Mass spectrum: M^+, 230 ($M^+ + 2$, 34% of M^+). Infrared ν_{max} (CCl_4) 3515, 1732, and 1642 cm^{-1}; ν_{max} (KBr disk) 1747, 1717, and 1640 cm^{-1}. Ultraviolet λ_{max} (EtOH) 284 mμ (ε 22 000); n.m.r. 2.93–3.84 τ (m, 2H), 5.93 τ (s, 1H), 6.20 τ (s, 3H), 7.19 τ (q, $|J|$ = 18–19 c.p.s., 2H), 8.07 τ (d, J = 5 c.p.s., 3H).

Anal. Calcd. for $C_{10}H_{11}O_4Cl$: C, 52.07; H, 4.81; Cl, 15.37. Found: C, 52.04; H, 4.80; Cl, 15.39.

Acknowledgments

The authors thank Mrs. H. Moore and Mrs. G. Aarts of the University of New Brunswick for the n.m.r. and mass spectrum determinations respectively.

1. G. M. Strunz, A. S. Court, J. Komlossy, and M. A. Stillwell. Can. J. Chem. **47**, 2087 (1969).
2. M. A. Stillwell. Can. J. Bot. **44**, 259 (1966).
3. W. J. McGahren, J. H. Van den Hende, and L. A. Mitscher. J. Amer. Chem. Soc. **91**, 157 (1969).
4. N. S. Bhacca and D. H. Williams. Applications of n.m.r. spectroscopy in organic chemistry. Holden-Day, Inc., San Francisco. (1964).

Structure of didehydrochelidonine

M. H. Benn and R. E. Mitchell
Department of Chemistry, The University, Calgary 44, Alberta

Received June 2, 1969

Gadamer's didehydrochelidonine is the internal carbinolamine ether **2***c*. The formation of this compound, as also its reduction back to the parent alkaloid, provides chemical proof that the relative stereochemistry of chelidonine is, as previously deduced from spectroscopic studies, that given in **1**.

Canadian Journal of Chemistry, 47, 3701 (1969)

Whilst studying the chemistry of chelidonine J. G. Gadamer observed that mercuric acetate oxidation of this alkaloid yielded a new compound which he named didehydrochelidonine (1).[1,2] Later he and his co-workers discovered that the same compound was obtained in superior yield when the oxidation was performed on chelidonine acetate (3), and that it was also a product of the permanganate oxidation of chelidonine (4).

Didehydrochelidonine was described as a colorless, noncrystalline, basic compound which yielded a number of crystalline derivatives, including a yellow hydrobromide and a colorless pseudocyanide (1, 3). Reduction of didehydrochelidonine, or its hydrobromide salt, with zinc and sulfuric acid was reported to yield unracemized chelidonine (1, 3), and it was also observed that the free base underwent ready dehydration to yield dihydrosanguinarine (**4**) (3).

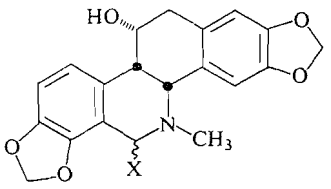
Gadamer believed that didehydrochelidonine was a carbinolamine (1, 3): in terms of the structure (**1**) subsequently established for chelidonine (without stereochemistry) (5), this would now be formulated as **2***a*(X = OH), and it is in fact commonly so described (6); although others have chosen to represent it as **2***b* (7), presumably to rationalize the dehydration. The salts of didehydrochelidonine have normally been written as **3**, and the pseudocyanide as **2***a*(X = CN) (6*a*).

We anticipated on the basis of experience in the diterpenoid alkaloid field (9) that, *if* the stereochemistry of chelidonine was, as deduced from infrared (8*a*) and proton magnetic resonance (8*b*, *c*) spectroscopic studies, that represented in **1**, didehydrochelidonine would in fact be the internal carbinolamine ether **2***c*. We further anticipated that protic acids would convert **2***c* to acyclic salts (**3**), from which **2***c* would be recovered on basification, except in certain cases, exemplified by basification with cyanide salts, where capture of nucleophile could produce a stable acyclic product (**2***a*) (e.g. X = CN).

