Communications

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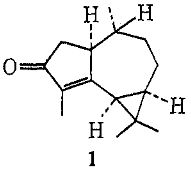
The Influence of Substituents on the Photochemical Behavior of Cross-Conjugated Cyclohexadienones. A Facile Total Synthesis of (−)-Cyclocolorenone[1]

Summary: (−)-Cyclocolorenone has been totally synthesized using photochemical rearrangement of an appropriately substituted cross-conjugated cyclohexadienone to produce the tricyclic ring skeleton of the natural product.

Sir: Büchi, Kauffman, and Loewenthal[2] have reported the synthesis of 1-epicyclocolorene (1) from santonin. This work also established the stereochemistry of cyclocolorenone (2). However, the synthetic sequence involved closure of the three-membered ring by reaction of the bromo enone 3 under basic conditions which caused epimerization at C-1. Thus the more thermodynamically stable tricyclic enone 1 was the only product isolated.



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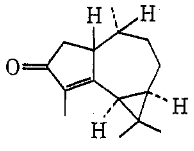

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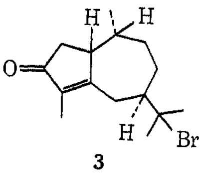

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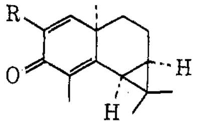
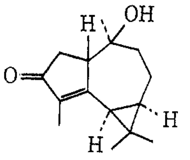
The photochemical rearrangement of the tricyclic cross-conjugated cyclohexadienone **4a**[3,4] appeared to be an attractive route to cyclocolorenone itself. By analogy with the behavior of related 4-methyl-substituted systems,[2,3,5] this compound was expected to give the tricyclic hydroxy ketone **5** on irradiation in aqueous acetic acid.[6] However, Streith and Blind[3] have reported that **4a** is unreactive toward uv light in this solvent and similar results have been obtained by Kropp and Krauss[4] using benzene or ether as the solvent.[7] We have confirmed these results and have found that, although rearrangement of **4a** can be induced using benzophenone as a photosensitizer, the process is accompanied by opening of the cyclopropane ring.[8] Thus the photochemical conversion of **4a** into a precursor of **2** does not appear to be possible.

Another possible route to a precursor of **2** appeared to involve photochemical rearrangement of the 2-carboxy derivative of **4a**, *i.e.*, **4b**. As we reported earlier,[9] the bicyclic dienone **6**, having an electron-withdrawing carboxyl group at C-2, is photochemically converted into 5/7-fused products in a variety of solvents. For example, irradiation of **6** in dioxane gave the decarboxylated dienone **7** in 67% yield. Thus it was felt that **4b** might undergo a similar photochemical reaction to give the tricyclic dienone **8** which would be expected to be convertible into **2** by selective hydrogenation of the exocyclic double bond.



4a, R = H
b, R = CO_2H



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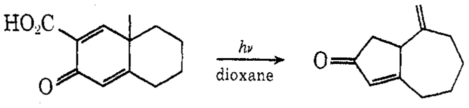

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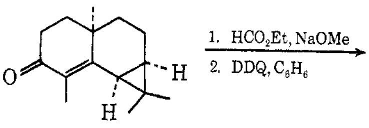

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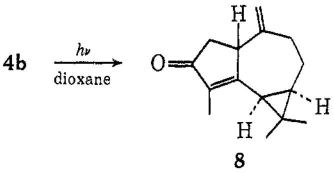

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The dienone acid **4b** was prepared by a procedure similar to that described for the synthesis of **6**.[9] Reaction of (−)-maalione (**9**)[10] with ethyl formate and sodium methoxide in benzene gave the 2-hydroxymethylene derivative which was oxidized to the corresponding 2-formyl dienone with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene and further to **4b** with Jones reagent.[11,12] The product showed mp 100–102°; $\lambda_{max}^{95\% EtOH}$ 220 nm (ϵ 10,300), 297 (4,500); ir $\nu_{max}^{CHCl_3}$ 2715 (carboxyl OH), 1730 (conjugated carboxyl

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[1] This investigation was supported by Public Health Service Research Grants No. Gm 15044 from the National Institute of General Medicine and No. CA 12193 from the National Cancer Institute.

[2] G. Büchi, J. M. Kauffman, and H. J. E. Loewenthal, *J. Amer. Chem. Soc.*, **88**, 3403 (1966).

[3] J. Streith and A. Blind, *Bull. Soc. Chem. Fr.*, 2133 (1968).

[4] P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 4118 (1967).

