Parthemollin, a New Xanthanolide from *Parthenice Mollis* Gray[1]

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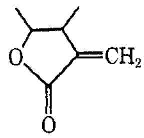
The structure of parthemollin, a new xanthanolide from *Parthenice Mollis* Gray, has been elucidated. Absolute configurations have been assigned to three of the four asymmetric centers.

The discovery of pseudoguaianolides in both *Ambrosia* and *Parthenium* species[2,3] was of interest because of the debate on the position of *Ambrosia* and its relatives, the ragweeds, in the general taxonomic scheme of the *Compositae*.[4] Since that time the distribution of sesquiterpene lactones in *Ambrosia* and related genera has received considerable attention[4,5] because of the possible utility of such knowledge in clarifying evolutionary relationships[6] within the group. However, in addition to the hints given by chemical examination of a few *Parthenium* species,[7] there are reasons based on morphology for suspecting that genera of the *Melampodiinae* may be on the road to the ragweeds.[8] As part of a general chemical investigation of this notion we now report the results of our study of *Parthenice mollis* Gray.[9]

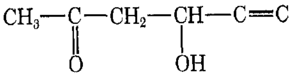
P. mollis, although containing a relatively large sesquiterpene lactone fraction, afforded only one chemically characterizable entity in approximately 0.05% yield which we have called parthemollin. Parthemollin, $C_{15}H_{20}O_4$, mp 116–118°, $[\alpha]_D$ −130.0°, had one hydroxyl group (infrared band at 3580 cm^{-1}, formation of monoacetate **1b**) and a conjugated γ-lactone (ir bands at 1775 and 1655 cm^{-1}, very strong end absorption at 205 nm). The presence of a second carbonyl function and a second double bond, probably not conjugated because of the uv spectrum, was suggested by ir bands at 1705 and 1620 cm^{-1}.

Although catalytic hydrogenation of parthemollin yielded a complex mixture, treatment with 1 mol equiv of sodium borohydride produced a crystalline dihydro derivative **2** whose uv and ir spectrum (see Experimental Section) indicated retention of the α,β-unsaturated lactone and reduction of the carbonyl group originally responsible for the ir band at 1705 cm^{-1}. Treatment of parthemollin with excess borohydride resulted in a tetrahydro derivative **3** by reduction of the carbonyl group and saturation of the lactone.

In the nmr spectra (Table I) the transformation of **1a** to **2** was attended by the appearance of an additional one-proton multiplet near 4.1 ppm signifying the formation of a new secondary hydroxyl group; this was accompanied by the conversion of a sharp three-proton singlet near 2.2 into a three-proton doublet at 1.16 ppm superimposed on a methyl doublet already present in the precursor **1a**. Evidently the reaction involved the reduction of a methyl ketone. The nmr spectra also confirmed the presence of partial structure A already indicated by the facile formation of a pyrazoline. **1a**, **1b**, and **2** exhibited the typical doublet of the conjugated exocyclic methylene group, whereas **3** displayed a third methyl doublet due to the reduction of A.

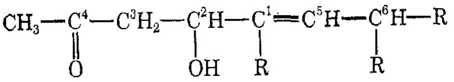


A



$CH_3-\underset{O}{\underset{\|}{C}}-CH_2-\underset{OH}{\underset{|}{CH}}-C=C$

B



$CH_3-\underset{O}{\underset{\|}{C^4}}-C^3H_2-\underset{OH}{\underset{|}{C^2H}}-\underset{R}{\underset{|}{C^1}}=C^5H-\underset{R}{\underset{|}{C^6H}}-R$

C

Manganese dioxide oxidation of parthemollin established the allylic nature of the hydroxyl group. The spectral properties of the product **4** [λ_{max} 294 and 210 nm (ε 16,200 and 17,500), ir bands at 1760, 1660 and 1600 cm^{-1}] were, however, not those expected from superposition of α,β-unsaturated ketone absorption on that of an α,β-unsaturated lactone. Instead the extended conjugation indicated by the uv spectrum and a positive ferric chloride test made likely the presence in **4** of an extended enolic β-diketone chromophore produced by oxidation of partial structure B. The conversion of **1b**, on treatment with basic alumina, to dienone **6** [λ_{max} 277 and 205 nm (ε 17,500 and 15,500[10])] provided further chemical support for this postulate.

