These results led to a study of the effect of N^b-acylation on the photooxygenation of tryptophan and tryptamine derivatives.

We wish to report here the direct isolation of 3a-hydroperoxypyrroloindole (**5a**) from the reaction of **4a** with singlet oxygen and the conversion of **5a** into the formylkynurenine derivative **7a**, the N^b-formylkynurenine derivative **8a**, as well as the 3a-hydroxypyrroloindole **6a**, and its acid catalyzed rearrangement to the 1,4-benzoxazine derivative **9**.

When a thoroughly O_2-saturated solution of **4a** (4.6 mmol) was irradiated in 5% pyridine in methanol with a 200-W halogen lamp for 3 h in the presence of rose bengal under ice-cooling followed by alumina and silica gel column chromatography, **6a**, mp 126–127 °C[5] (18%), **7a**, mp 97.5–99 °C (9%), and **8a** (18%) were isolated[6] (**6a**: λ_{max}^{EtOH} nm (ϵ) 242 (8750), 298 (2390); NMR ($CDCl_3$) δ 5.10 (1 H, s, NCHN). **8a**: λ_{max}^{EtOH} 228, 257, 364 nm; mass 250 (60) M^+; picrate, mp 99.5–100.5 °C). Alkaline hydrolysis of **6a** gave the parent compound, **2b**: mp 173.5–175 °C; λ_{max}^{EtOH} nm (ϵ) 243.5 (8275), 301.5 (2440), $\lambda_{max}^{EtOH\text{-}HCl}$ 236 (7840), 294 (2350); NMR (pyridine-d_5) 5.32 (1 H, s, NCHN). Both **7a** and **8a** were deformylated to give N^b-methoxycarbonylkynureamine, mp 98–99 °C, when refluxed with Al_2O_3 in methanol. Likewise, irradiation of **4b** in similar conditions gave **6b**, mp 124–125 °C (14%), **7b**, mp 128–129 °C (18%), and **8b**, mp 115–116 °C (8%).[7] The