[5] (a) D. H. R. Barton, P. De Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957); (b) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964); (c) P. J. Kropp, *ibid.*, **29**, 3110 (1964); (d) E. Piers and K. F. Cheng, *Can. J. Chem.*, **45**, 1591 (1967); (e) E. Piers and K. F. Cheng, *Chem. Commun.*, 562 (1969); (f) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970).

[6] Streith and Blind[3] have reported the synthesis of **5** *via* a procedure involving irradiation of dehydro-(−)-7-epi-α-cyperone in aqueous acetic acid to give a 5/7-fused hydroxy ketone followed by closure of the three-membered ring.

[7] The steroidal dienone, *O*-acetyl-1-dehydro-6α,7α-methylenetestosterone, related to **4** has also been shown to be stable toward uv irradiation: J. Pfister, H. Wehrli, and K. Schaffner, *Helv. Chem. Acta*, **50**, 166 (1967).

[8] The results of irradiation of **4a** using benzophenone as a photosensitizer will be discussed later in a full paper.

[9] D. Caine, J. F. DeBardeleben, Jr., and J. B. Dawson, *Tetrahedron Lett.*, 3627 (1966).

[10] R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960).

[11] K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[12] Correct elemental analyses and mass spectral data have been obtained on all new compounds.

C=O), 1645 (conjugated C=O), 1580 cm^{-1} (conjugated C=C); nmr $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 0.84 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.97 (d, J = 1 Hz, 3 H, vinyl CH_3), 1.00–2.20 (broad absorption, 6 H), 8.16 ppm (s, 1 H, vinyl H); $[\alpha]^{25}\mathrm{D}$ $-51°$ (c 0.226, $CHCl_3$). On irradiation for 5 hr in dry dioxane at room temperature using a 450-W Hanovia high pressure mercury lamp fitted with a Pyrex probe and rapid chromatography of the photolysis mixture on silica gel, the tricylic dienone **8** was isolated in ~60% yield as a white crystalline solid: mp 57–58°; $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ 262 nm (ϵ 7500); ir $\nu_{\max}^{\mathrm{CHCl_3}}$ 1695 (conjugated cyclopentenone), 1630 (conjugated C=C), 885 cm^{-1} $\left(=\mathrm{C}<^{\mathrm{H}}_{\mathrm{H}}\right)$; nmr $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 1.00 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.70 (d, J = 2 Hz, 3 H, vinyl CH_3), 2.55 (d, J = 5 Hz, 2 H, C-2 CH_2), 3.40 (br t, 1 H, C-1 H), 0.80–2.80 (broad absorption, 6 H), 4.84 (br s, 1 H, vinyl H), 4.96 ppm (t, J = 1.5 Hz, vinyl H); $[\alpha]^{25}\mathrm{D}$ $-417°$ (c 0.134, $CHCl_3$).

Examination of a molecular model of **8** having the B ring in the most stable comformation revealed that the β face of the molecule should be the less hindered, and selective introduction of the C-10 hydrogen cis to the C-1 hydrogen was expected to occur on catalytic hydrogenation. Thus, when **8** was dissolved in ethyl acetate and shaken with hydrogen for 40 min in the presence of 5% palladium on charcoal, saturation of the exocyclic double bond took place in essentially quantitative yield. Glc analysis (SE-30 column) of the product revealed the presence of >90% of one major dihydro product. Distillation of this material gave a colorless oil [bp 110–115° (bath temperature) at 0.05 mm] at which was essentially one component by glc and exhibited identical ir and nmr spectra with those of an authentic sample of (−)-cyclocolorenone.[13] Other physical properties of the material were also in agreement with those reported[2,14] for the natural product.

A complete explanation for the photolability of the dienone acid **4b** compared with that of the unsubstituted compound **4a** is not possible at this time. The carboxyl substituent may influence the energy and electronic distribution of the photoexcited species sufficiently to allow the formation of a zwitterionic cyclopropyl intermediate analogous to that suggested to be involved in the rearrangement of the dienone acid **6**.[9] Such a species could then collapse to a β-keto acid which could undergo decarboxylation to give **8**. However, it is possible that a somewhat different reaction pathway may intervene in this case. Irrespective of the exact details of the process, the high degree of stereospecificity normally involved in photochemical rearrangements of simpler cross-conjugated dienones appears also to obtain in this case. Further studies on the photochemistry of other dienones related to **4** are in progress.

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(13) We are grateful to Professors G. Büchi and R. E. Corbett for providing us with copies of spectra of authentic samples of cyclocolorenone.

(14) R. E. Corbett and R. N. Speden, *J. Chem. Soc.*, 3710 (1958).

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