The nmr spectra were in harmony with reactions based on partial structure B and permitted elaboration to C. Oxidation of **1a** to **4** resulted in disappearance of

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[1] Supported in part by a grant from the U. S. Public Health Service (GM-05814).

[2] W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

[3] W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, **84**, 2601 (1962).

[4] For leading references, see W. Herz, in "Recent Advances in Phytochemistry," T. J. Mabry, R. E. Alston, and V. C. Runeckles, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, pp 229–269.

[5] For the most recent reports, see (a) T. E. Winters, T. A. Geissman, and D. Safir, *J. Org. Chem.*, **34**, 153 (1969); (b) T. A. Geissman, S. Griffin, T. G. Waddell, and H. H. Chen, *Phytochemistry*, **8**, 145 (1969); (c) F. P. Toribio and T. A. Geissman, *ibid.*, **8**, 313 (1969); (d) W. Herz, G. Anderson, S. Gibaja, and D. Raulais, *ibid.*, **8**, 877 (1969).

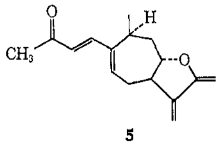
[6] For example, H. E. Miller, T. J. Mabry, B. L. Turner, and W. W. Payne, *Amer. J. Botany*, **55**, 316 (1968).

[7] *Parthenium hysterophorus* L., ref 3 and A. Romo de Vivar, E. A. Bratoeff, and T. Rios, *J. Org. Chem.*, **31**, 673 (1966); *Parthenium incanum* HBK, ref 3; *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins, H. Rüesch and T. J. Mabry, *Tetrahedron*, **25**, 805 (1969); *P. hispidum* Raf., and *P. integrifolium* L., W. Herz, unpublished work.

[8] Private communication from Dr. W. W. Payne, University of Illinois, Urbana, Ill.

[9] The monotypic genus *Parthenice* stands next to *Parthenium* in subtribe *Melampodiinae*, tribe *Heliantheae*. The range of its single genus *P. mollis* Gray is Southern Arizona and Northern Mexico.

[10] Compare with the 276-nm maximum of xanthatin (**5**).[11]



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[11] T. A. Geissman, P. G. Deuel, E. K. Bonde, and F. A. Addicott, *J. Amer. Chem. Soc.*, **76**, 685 (1954); P. G. Deuel and T. A. Geissman, *ibid.*, **79**, 3778 (1959); L. Dolejs, V. Herout, and F. Šorm, *Collect Czech. Chem. Commun.*, **23**, 504 (1958); T. A. Geissman, *J. Org. Chem.*, **27**, 2692 (1962).

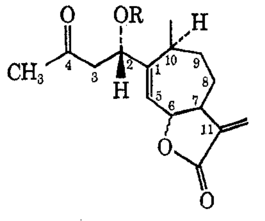
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF PARTHEMOLLIN AND ITS DERIVATIVES[a]