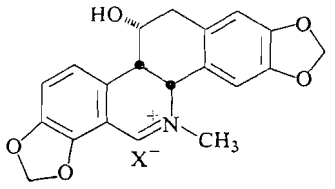
Of the other reactions of didehydrochelidonine, the facile reduction to yield chelidonine is in keeping with the known case of reduction of strained carbinolamine ethers (10) and immonium salts, and we visualized the dehydration to

[1]This is one of several historically interesting examples of Gadamer's early use of mercuric acetate oxidations in the structure–determination of alkaloids (2).

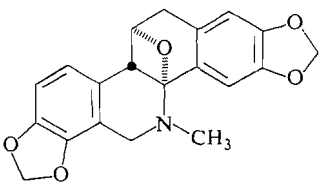
[2]In modern terminology the name dehydrochelidonine is to be preferred.



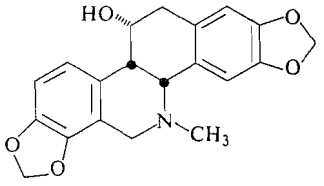
2*a*



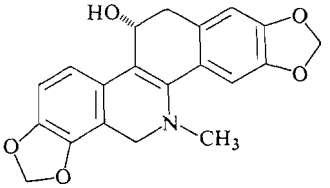
3



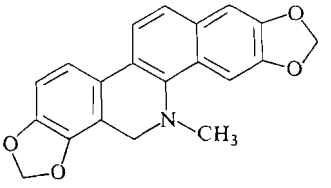
2*d*



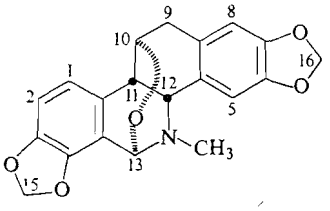
1



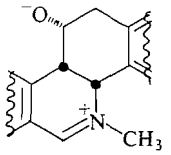
2*b*



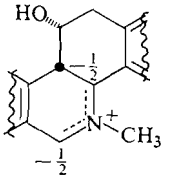
4



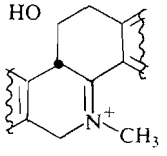
2*c*



2*e*



2*f*

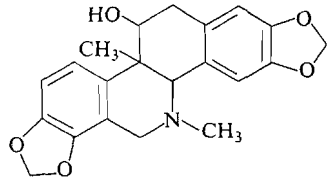


2*g*

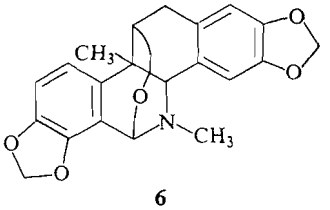
dihydrosanguinarine as proceeding through the sequence **2***c* ⇌ **2***e* ⇌ **2***f* ⇌ **2***g* ⇌ **2***b* → **4**.[3]

We obtained didehydrochelidonine, from the products of the permanganate oxidation of chelidonine, and characterized it as the crystalline hydrobromide and pseudocyanide; like other workers we were unable to persuade the free base to crystallize. Sodium borohydride reduced the free base back to chelidonine.

Prompted by a recent report which describes a permanganate oxidation product of corynoline (**5**) as **6** (12), we record here the evidence which established that **2***c* is indeed the correct structure for didehydrochelidonine.



5



6

The mass spectrum of didehydrochelidonine free base had an apparent M^+ species at *m/e* 351, as required for **2***c*.

Significantly, as judged by the absence of absorption in the 4000–3050 cm^{-1} region of its infrared spectrum, didehydrochelidonine free base did not contain an OH function. (In contrast, the infrared spectrum of didehydrochelidonine hydrobromide had strong absorption at 3300 cm^{-1}.)[4]

[3]The mechanism for the conversion **2***c* ⇌ **2***g* is similar to that proposed for the isomerization of the oxazolidine system in some diterpenoid alkaloids (11).

