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SPECIALIA

Structure of α-Dicarvelone

Zinc dust reduction of carvone (I) in basic medium[1] gives dihydrocarvone (II); however, this reduction is accompanied by the formation of a crystalline diketone, α-dicarvelone, to which 2 structures (III and IV) were assigned. WALLACH[2], mainly on the basis of positive haloform reaction on an uncharacterized keto-acid prepared by chromic acid oxidation, suggested tentatively structure (IV) for α-dicarvelone. In this communication, we wish to report the chemical and spectroscopic evidence which establish conclusively that the structure of α-dicarvelone, without stereochemical implications, should be represented by the formula (IV).

The molecular formula of α-dicarvelone was found to be $C_{20}H_{30}O_2$, further confirmed by high resolution mass measurement on its several derivatives (Table I). α-Dicarvelone[3], m.p. 150–152 °C (lit. m.p. 148–149 °C)[2] showed IR-absorption bands at 1710 cm^{-1} (carbonyl in a 6-membered ring), 888 and 1644 cm^{-1} (terminal methylene). It gave yellow colouration with tetranitromethane; displayed no characteristic absorption maximum in the longer wave-length region above 210 nm. The NMR-spectrum ($CDCl_3$) exhibited a readily discernible sharp 6-proton doublet centred at 9.02 τ ($J = 6$ c/s) indicative of the presence of 2 secondary methyl groups in the molecule, which obviously makes structure (III) untenable. Furthermore, a 6-proton signal at 8.23 τ and a 4-proton singlet with fine structure at 5.21 τ indicate 2 vinylic methyl and 2 $>C=CH_2$ groups.

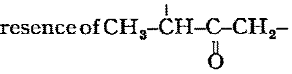
α-Dicarvelone contains 2 carbonyl functions as it readily gives a *bis*-oxime, m.p. 226–228 °C; IR-spectrum: oxime bands – 3245 (ν^{OH}), 1673 ($\nu^{C=N}$) and 936 cm^{-1} (ν^{N-O}); 903 and 1645 cm^{-1} ($>C=CH_2$). NMR-spectrum (pyridine-d_5) τ: 5.12 (4H, broadened singlet, two $>C=CH_2$), 8.24 (6H, singlet, two $CH_3-\overset{|}{C}=CH_2$), 8.77 (6H, doublet, $J = 6.5$ c/s, two $CH_3-\overset{|}{C}H-$).

Catalytic hydrogenation of α-dicarvelone in ethylacetate (Pd-C or Pt) resulted in rapid uptake of 2 moles of hydrogen yielding tetrahydro-α-dicarvelone (V), m.p. 132 °C; no colouration with tetranitromethane; absence of UV end absorption; IR-spectrum: 1707 cm^{-1} ($>C=O$); no isopropenyl band, confirmed by its NMR-spectrum (CCl_4) which lacked any resonance in olefinic region. However, it featured 2 partly overlapped doublets at 9.04 and 9.14 τ due to 2 secondary methyl and 2 isopropyl groups.

WOLFF-KISHNER reduction of α-dicarvelone afforded the corresponding hydrocarbon, α-dicarvelane, b.p. 155–160 °C (bath)/2 mm, n_D^{23} 1.4945, single spot on TLC plate; ν_{max}^{film} 886 and 1648 cm^{-1} ($>C=CH_2$); M.S.: M^+ peak at m/e 274 (3.43% Σ_{41}), base peak at m/e 81 (9.07% Σ_{41}); NMR (CCl_4) τ: 9.06 (6H, doublet, $J = 6.3$ c/s, two $CH_3-\overset{|}{C}H-$), 8.32 (6H, singlet, two $CH_3-\overset{|}{C}=CH_2$), 5.37 (4H, singlet, two $>C=CH_2$). α-Dicarvelane absorbed 2 moles of hydrogen to give a fully saturated hydrocarbon, $C_{20}H_{38}$, M^+ peak at m/e 278 (2.38% Σ_{41}). Its NMR-spectrum (CCl_4) exhibited a doublet at 9.14 τ (18H, $J = 5.5$ c/s), which can be ascribed to 2 secondary methyl and 2 isopropyl units.

Key experiment in establishing the environment of carbonyl group was the deuteration[4] of α-dicarvelone (IV) in CH_3OD/D_2O containing KOD which led to the incorporation of 6 deuterium atoms. This was further corroborated by deuteration of tetrahydro-α-dicarvelone (V). (Table I.)