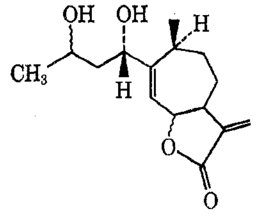
Compd	H-2	H-3	H-5	H-6	H-7	H-13	C-4 Me	C-10 Me	Misc
1a	4.7 (t, br) (6.5)	2.62 (d) (6.5)[b]	5.75 (m)[c]	5.57 (ddd) (9,3,1.5)	3.1 (c)	6.31 (d) (3) 5.60 (d) (3)	2.23	1.16 (7)	
1b	5.56[d]	2.69 (m)[b]	5.56[d]	5.40 (d, br) (9)	3.16	6.30 (d) (3) 5.56 (d) (3)	2.17	1.18 (d) (7)	2.04[e]
2	4.58 (m)	f	5.78 (m)	5.48 (m)	3.1 (c)	6.30 (d) (3) 5.60 (d) (3)	1.24 (d) (7)	1.12 (d) (7)	4.10 (m)[g]
3	4.40 (m)	f	5.70 (m)	5.2 (m)	2.7 (c)	h	h	h	4.08 (m)[g]
4		5.60	6.07 (dd) (3.5, 0.5)	5.47 (m)	3.1 (c)	6.29 (d) (3) 5.60 (d) (3)	2.10	1.20 (d) (7)	
6	7.12 (d) (16)	6.34 (d) (16)	6.03 (dd) (3.5, 0.5)	5.45 (m)	3.25 (c)	6.29 (d) (3) 5.62 (d) (e)	2.28	1.20 (d) (7)	
9	4.65 (m)	2.04 (d) (6)[b]	5.84 (m)	5.48 (m)	2.9 (c)	6.31 (d) (3)	1.87	1.20 (d) (6.5)	

[a] Spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; m, multiplet; c, complex band whose center is given; br, somewhat broadened singlet; unmarked signals are singlets. Numbers in parentheses are line separations in hertz. Signals in the first six columns correspond to one proton unless marked otherwise; in seventh and eighth columns to three protons. [b] Two protons. [c] Apparent quintet; line separations, ~1 Hz. [d] Superimposed on other signal. [e] Acetate. [f] Obscured by other signals. [g] H-4. [h] Three methyl doublets at 1.16, 1.14, and 1.05 (7).

a broadened triplet at 4.7 (H-2 of C, exhibits the usual paramagnetic shift on acetylation to **1b**) and a two-proton doublet at 2.62 ppm (H-3) and introduced a one-proton singlet at 5.60 ppm (vinyl proton α to carbonyl). Simultaneously a narrowly split multiplet, found near 5.8 in the nmr spectra of **1a**, **1b**, **2**, and **3**, clearly the signal of a third vinyl proton (H-5, disappears on hydrogenation), moved downfield and simplified to a doublet[12] whose chemical shift was consonant with its new position at the terminus of a conjugated system and whose multiplicity suggested that it was adjacent to a methinyl group. Conversion of **1b** into **6** effected the same change in chemical shift and appearance of the H-5 signal. In addition the appearance in **6** of an AB system characteristic of two *trans*-oriented vinyl hydrogens α and β to a carbonyl group at 6.34 and 7.12 ppm (J = 16 Hz) could be noted. The absence of other



1a, R = H
b, R = Ac



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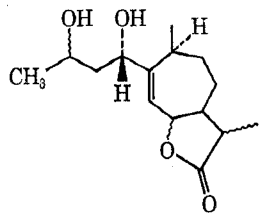

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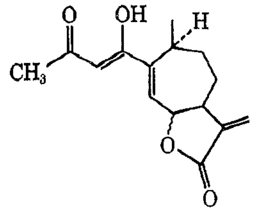

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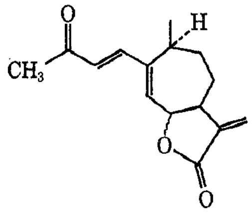

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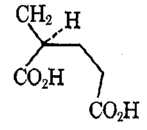

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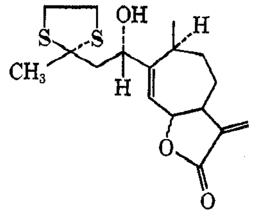

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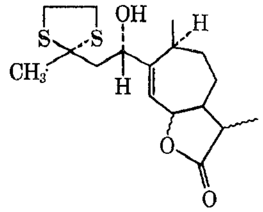

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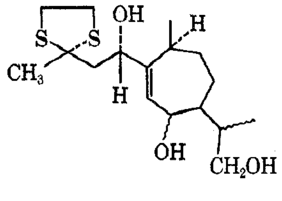

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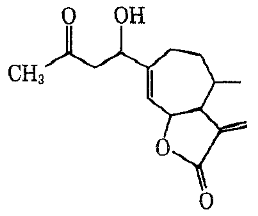

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[12] The additional small splitting shown in Table I was tentatively ascribed to allylic coupling (for verification *vide infra*).

vinylic signals and the lack of further coupling in the components of the AB system required the substitution depicted in C.

