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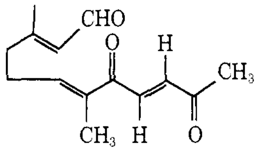
Cyclopentanoid Norsesquiterpenes from Gyrinid Beetles

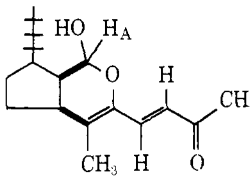
Sir:

Although beetle secretions contain relatively simple compounds,[1] steroids and other more complex molecules have been identified recently.[2] The "whirl-a-gig" beetle (*Dineutes discolor* aubé, Coleoptera; *Gyrinidae*) secretes a complex mixture of C$_{14}$ polycarbonyl compounds from its pygidial glands which have a defensive function toward fish.[3] Schildknecht and coworkers[4] and Meinwald and coworkers[5] have investigated four related species all of which contain an acyclic $C_{14}H_{18}O_3$ aldehyde (**1**) as the major component.

The major component of our secretion, gyrinidone (**2**), was separated from other glandular components and contaminants by extensive silicic acid column and thin layer chromatography.[6] It exhibited the following spectral properties: pmr ($CDCl_3$) δ 1.1 (d, J = 5.5 Hz, 4 H), 1.8 (narrow d, $J < 1$ Hz, 3 H), 2.3 (s, 3 H), 5.05 (d, J = 5.5 Hz, 1 H coupled to a proton at 1.78), 6.5 (d, J = 16 Hz, 1 H), 7.4 (d, J = 16 Hz, 1 H with seven additional protons between 1.1 and 2.3); ir 2.9, 5.98, 6.16, and 6.30 μ; uv (EtOH) 318 nm (ϵ 8700) and 234 (5600); mass spectra *m/e* 236.140 (33), 175 (22), 125 (58), 109 (50), 98 (68), and 43 (100). $C_{14}H_{20}O_3$ requires *m/e* 236.141. The appearance of hydroxyl absorption in the infrared spectrum was confirmed by formation of a monotrimethylsilyl ether having a molecular ion at *m/e* 308.[7] However, **2** formed a trimethoxime[8] (*m/e* 323) indicating that one oxygen functions either as carbonyl or hydroxyl.

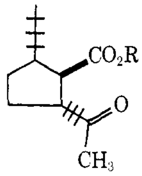


1



2

Oxidation of **2** with ruthenium tetroxide[9] gave only one acid (*m/e* 170) with large peaks at *m/e* 155, 152, 82, 81, and 43. Its methyl ester exhibited *m/e* 184, 169, 153, 152, 142, 129, 109, 100, and 43. The 2,4-dinitrophenylhydrazones of the epimerized[10a] acid and ester were identical with those of authentic[10b] **3a** and **3b**, which exhibit, respectively: **3a**, *m/e* 350, 315, 304, 297, 227; R_f 0.39 (benzene–ethyl acetate, 2:1); mp 170–173°; mmp 170–173° (lit.[10a] 170–172°); **3b**, *m/e* 364, 333, 329, 297, 246; R_f 0.50 (benzene–ethyl acetate, 10:1); elution at 270° on 1% OV-17 column on Supelcoport. Since the stereochemistry of **3a** from nepetalactone is known[10a] and the 2,4-DNP of our material exhibits the same sign of rotation and the same type curve as the authentic material, $[\alpha]^{25}{}_{578}$ −25° (c 0.04, C_2H_5OH), the sterochemistry of **2** is as shown.



3a, R = H
3b, R = CH_3

Isolation of **3a** from oxidation of **2** establishes the constitution of nine of the original 14 carbons in gyrinidone. The α,β-unsaturated ketone system in **2** constitutes four of the other five carbons as indicated by the absorption at δ 2.3, 6.5, and 7.4 in the pmr spectrum[11] and by the base peak at *m/e* 43 (CH_3CO^+) in the mass spectrum. The trans nature of the α and β protons is indicated by their large coupling constant (16 Hz). Since both protons appear as doublets, no other protons are adjacent to either. Their chemical shifts and the ultraviolet spectrum indicate an extended chain of conjugation which must be connected to the unsaturated methyl group in **2** (δ 1.8). The dual nature of one of the oxygens is accommodated by the hemiacetal linkage in **2**, the absorption at 5.05 being assigned to the proton H_A.[12,13]

The similarity of **2** to iridodial,[14] nepetolactone,[14] and plant iridoid glycosides[13] is striking. No cyclopentanoid norsesquiterpene has been found previously in nature.[15]

Three minor components of the secretion are isomeric $C_{14}H_{20}O_3$ compounds which contain a free aldehydic function indicated by a multiplet at δ 9.8. Prolonged contact (18 hr) with either silica gel or alumina isomer-

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(1) J. Weatherston, *Quart. Rev., Chem. Soc.*, **21**, 287 (1967); T. Eisner and J. Meinwald, *Science*, **153**, 1341 (1966); L. M. Roth and T. Eisner, *Annu. Rev. Entomol.*, 7, 107 (1962); R. L. Beard, *ibid.*, **8**, 1 (1963); P. Karlson and A. Butenandt, *ibid.*, 4, 39 (1959).