The NMR spectrum ($CDCl_3$) of d_6-analog (VI) revealed that the doublet, originally present in the spectrum of (IV), was no longer present; instead, there was a sharp 6-proton singlet at 9.05 τ due to $CH_3-\overset{|}{C}D-$ system. These facts conclusively establish the presence of



$CH_3-\overset{|}{C}H-\underset{\underset{O}{\|}}{C}-CH_2-$

moiety in α-dicarvelone (IV). Comparative study of the NMR-spectra of IV, V, VI and VII enabled us to integrate hydrogens alpha to carbonyl, which appeared as a 6-proton multiplet ranging from (a) 7.50–7.71 τ for IV, (b) 7.53–7.83 τ for V. Dihydro- and tetrahydrocarvone and their d_3-analogs were used as model compounds. This was further confirmed by their high resolution mass spectra[5].

Table I. Exact masses and composition of ions

	m/e observed	m/e calculated	Composition
α-Dicarvelone (IV)	302.2247	302.2246	$C_{20}H_{30}O_2$
d_6-Analog (VI)	308.2706	308.2706	$C_{20}H_{24}D_6O_2$
Tetrahydro-α-dicarvelone (V)	306.2564	306.2559	$C_{20}H_{34}O_2$
d_6-Analog (VII)	312.2935	312.2935	$C_{20}H_{28}D_6O_2$
Olefin (X)	274.2664	274.2661	$C_{20}H_{34}$

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[1] O. WALLACH, Justus Liebigs Annln Chem. *279*, 377 (1894).

[2] O. WALLACH, Justus Liebigs Annln Chem. *403*, 79 (1914).

[3] Melting points are uncorrected. All compounds described herein gave satisfactory elemental analyses. Unless otherwise stated, IR-spectra were run in KBr pellets on Perkin-Elmer Infracord, Model 337, calibrated with polystyrene film. NMR-spectra were obtained with Varian A-60 spectrometer using TMS as an internal standard.

[4] G. BÜCHI, M. S. VON WITTENAU and D. M. WHITE, J. Am. chem. Soc. *81*, 1968 (1959).

[5] High resolution mass spectra were recorded on an Associated Electronic Industries MS-9 double focusing mass spectrometer with an apparent resolution of 12,000. Samples were introduced through a heated inlet system at 185 °C. We sincerely thank Dr. HOGG for the spectra. A complete account of the mass spectra of these compounds will be published separately.

The mass spectrum of α-dicarvelone (IV) featured an important peak at m/e 95 shown by high mass measurement to be due to $C_6H_7O^+$ fragment (b). The shift of m/e 95 to m/e 96 in its d_6-analog (VI) is indicative of its formation by stepwise (a → b) or concerted (c → b) mechanism[6], initial step being usual α-cleavage[7-10] yielding (a). (Scheme I.)

Important peaks in the mass spectrum of α-dicarvelone (IV) are summarized in Table II; however, the modes of their fragmentation will be discussed at a later date. It is pertinent to note that the mass spectrum of IV in the lower mass range is very much similar to that of dihydrocarvone (II).

Scheme I

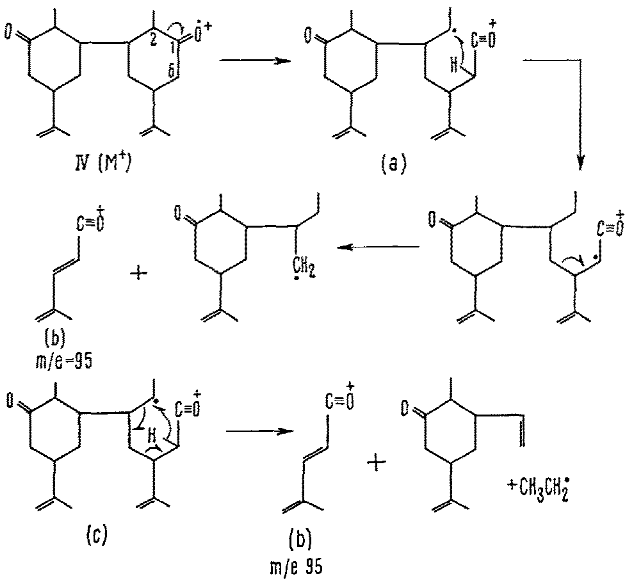
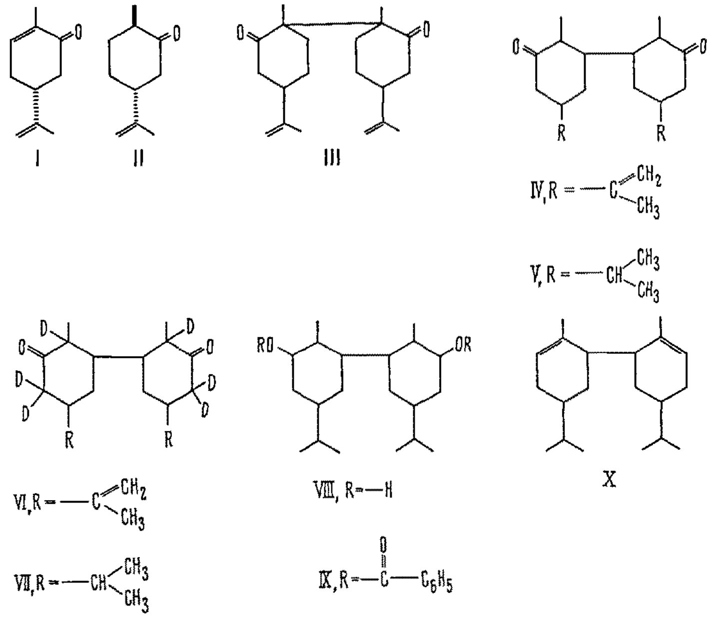


