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Cudranone: A Novel Benzophenone Derivative from *Cudrania chochinchinensis* var. *gerontogea*

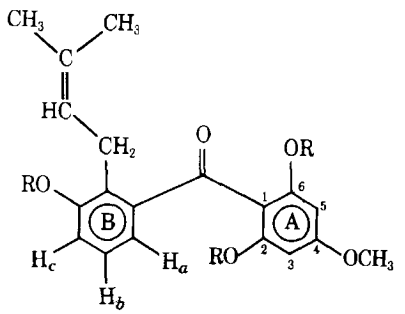
Keyphrases □ Cudranone—isolated and identified from stems and roots of *Cudrania chochinchinensis*, antimicrobial activity evaluated □ Benzophenone derivative—cudranone isolated and identified from stems and roots of *Cudrania chochinchinensis*, antimicrobial activity evaluated □ Antimicrobial agents, potential—cudranone, isolated and identified from stems and roots of *Cudrania chochinchinensis*

To the Editor:

In a largescale program for screening higher plants for antimicrobial activity, an ethanolic extract of the stems and roots of the Chinese plant[1] *Cudrania chochinchinensis* (Lour.) Kudo & Masam. var. *gerontogea* (Sieb. & Zucc.) Kudo & Masam. (Moraceae) exhibited strong activity against a wide range of microorganisms. Partitioning the alcohol extract between water and chloroform concentrated the antimicrobial activity in the chloroform phase. This fraction was then chromatographed over silica gel, using increasing amounts of ether (4–40%) in benzene as the solvent system. Several known crystalline compounds[2] were isolated from the column fractions.

The 4% ether in benzene fraction yielded, upon crystallization from *n*-hexane–ethyl acetate, a novel crystalline substance which was named cudranone (I). This new compound occurred in the form of bright-yellow needles, mp 172–173°, and had a molecular formula of $C_{19}H_{20}O_5$, as supported by elemental analysis and high-resolution mass spectral data.

The 60-MHz ^{1}H-NMR spectrum (taken in acetone-d_6 with tetramethylsilane as the internal standard) provided information on most functional groups of this compound. It revealed the presence of a β,β-dimethylallyl group (two vinylic three-proton singlets at δ 1.53 and 1.50; a broad one-proton triplet at δ 5.23, J = 8 Hz; and a two-proton doublet at δ 3.37, J = 8 Hz). It also exhibited a methoxy singlet at δ 3.83 and three exchangeable phenolic protons as a broad signal at δ 10.17. The aromatic region of the

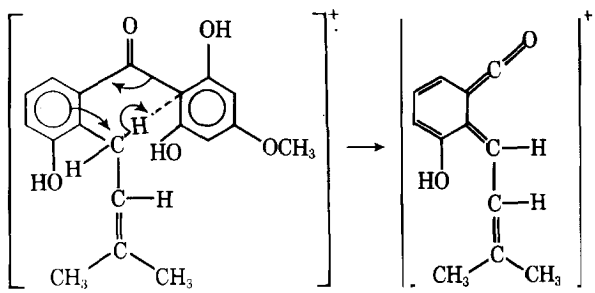


I: R = H
II: R = CH_3
III: R = CCH_3 (=O)

NMR spectrum showed a two-proton singlet at δ 6.00 and a three-proton group of signals forming a complex *ABC* system centered at δ 6.91. The IR spectrum confirmed the phenolic nature of the compound and showed a carbonyl absorption band at λ_{max} (potassium bromide) 6.06 μm, assigned to a hydrogen-bonded ketonic carbonyl function. Thus, by assuming that the compound had two aromatic rings, it was concluded that it must have a benzophenone skeleton rather than a xanthone skeleton like some reported constituents of the *Cudrania* species (1, 2).

The nature of ring A was revealed when the compound gave, in low yields, phloroglucinol monomethyl ether[3] by heating with solid potassium hydroxide at 245–250°. This finding indicated that the rest of the benzophenone moiety must be substituting ring A at C-1 rather than at C-3 or C-5 to account for the equivalency of the two aromatic protons of ring A appearing in the NMR spectrum as a sharp singlet at δ 6.00. This finding also indicated that the β,β-dimethylallyl group and the remaining hydroxyl group should be substituting ring B.

Compound I yielded the trimethyl ether (II) as white needles, mp 126–127°, by treatment with dimethyl sulfate and aqueous sodium hydroxide. The NMR spectrum of II taken in deuterochloroform still showed the complex *ABC* three-proton system in the aromatic region. However, this system was simplified and showed first-order splitting when benzene-d_6 (100%) was used as the solvent. It showed a one-proton doublet[4] at δ 7.23, J = 8 Hz; a one-proton triplet at δ 6.80, J = 8 Hz; and another one-proton doublet[4]



m/e 328 (10%) IV *m/e* 188 (100%)

Scheme I

[1] The plant material was collected in Chia-Yi, Taiwan, in 1974. Its identity was confirmed by Dr. Ping C. Cheng, Taipei Medical College. A voucher specimen is deposited in the herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi.
[2] To be reported later.
[3] Characterized by direct comparison with an authentic sample (superimposable IR, NMR, and mass spectra and identical R_f values on TLC and retention times on GLC).
[4] The doublets due to H_a and H_c were slightly split (J = 2 Hz) due to *meta*-coupling to each other.

at δ 6.42, J = 8 Hz. This pattern indicated that the three remaining aromatic protons in I must be located on three successive carbon atoms in ring B with the one most downfield (H_a) *ortho* to the ketone group, the one most upfield (H_c) *ortho* to the phenolic hydroxyl group, and the one in between (H_b) on the middle of these three carbons. This finding was further confirmed by the presence in the mass spectrum of the base peak IV, derived by acyl cleavage associated by hydrogen migration to ring A (3) (Scheme I). The highly conjugated nature of this fragment accounts for its abundance in the mass spectrum. The formation of fragment IV is favorable only if the β,β-dimethylallyl group is located *ortho* to the ketone group.