(2) H. Schildknecht, *Angew. Chem., Int. Ed. Engl.*, **9**, 1 (1970).

(3) E. F. Benfield, *Ann. Entomol. Soc. Amer.*, in press. The biological activities of 2 and 4 are being examined.

(4) For *Gyrinus natator* L., see H. Schildknecht and H. Neumaier, *Chem. Ztg., Chem. App.*, **94**, 25 (1970); H. Schildknecht, B. Tauscher, and D. Krauss, *ibid.*, **96**, 33 (1972); H. Schildknecht, H. Neumaier, and B. Tauscher, *Justus Liebigs Ann. Chem.*, **756**, 155 (1972).

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(6) Abstracted in part from the Ph.D. Dissertation of S. K. Oh, Howard University, 1970. Details are contained therein.

(7) Tri-sil, Pierce Chemical Co., Rockford, Ill.

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(10) (a) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Amer. Chem. Soc.*, **80**, 3420 (1958). (b) We thank Professor E. J. Eisenbraun, Oklahoma State University, for his generous gift of authentic samples.

(11) See, for example, β-ionone, spectrum no. 17 in N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963.

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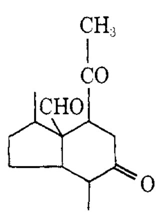
(13) J. M. Bobbitt and K.-P. Segebarth in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969.

(14) G. W. K. Cavill in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A.R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969.

(15) A cyclopentanoid sesquiterpene has been isolated previously: S. Nozoe, M. Goi, and N. Morisaki, *Tetrahedron Lett.*, 1293 (1970); B. E. Cross, R. E. Markwell, and J. C. Stewart, *Tetrahedron*, **27**, 1663 (1971).

ized gyrinidone to a mixture containing large amounts of the three aldehydes. However, chromatography (gas and thin layer) of material obtained by either wiping or dissecting glands verified the presence of these aldehydes as well as gyrinidone in the original secretion. Each[16] has a base peak at *m/e* 151 suggesting loss of CHO and C_4H_8 from the original aldehyde. Although all three aldehydes still contain the CH_3CO group (*m/e* 43), loss of the conjugated system is indicated by the absence of absorption in the vinyl proton region of their pmr spectra, their ultraviolet spectra (231 nm (ϵ 4100) and 311 (410)), and their infrared spectra (5.85 and 5.95 μ). Although **2** exhibited slight optical activity, $[\alpha]^{25}_{400}$ $-69°$, $[\alpha]_{350}$ $-103°$, $[\alpha]_{255}$ $+138°$ (*c* 0.058, C_2H_5OH), the mixture **4** showed $[\alpha]^{25}_{400}$ $+57°$, $[\alpha]_{350}$ $+48°$, $[\alpha]_{320}$ $-38°$, $[\alpha]_{300}$ $+280°$, $[\alpha]_{280}$ $+760°$ (*c* 0.21, C_2H_5OH).

Air oxidation of the mixture of aldehydes gave isomeric acids (*m/e* 252) which were converted to their isomeric methyl esters (*m/e* 266) each of which still contains a base peak at *m/e* 43 and forms a dimethoxime (*m/e* 324). A Michael addition leading to epimers of **4** is postulated for the isomeric aldehydes.



4

Acylic aldehyde **1** may well be the precursor for **2** involving addition across the conjugated system.[17] A second addition to the remaining double bond would give **4**.

(16) The aldehyde mixture could not be separated by tlc and was analyzed by combined gas chromatography–mass spectrometry on an LKB-9000 combined gas chromatograph–mass spectrometer using columns containing 1% OV-17 on Supelcoport (Supelco, Inc., Bellefonte, Pa.).

(17) Examination of milkings from other species (*Dineutes assimilis* and *Gyrinus analis*) by gas chromatography–mass spectrometry indicates that some species contain isomers of both $C_{14}H_{18}O_3$ and $C_{14}H_{20}O_3$ while other gyrinids have isomers of only one molecular formula.

(18) This work was completed during the tenure of a special fellowship at the National Institutes of Health in the laboratory of H. M. Fales. We thank Dr. Fales, Dr. R. J. Highet, and Dr. G. W. A. Milne for valuable discussions and assistance and the Public Health Service for financial support (CC-00270).