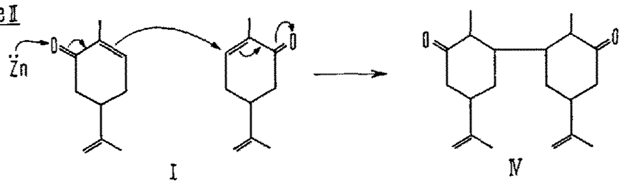
Table II. Important peaks (in order of decreasing abundance) in the mass spectrum of α-dicarvelone (IV)

m/e	Relative abundance	% Σ_{41}
151	100.00	13.86
67	23.09	3.20
95	21.82	3.02
41	20.82	2.89
302	20.54	2.85
110	7.09	0.98
54	2.36	0.33
219	1.09	0.15

Chart I



Scheme II



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[6] D. H. Williams, H. Budzikiewicz, Z. Pelah and C. Djerassi, Mh. Chem. *95*, 166 (1964).

[7] Two types of α-cleavage (a) C_1-C_2 (b) C_1-C_6 are theoretically possible. In dihydrocarvone (II) both processes compete favourably whereas, in α-dicarvelone (IV) process (a) predominates.

[8] R. I. Reed in *Mass Spectrometry of Organic Ions* (Ed. F. W. McLafferty; Academic Press, N.Y. 1963), p. 666.

[9] J. Seibl and T. Gäumann, Z. analyt. Chem. *197*, 33 (1963).

[10] K. Biemann, Mass Spectrometry (McGraw-Hill Book Comp. Inc., N.Y. 1962), p. 101.

The correctness of the structure (IV) was further verified by the following experiments. Tetrahydro-α-dicarvelone (V) on reduction with LAH as well as with $NaBH_4$ furnished the diol (VIII), m.p. 215–216 °C; ν_{max} 3330 and 1024 cm^{-1} (hydroxyl), no carbonyl band; NMR ($CDCl_3$) τ: 9.04, 9.11 (doublet, partly overlapped, two CH_3–$\overset{|}{C}$H– and two CH_3–$\overset{|}{C}$H–CH_3), 8.48 (sharp singlet, $>$CHO*H*, disappeared after exchange with D_2O). Benzoylation of the diol (VIII) in pyridine at room temperature afforded dibenzoate (IX), m.p. 199 °C; IR-spectrum: 1714, 1276 and 1110 cm^{-1} (aromatic ester); NMR ($CDCl_3$) τ: 1.91, 2.46 (10H, multiplet, two C_6H_5–$\overset{O}{\overset{\|}{C}}$–), 4.62 (2H, broadened singlet, two –$\overset{|}{C}H$–O–), 9.03 and 9.12 (18H, doublet, partly overlapped, two CH_3–$\overset{|}{C}$H– and two CH_3–$\overset{|}{C}$H–CH_3). Pyrolysis of dibenzoate (IX) at 280 ± 10°C in atmosphere of nitrogen yielded an olefin (X), b.p. 150–160 °C (bath)/2 mm; single spot on TLC plate; IR-spectrum (liquid film): 816 and 1649 cm^{-1} (trisubstituted double bond); NMR (CCl_4) τ: 4.50 (2H, sharp singlet, two $H\overset{|}{C}=\overset{|}{C}$–), 8.36 (6H, singlet, two CH_3–$\overset{|}{C}=\overset{|}{C}$H)[11], 9.09 (12H, doublet, $J = 5.5$ c/s, two –CH(CH_3)$_2$); M.S.: m/e 274 (3.23% Σ_{41}, M^+), m/e 164 (9.24% Σ_{41}, base peak), m/e 55 (2.51% Σ_{41}). High resolution measurements with (X) demonstrate that the ion of mass 55 is almost due to $C_4H_7^+$ and its formation can be rationalized by invoking a reverse DIELS-ALDER fragmentation of (X) followed by elimination of a methyl radical[12]. Thus, the formation of a trisubstituted olefin (X) coupled with earlier results clearly rule out the structure (III) and establish unequivocally the structure (IV) for α-dicarvelone whose formation can be satisfactorily explained by the pathway[13] depicted in Chart I (Scheme II).