[4]The infrared spectrum of the hydrobromide also had absorption at 1655 cm^{-1} absent in the spectrum of the free base, which may be ascribed to the C=N$^+$ function. Other evidence which supports **3** (X = Br) as the structure for the hydrobromide includes the ultraviolet light absorption at 397 mμ (ε ~ 7000) consistent with the 3,4-dihydro-2-methyl-6,7-methylenedioxyisoquinolinium chromophone, absent in the spectrum of the parent free base.

The proton magnetic resonance spectrum of didehydrochelidonine free base was most informative. Based on the N—CH_3 signal, the spectrum integrated for 17 protons, a result again in accord with **2***c*, but not with **2***a*(X = OH). An analysis of the spectrum is provided in the Experimental, and we comment here only that it was completely consistent with that required for **2***c*, and excludes structures **2***b* and **2***d*.

We conclude that the structure of didehydrochelidonine is **2***c*, and note that the formation of this compound from chelidonine (as well as its reduction back to chelidonine) constitutes *chemical* proof that the relative stereochemistry of chelidonine is as depicted in **1**.

Experimental

Melting points were determined in capillaries, and are uncorrected. Infrared and ultraviolet spectra were recorded on Perkin–Elmer 337 and 202 spectrophotometers, respectively. Proton magnetic resonance spectra were recorded on Varian HA-100 and A-60 spectrometers, with tetramethylsilane as an internal standard. Optical rotations were measured using a Durrum-JASCO U.V.-O.R.D./5 spectrometer. The mass spectrum was recorded on an AEI-MS9 spectrometer, at the University of Alberta, Edmonton, and we report only ions whose abundance was over 20% of the base peak.

Didehydrochelidonine (2c)

Finely powdered potassium permanganate (360 mg, 2.28 mmoles) was added over the course of 1 h to a stirred solution of chelidonine (500 mg, 1.42 mmoles) in acetone (20 ml). After having been stirred at room temperature for a further hour, the reaction mixture was filtered (Celite) and, after washing the filter-cake with acetone, the yellow filtrate and washings were evaporated to dryness under reduced pressure. The residue was taken up in benzene and chromatographed on a column of Florisil (25 g, 1.8 × 20 cm) packed in benzene. Chelidonine was eluted with benzene–ether (9:1, v/v) followed, as the concentration of ether was increased, by didehydrochelidonine.[5]

The yield of didehydrochelidonine, obtained as an almost colorless glass, contaminated with a very faint trace (t.l.c.) of chelidonine, was 195 mg, and a further 185 mg of material containing slightly more chelidonine was also isolated. The total yield of didehydrochelidonine was 76%: λ_{max} (EtOH) 235 (sh) (ε 8720) and 293 mμ (ε 6000), λ_{min} 257 mμ (ε 1100); on addition of one drop of ca. 1% EtOH–HCl, λ_{max} 241, 302 and 394 mμ, λ_{min} 225 and 253 mμ; ν_{max} (KBr or $CHCl_3$) 1610 cm^{-1} (weak), and nothing in the region 4000–3050 cm^{-1}; τ($CDCl_3$) 3.22 (s) (2H), 3.32 (s) (1H) and 3.37 (s) (1H) (4 aromatic protons, probably those at C-1 and -2, C-5 (or -8), and C-8 (or -5), respectively), 4.02 (s) (2H), 4.07 (d) and 4.11 (d) (AB quartet J = 2 c.p.s.) (2H) (4 methylenedioxy protons, probably those at C-16, and C-15, respectively), 4.69 (s) (1H) (H at C-13), 6.08 (broad multiplet) (a complex quintuplet, possibly made up of overlapping quartets, J = 2 c.p.s.) (1H) (H at C-10), 6.85–7.03 (broad, unresolved, complex multiplet) (4H) (H at C-9, C-11 and C-12), and 7.84 (s) (3H) (protons of *N*-CH_3); *m/e* (rel. intensity) 351 (46), 333 (41), 332 (35), 188 (100), and 43 (32).[6]

Didehydrochelidonine hydrobromide was obtained as yellow needles, from 2-propanol, with no distinct m.p. (sinters and decomposes > 210°); λ_{max} (EtOH) 233 (ε 11 000), 298 (ε 9740) and 397 mμ (ε 1690); ν_{max} (KBr) 3300 (strong), and 1655 cm^{-1} (strong); $[\alpha]_D^{27}$ +390 (±5)° (*c* 0.1, EtOH). Literature (3) $[\alpha]_D$ +412° (*c* 1, EtOH).