Since the empirical formula required that parthemollin be monocyclic, since partial formulas A and C accounted for 12 of the 15 carbon atoms, and since the nmr spectrum (see Table I) had revealed the presence of a secondary methyl group and another low field proton at 5.47 ppm plausibly associated with the lactone oxygen, it was logical to formulate parthemollin as **1a** (exclusive of stereochemistry).[13] Carbon atoms 8, 9, and 10 not represented in A and C were accounted for by degradation of parthemollin to (*S*)-(+)-α-methylglutaric acid (**7**) in the manner previously described for parthenin.[3] This result allowed only two possible expressions for parthemollin, **1a**, and the biogenetically highly implausible **12**.

A decision between these two possibilities was reached by spin-decoupling experiments at 90 MHz, whose results are given in Table II.[21]

Table II

90-MHz Spectrum of Parthemollin[a]

H-2	4.67 (t, br)[b]	$J_{2,3} = 6$, $J_{2,5} = 1.2$, $J_{2,6} = 1.5$, $J_{2,10} \leqq 0.5$
H-3	2.59 (d)[c,d]	$J_{3,2} = 6$
H-5	5.71 (m)[e]	$J_{5,2} = 1.2$, $J_{5,6} = 3$, $J_{5,10} = 1$
H-6	5.54 (ddd, br)	$J_{6,2} = 1.5$, $J_{6,5} = 3$, $J_{6,7} = 8.5$, $J_{6,10} = 0.5$
H-7	3.02 (c)	$J_{7,6} = 8.5$
H-8, H-9[f]	1.13–1.30 (c)	
H-10	2.6 (c)[g]	
H-13a	6.25 (d)	$J_{7,13a} = 3$
H-13b	5.58 (d)	$J_{7,13a} = 2.8$
H-14[h]	2.19	
H-15[h]	1.15 (d)	$J_{10,15} = 7$

[a] Symbols are those in Table I. Values of J are accurate to ±0.3 Hz. [b] Components of triplet resemble a broad triplet. [c] Two protons. [d] Superimposed on broad signal of H-10. [e] Resembles 1:2:2:2:1 quintuplet. [f] Four protons. [g] Superimposed on doublet of H-3. [h] Three protons.

Identification of the signal due to H-7 was achieved by irradiating at the frequencies of the narrow doublet of the exocyclic methylene group. This caused simplification of a multiplet at 3.02 ppm (H-7). Conversely, irradiation at 3.02 collapsed the doublet at 6.25 and 5.58 (H-13a and H-13b) and affected a series of signals corresponding to four protons in the region of 1.13–1.30, probably the methylene protons of the ring portion giving rise to α-methylglutaric acid. Simultaneous simplification of a multiplet at 5.54 ppm to a narrowly split slightly broadened doublet of doublets (line separation 3 and 1.5 Hz) showed that this signal had been correctly assigned to H-6.

Irradiation at the frequency of H-6 affected the signal of H-7, collapsed the multiplet of H-5 at 5.71 to a broad singlet, and sharpened the broad triplet of H-2 at 4.67 ppm. Hence H-2 and H-6 were coupled homoallylically. In turn, irradiation at the frequency of H-2 reduced the H-6 signal to a slightly broadened doublet of doublet separated by 8.5 ($J_{6,7}$) and 3 Hz ($J_{5,10}$), collapsed a two-proton doublet at 2.59 superimposed on a broad one-proton multiplet to a singlet, and sharpened the multiplet of H-5 to a doublet of doublets separated by 3 ($J_{5,6}$) and 1 Hz ($J_{5,10}$). Hence the two-proton multiplet at 2.59 ppm represented H-3, and H-2 and H-5 were coupled allylically ($J \sim 1.2$ Hz).