Although the evidence that I is the structure of cudranone was convincing, it was uncertain why the NMR signal of H_a was never as far downfield as expected for a proton *ortho* to a carbonyl group. This position was found not only for the H_a signal in I but also its trimethyl ether (II) and triacetate[5] (III) when taken in acetone-d_6 or deuterochloroform. A possible explanation for the shielding of H_a can be provided by assuming that I adopts a conformation that leads to the placing of H_a in the shielding zone of ring A. The assigned structure was confirmed by X-ray crystallographic analysis[6].

The structure of cudranone proves that biogenetic isoprenylation of xanthones does not take place after the cyclization of the corresponding benzophenones as suggested previously (4).

Cudranone exhibited significant activity against *Staphylococcus aureus* (MIC 25 μg/ml) and *Bacillus subtilis* (MIC 12.5 μg/ml) and even greater activity against *Mycobacterium smegmatis* (MIC 1.6 μg/ml)[7]. Further evaluation of antimicrobial activity of I is in progress.

(1) J. E. Knapp and P. L. Schiff, Jr., *J. Pharm. Sci.*, **60**, 1729 (1971).

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(4) I. Carpenter, H. D. Locksley, and F. Scheinmann, *Phytochemistry*, **8**, 2013 (1969).

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[5] Prepared by treating cudranone with acetic anhydride in pyridine at room temperature overnight. It crystallized from methanol as prisms, mp 100–101°.

[6] The details will be published.

[7] The minimum inhibitory concentration against these microorganisms was determined by the serial dilution method using streptomycin as a positive control. The results were read after incubation at 37° for 24 hr.

BOOKS

REVIEWS

Marihuana: An Annotated Bibliography. By COY W. WALLER, JACQUELINE J. JOHNSON, JUDY BUELKE, and CARLTON E. TURNER. Macmillan, 866 Third Ave., New York, NY 10022, 1976. 560 pp. 18.5 × 25.5 cm. Price $13.95.

This handbook will be most appreciated by those interested in the world literature on any aspect of marihuana (*Cannabis* species), its constituents, pharmacology, metabolism, toxicology, chemistry, synthesis, botany, *etc.* Every conceivable type of citation is found, ranging from reviews and books to original research reports, notes, communications, letters to the editor, rebuttals, book reviews, patents, dissertations, UN documents, introductory remarks to symposia, and the like.

The compilation was assembled by the Waller–Turner group, who have been actively engaged in *Cannabis* research for several years at the Research Institute of Pharmaceutical Sciences, University of Mississippi, under sponsorship of the National Institute of Mental Health. Literature coverage is stated to be from the beginning of 1964 through 1974, and "3045 entries covering the international scientific publications" are included (all entries are definitely not "scientific"). In all cases, the full citation of each entry is given, *i.e.*, all author names, journal title, volume, issue number, full pagination (in most, but not all, cases), and year of publication. Foreign language titles are given with parenthetical English translations in some cases.

Articles are entered alphabetically by senior author name. Most citations are followed by a brief abstract prepared by the editors. Author and subject indexes are included, as well as a summary table, the Biological Actions of Marihuana in Various Animals. The structure, molecular formula, and molecular weight of each known "natural" cannabinoid are given. Also, all of the names and structures of the metabolities of Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, cannabinol, and cannabidiol are given, with an indication of those that are "active," although the term "active" is undefined.

Although this useful handbook represents a monumental effort on the part of the Mississippi group and was apparently prepared without governmental support (no acknowledgment was found to this effect), a number of minor deficiencies, as judged by this reviewer, and errors should be pointed out so that the user may be forewarned.

There is no statement concerning where the citations were obtained and how systematic the literature coverage may have been. For example, were "Chemical Abstracts" and "Biological Abstracts" covered completely for the stated time period? Were the brief abstracts derived from abstracts or from reading the original papers or books? Since the entries covered range from citations of introductory remarks to *Cannabis* symposia through entries in "Encyclopedia Britannica," one must wonder where the literature coverage started and ceased. For example, the authoritative book by H. Wagner, "Rauschgift-Drogen" (Springer-Verlag, Berlin, Germany, 1969), most surely should have been included in the handbook.

A useful addition to each citation would have been either the mailing address of the senior author and/or the secondary source, since the articles in some obscure journals would have to be verified before obtaining an interlibrary loan of the journal.

To this reviewer, the subject index was difficult to use. For example, no major heading concerning Isolation of Constituents was found. A major heading "Trigonelline (isolation from *Cannabis*)" was found, but no major headings for "Friedelin," "Epifriedelanol," "Sitosterol," "Stigmasterol," "Campesterol," and most other noncannabinoids isolated from *Cannabis* were entered. The major subject heading "Biochemistry" lists