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Synthesis of Disulfide Analogs of Penicillins[1]

Sir:

In the past few years we have been concerned with the synthesis of azetidinone compounds related to cephalosporins and penicillins. Our initial efforts were concentrated on the preparation of key intermediates which could be used in the synthesis of modified azetidinone derivatives. The results of these investigations were described recently.[2] In this paper we report the synthesis of 2-carboxy-3,3-dimethyl-8-oxo-7-phthalimido-4,5-dithia-1-azabicyclo[4.2.0]octane and related compounds.

The starting material, 2-chloro-1-((1′*S*)-alkyloxycarbonyl-2′-chlorothio-2′-methylpropyl)-(3*R*)-phthalimido-4-azetidinone (**1a,b**), prepared by chlorinolysis of the corresponding penicillin ester,[2] is treated with an alkanethiol at room temperature for 5 min to give disulfide **2a** or **2b** (R_1 = *p*-$MeOC_6H_4CH_2$ or *t*-Bu) in almost quantitative yield. These disulfides are isolated as colorless amorphous solids by chromatography and their ir spectra ($CHCl_3$) show peaks for **2a** (R_1 = *p*-$MeOC_6H_4CH_2$) at 1794 (azetidinone CO), 1782 and 1730 (phthalimido CO), and 1750 cm^{-1} (ester CO), and for **2b** (R_1 = *p*-$MeOC_6H_4CH_2$) at 1797 (azetidinone CO), 1785 and 1730 (phthalimido CO), and 1750 cm^{-1} (ester CO). The structures of **1** and **2** were ascertained by analysis and spectral data (see Table I).

Table I. Chemical-Shift Values ($CDCl_3$)[a,b]

Compd[c]	$-(CH_3)_2$	*R*[d]	H_2	H_6	H_7
2a	100, 102	229	278	335 (d, *J* = 2.0)	366 (d, *J* = 2.0)
2b	100 (s, 6 H)	309	277	329 (d, *J* = 1.5)	358 (d, *J* = 1.5)
3a	94, 108	230	251	313 (d, *J* = 2.0)	323 (q, *J* = 1.0, 2.0)
3b	87, 110	309	256	312 (d, *J* = 2.0)	326 (q, *J* = 1.0, 2.0)
3c	92, 105		255	314 (d, *J* = 1.5)	331 (d, *J* = 1.5)
4a	84, 120	230	270	334 (d, *J* = 4.5)	346 (d, *J* = 4.5)
4b	82, 120	320	274	332 (d, *J* = 4.5)	345 (d, *J* = 4.5)
4c	87, 118		268	333 (d, *J* = 4.5)	341 (d, *J* = 4.5)

[a] *J* values in hertz. [b] We thank L. A. Spangle and T. Elzey for determination of the nmr spectra. [c] Satisfactory elemental analyses were obtained for all compounds. [d] **a** = CH_3 and **b** = *p*-nitrobenzyl group.

The reaction of disulfide **2** (**a** or **b**, R_1 = *p*-$MeOC_6H_4CH_2$ or *t*-Bu) with boiling trifluoroacetic acid (TFA) for 30–60 min yields a mixture from which four compounds are isolated by chromatography over silica gel. Comparison of the nmr and ir spectra of the separated compounds indicates the presence of an azetidinone function in two compounds, **3** and **4**, and the absence of the same function in compounds **5** and **6**. Compound **3a** is isolated as a colorless amorphous solid: $[\alpha]_D$ $+175.6°$ (MeCN); ir ($CHCl_3$) 1790 (azetidinone CO), 1785 and 1730 (phthalimido CO), and 1752 cm^{-1} (ester CO). Compound **4a** is obtained as colorless prisms: mp 185–186°; $[\alpha]_D$ $+161.1°$ (MeCN); ir ($CHCl_3$) 1790 (azetidinone CO), 1779 and 1739 (phthalimido CO), and 1745 cm^{-1} (ester CO).[3] The magnitudes of the coupling constants (Table I) establish that compound **3** has the trans arrangement of azetidinone protons (*J* = 2.0 Hz) while **4** is of the

(1) Azetidinone Antibiotics. VII.

(2) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6267 (1971); S. Kukolja and S. R. Lammert, *ibid.*, **94**, 7169 (1972); S. Kukolja and S. R. Lammert, *Croat. Chem. Acta*, **44**, 299, 423 (1972).

(3) The ester **3b**, mp 143–144°, $[\alpha]_D$ $+86°$ (MeCN), has an ir spectrum almost identical with that of **3a**. The ir carbonyl peaks of **4b**, $[\alpha]_D$ $+128.1°$ (MeCN), are nearly the same as those of **4a**.