Irradiation at the frequency of the methyl doublet (1.15 ppm) produced a change in the broad one-proton multiplet at 2.6 ppm underlying the signal of H-3. Hence the origin of this signal could be attributed to the methinyl group present also in the degradation product α-methylglutaric acid. Now irradiation at the frequency of H-7 had produced no change in the 2.6-ppm region and, conversely, irradiation at 2.6 ppm, while collapsing the signals of H-2 and the secondary methyl group and affecting the signals in the methylene region,[22] did not exert any influence on the signal of H-7. Hence formula **12** was ruled out and parthemollin was correctly represented by **1a**.

As concerns stereochemistry, isolation of (*S*)-(+)-α-methylglutaric acid by degradation of parthemollin showed that the absolute configuration at C-10 was C-10 methyl β and therefore identical with the absolute configuration of other xanthanolides and pseudoguaianolides isolated from related species. The absolute configuration of C-2 was found by application of Horeau's method of asymmetric esterification[23] which has been found applicable to sesquiterpene lactones.[24] Reaction of parthemollin with an excess of (±)-α-phenylbutyric anhydride resulted in recovery of (−)-α-phenylbutyric acid. Hence the configuration at C-2 was *S*, or -OH α.

If one assumes, as is plausible, that the absolute configuration of the C-7 side chain is β as in all other sesquiterpene lactones of established stereochemistry, the remaining problem was elucidation of the stereochemistry of C-6. Since examination of molecular models showed that knowledge of the coupling constants $J_{2,5}$ (1.2 Hz), $J_{2,6}$ (1.5), $J_{5,6}$ (3), and $J_{6,7}$ (8.5) was not suffi-

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(13) Compounds of this type, all of them, however, with the lactone ring closed to C-8, have been described[14] as xanthanolides because of their prevalence in *Xanthium* and related species: xanthinin and xanthatin,[11] xanthumin,[15] xanthanol,[16] isoxanthanol,[16] and ivalbin.[17] Some other members of this class have been isolated from species in the tribe Inuleae: carabrone,[18] gafrinin,[19] and griesenin.[20]

(14) T. G. Waddell, W. Stöcklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(15) H. Minato and I. Horibe, *J. Chem. Soc.*, 7009 (1969).

(16) T. E. Winters, T. A. Geissman, and D. Safir, *J. Org. Chem.*, **34**, 153 (1969).

(17) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *ibid.*, **32**, 682 (1967).

(18) H. Minato, S. Nosaka, and I. Horibe, *J. Chem. Soc.*, 5503 (1964); H. Minato and I. Horibe, *ibid.*, 2131 (1968); E. Diaz T., *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **20**, 84 (1968).

(19) L. A. P. Anderson, W. T. de Kock, and K. G. R. Pachler, *ibid.*, **24**, 1701 (1968).

(20) W. T. de Kock, K. G. R. Pachler, W. F. Ross, P. L. Wessels, and I. C. DuPreez, *Tetrahedron*, **24**, 6037 (1968).

(21) These were carried out on a Bruker 90-MHz nmr spectrometer purchased with the aid of a grant from the National Science Foundation for which we express our thanks. Chemical shifts on the 90-MHz instrument differed slightly from the values given in Table I, which were obtained on a Varian A-60 instrument, because of small calibration errors.

(22) Irradiation at the frequency of H-10 also simplified the signal of H-5 to a doublet of doublets, showing that H-5 was allylically coupled to H-10 ($J \sim 1$ Hz) as well as to H-2 and removed a very small coupling (≤ 0.5 Hz) from the signal of H-6. Hence H-6 was homoallylically coupled to H-10 as well as to H-2. Because the components of the broad H-2 triplet were only sharpened, but not resolved into doublets by irradiation of H-5 or H-6, H-2 was apparently coupled ($J \leqq 0.5$ Hz) to another proton, probably H-10. An attempt to demonstrate this by irradiation of H-10 failed since H-3 and H-10 had very nearly the same chemical shift.

(23) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).

(24) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

cient to decide unambiguously between a *cis* or *trans* fusion of the lactone ring,[25] information bearing on the stereochemistry at C-6 was sought.