Didehydrochelidonine pseudocyanide was obtained as colorless prisms, from ethanol, m.p. 194–196°. Literature (3) m.p. 194–195°.

Sodium Borohydride Reduction of Didehydrochelidonine

Sodium borohydride (2.2 mg, 0.057 mmole) was added to a stirred solution of didehydrochelidonine (40 mg, 0.114 mmole) in ethanol (1 ml). After 30 min the solution was acidified and allowed to stand for a few minutes. The solution was then basified (Na_2CO_3) and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated. The residue, which gave a single spot on t.l.c. identical in R_f to chelidonine, was recrystallized from ethanol, and gave off-white crystals, m.p. 120–130° (30 mg, 75%), undepressed on admixture with authentic chelidonine (which also had m.p. 120–130°); the infrared spectrum of the reduction product was also superimposable on that of chelidonine.

Acknowledgments

We are grateful to the National Research Council of Canada for the Grant A-4547 which contributed to the support of this work, and also for the Postgraduate Scholarship awarded to R. E. Mitchell.

1. J. GADAMER. Arch. Pharm. **257**, 298 (1919).
2. J. GADAMER. Arch. Pharm. **253**, 274 (1915); Chem. Abstr. **10**, 1033 (1915).
3. J. GADAMER and K. WINTERFELD. Arch. Pharm. **262**, 452 (1924).
4. J. GADAMER and M. THEISSEN. Arch. Pharm. **262**, 578 (1924).
5. F. VON BRUCHHAUSEN and H. W. BERSCH. Ber. **63**, 2520 (1930); F. VON BRUCHHAUSEN and H. W. BERSCH. Ber. **64**, 947 (1931); E. SPATH and F. KUFFNER. Ber. **64**, 370 (1931).
6. See for example: (*a*) R. H. F. MANSKE. *In* The alkaloids. Vol. 4 *Edited by* R. H. F. Manske and

[5]The chromatogram was monitored by thin-layer chromatography on silica gel-G, with Dragendorf reagent for location of the products: the R_f values for chelidonine and didehydrochelidonine were respectively 0.57 and 0.44 in methanol–benzene (5:95, v/v), and 0.48 and 0.60 in diethylamine-ether (2:98, v/v).

[6]Of the prominent ions in the mass spectrum, other than M^+ at *m/e* 351, we attribute that at *m/e* 333 to the radical–cation of 4, that at *m/e* 332 to the sanguinarine cation, and that at *m/e* 188 to the 2-methyl-6,7-methylenedioxyisoquinolinium cation.

H. L. Holmes. Academic Press, New York. 1954. p. 259; (*b*) K. W. BENTLEY. The isoquinoline alkaloids. Pergamon Press, Oxford. 1965. p. 212.
7. E. DOMAGALINA and J. OCHÝNSKA. Chem. Anal. (Warsaw) **12**, 267 (1967).
8. (*a*) F. SANTÁVY, M. HORÁK, M. MATUROVA, and J. BRABENA. Coll. Czech. Chem. Comm. **25**, 1344 (1960); (*b*) E. SEONE. Anales real soc. espan. fis. y quim., (Madrid) **61B**, 755 (1965); (*c*) C.-Y. CHEN and D. B. MCLEAN. Can. J. Chem. **45**, 3001 (1967).
9. (*a*) R. ANET, D. W. CLAYTON, and L. MARION. Can. J. Chem. **35**, 397 (1957); (*b*) K. WIESNER, S. ITO, and Z. VALENTA. Experientia, **14**, 167 (1958); T. SUGASAWA. Chem. Pharm. Bull. (Japan) **9**, 897 (1961). See also: N. J. LEONARD and W. K. MUSKER. J. Am. Chem. Soc. **82**, 5148 (1960).
10. D. DVORNIK and O. E. EDWARDS. Tetrahedron, **14**, 54 (1961); S. W. PELLETIER. Tetrahedron, **14**, 76 (1961), and references therein.
11. (*a*) S. NARUTO, S. ARAKAWA, and H. KANEKO. Tetrahedron Letters, 1705 (1968); (*b*) N. TAKEO. Chem. Pharm. Bull. (Japan), **11**, 1306, 1312 (1963).
12. (*a*) C. DJERASSI, C. R. SMITH, A. E. LIPMANN, S. K. FIGDOR, and J. HERRAN. J. Am. Chem. Soc. **77**, 4801 (1955); (*b*) K. WIESNER and Z. VALENTA. Fortschr. Chem. org. Naturstoffe, **16**, 26 (1958).