We are currently investigating the structure of β- and γ-isomer reported by WALLACH. This work along with their stereochemistry will be reported in our next communication[14].

Zusammenfassung. Die Struktur des Terpens α-Dicarvelon wird endgültig aufgeklärt.

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Victoria (B.C., Canada), 6 September 1967.

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[11] K. SUGA, S. WATANABE and K. KAMMA, Can. J. Chem. *45*, 933 (1967).

[12] A. F. THOMAS and B. WILLHALM, Helv. chim. Acta *47*, 475 (1964).

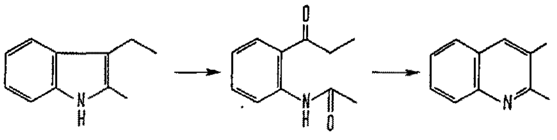
[13] Dimerization of carvone during methylation studies has been recently reported. See, D. W. THEOBALD, Tetrahedron *23*, 2767 (1967).

[14] Financial assistance by the National Research Council of Canada and the University of Victoria Research Grant is gratefully acknowledged. We thank Professors D. J. MACLAURIN and A. J. WOOD for their interest in this work. One of the authors (T.C.J.) is especially indebted to Drs. O. E. EDWARD, T. J. KING and V. BOEKELHEIDE for stimulating discussions.

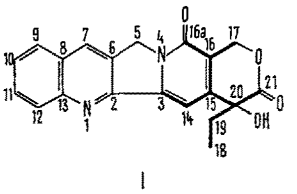
A Numbering System for Camptothecin Based on Its Biogenesis

The unusual pentacyclic alkaloid camptothecin (I), isolated by WALL and co-workers from *Camptotheca acuminata* (Nyssaceae)[1], is most probably of tryptophane-terpene origin.

The quinoline system must be formed by oxidation of an indole double bond, followed by recyclization and aromatization:



The remainder of the camptothecin (I) molecule incorporates the well recognized 10 carbon moiety (here represented by thick lines) which is also present in ajmalicine (II). In the case of the indole alkaloids, this 10 carbon fragment has been clearly shown to be of terpenoidal origin[2–6].



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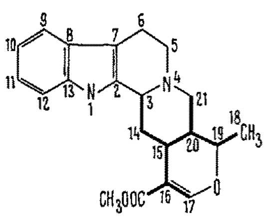

II

Following the LE MEN-TAYLOR system[7], the numbering system below is therefore suggested for camptothecin (I), in analogy with ajmalicine (II).

The pyridone carbonyl carbon in camptothecin has been designated 16a for convenience, although this atom is not assigned a number in the LE MEN-TAYLOR scheme.

Résumé. Un mode de numérotation pour la camptothecin est proposé, basé sur la biogenèse de cet alcaloïde.

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State University, University Park (Pennsylvania
16802, USA), 20 November 1967.

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[1] M. E. WALL, M. C. WANI, C. E. COOK and K. H. PALMER, J. Am. chem. Soc. *88*, 3888 (1966).

[2] A. R. BATTERSBY, R. T. BROWN, R. S. KAPIL, A. O. PLUNKETT and J. B. TAYLOR, Chem. Commun. 46 (1966).

[3] A. R. BATTERSBY, R. T. BROWN, J. A. KNIGHT, J. A. MARTIN and A. O. PLUNKETT, Chem. Commun. 346 (1966).

[4] P. LOEW, H. GOEGGEL and D. ARIGONI, Chem. Commun. 347 (1966).

[5] E. S. HALL, F. MCCAPRA, T. MONEY, K. FUKUMOTO, J. R. HANSON, B. S. MOOTOO, G. T. PHILLIPS and A. I. SCOTT, Chem. Commun. 348 (1966).

[6] E. LEETE and J. N. WEMPLE, J. Am. chem. Soc. *88*, 4743 (1966).

[7] J. LE MEN and W. I. TAYLOR, Experientia *21*, 508 (1965).