Central nervous system depressants. XVI. Some newer hydantoins and thiohydantoins

SATISH CHANDRA AND P. C. DANDIYA
Department of Pharmacology, S.M.S. Medical College, Jaipur, India

Received February 4, 1969

The synthesis of hydantoin and thiohydantoin derivatives is described.

Canadian Journal of Chemistry, 47, 3704 (1969)

5,5-Disubstituted hydantoins are known to possess hypnotic, anticonvulsant, and hypoglycemic properties (1–5). The introduction of methoxy groups has been reported to increase the anticonvulsant activity (6). Oldfield and Cashin (7) synthesized a number of substituted cycloalkanespiro-5-hydantoins which were reported to potentiate hexobarbital-induced hypnosis. Shaffer *et al.* (8) synthesized *N*-3-propionic acid, its ethyl ester, and *N*-3-(2-cyanoethyl) derivatives of 5,5-disubstituted hydantoin and reported that spontaneous motor activity was depressed by these compounds. Further, Dandiya and coworkers (9) have shown that unsaturation in the side chain is one of the most important factors causing central nervous system depressant effect. This led us to the synthesis of hydantoin and thiohydantoin derivatives possessing the methoxy groups and having unsaturation in the side chain.

Experimental

The thiohydantoin and hydantoin derivatives (Table I) were prepared by the following methods.

2-Thio-5-(2,4,5-trimethoxybenzylidene) Hydantoin (Th-1)

A mixture of 2,4,5-trimethoxybenzaldehyde (2.0 g; 0.01 mole), 3-benzoyl-2-thiohydantoin (2.0 g; 0.01 mole),

TABLE I

Analytical data of some trimethoxybenzylidene hydantoins and thiohydantoins.

Compound	Molecular formula	Melting point °C	% yield	% calculated			% found		
				C	H	N	C	H	N
2-Thio-5-(2,4,5-trimethoxybenzylidene) hydantoin(**Th-1**)	$C_{13}H_{14}N_2O_4S$	227–228	37	53.06	4.76	9.53	53.45	5.03	9.34
2-Thio-5-(3,4,5-trimethoxybenzylidene) hydantoin(**Th-2**)	$C_{13}H_{14}N_2O_4S$	216–217	33	53.06	4.76	9.53	52.96	4.99	9.45
2-Thio-5-(2,3,4-trimethoxybenzylidene) hydantoin(**Th-3**)	$C_{13}H_{14}N_2O_4S$	186	33	53.06	4.76	9.53	52.97	4.99	9.47
5-(2,4,5-Trimethoxybenzylidene) hydantoin (**H-1**) (10)	$C_{13}H_{14}N_2O_5$	>250	40	56.12	5.03	10.07	56.44	5.15	9.77
5-(3,4,5-Trimethoxybenzylidene) hydantoin (**H-2**) (11)	$C_{13}H_{14}N_2O_5$	>250	36	56.12	5.03	10.07	55.97	5.21	9.92

NOTE. The compounds listed gave infrared spectra that were in accord with the proposed structures.