It has been suggested recently[14] that the sign of the lactone Cotton effect of a sesquiterpene lactone which incorporates partial structure A offers a clue to the solution of this problem. The generalization has been made[14] that, regardless of structural type, *cis*-fused lactones closed to C-8 exhibit negative Cotton effects, and that in *trans*-fused lactones closed to C-8 the Cotton effect is positive. The reverse situation prevails in lactones closed to C-6: *cis*-fused lactones display positive Cotton effects; *trans*-fused lactones show negative values. The strongly negative Cotton effect exhibited by parthemollin [λ_{max} 255 nm (Θ −3400)] comparable in magnitude with the Cotton effect of other xanthanolides[14] would on this basis require a *trans*-lactone fusion (H-6 β).

Because all C-6 closed pseudoguaianolides previously isolated from *Parthenium* and related species are *cis*-lactones (H-6 α)[4-7,29-34] and might conceivably[12] be related to parthemollin through a common guaianolide intermediate, and because several exceptions to the generalization had been noted,[14] independent verification of the existence of a *trans*-fused lactone ring fusion in parthemollin seemed desirable. Accordingly we investigated the possibility of applying to parthemollin the modified Hudson–Klyne rule[35] which had proved serviceable in establishing the C-6 stereochemistry of parthenin.[3]

Protection of the lactone function by thiaketalization to **9** and sodium borohydride reduction of the latter afforded a lactone **10**, $[\alpha]_D$ −34.0°. Lithium aluminum hydride treatment of **10** gave the triol **11**, $[\alpha]_D$ −13.7°. The observed change in rotation indicated that, if the rule were applicable, parthemollin should be a *cis*-fused lactone with H-6 α, a result directly contradictory to the conclusion reached earlier by considering the CD curve of parthemollin.

Attempts to resolve this contradiction and to ascertain the correct stereochemistry of parthemollin at C-6 will be the goal of future studies. In the meantime, the isolation from *P. mollis* of a xanthanolide which appears to stem from the same precursor as the pseudoguaianolides of *Ambrosia* species seems to support the postulate of a relatively close relationship between the two genera.

Experimental Section[36]

Isolation of Parthemollin.—Powdered above-ground *Parthenice mollis* Gray, wt 10.4 kg, collected by Mr. R. Barr on Sept 10, 1968 (Barr #68-573, on deposit in herbarium of Florida State University), along a wash, 1 mile south of Tubac, Santa Cruz County, Ariz., was extracted with chloroform in the usual manner.[37] The crude gum, wt 135 g, was chromatographed over 1.3 kg of silicic acid, 800-ml fractions being collected. Fractions 1–28 (benzene) and 29–40 (benzene–chloroform, 2:1) eluted noncrystallizable gums. Fractions 41–44 (benzene–chloroform, 1:2) eluted approximately 15 g of semicrystalline material which yielded 5.0 g of pure parthemollin after recrystallization from ethyl acetate. The more polar fractions (chloroform and chloroform–methanol, 9:1) eluted gums which could not be induced to crystallize and represented mixtures (tlc) subject to polymerization.

Pure parthemollin melted at 116–118°: $[\alpha]^{24}{}_D$ −130.0° (*c* 4.285); ir 3580, 1775, 1705, 1655, and 1620 cm^{-1}; uv end absorption (ϵ 13,200 at 205 nm); CD curve (1-cm cell) λ_{max} 255 nm (Θ −3400).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.12; H, 7.60; O, 24.05.

Acetylation of 0.25 g of **1a** with acetic anhydride–pyridine at room temperature and work-up in the usual manner gave crude acetylparthemollin (**1b**) which was purified by filtration through silica gel and recrystallization from ethyl acetate–petroleum ether. Pure **1b** was obtained in a 0.20-g yield: mp 103–104°; $[\alpha]^{24}{}_D$ −135.0° (*c* 5.0); ir 1755, 1735, 1720, 1655, and 1625 cm^{-1}; uv end absorption (ϵ 18,300 at 206 nm).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.42; H, 7.31; O, 26.35.

To a solution of 0.09 g of **1a** in 10 ml of tetrahydrofuran was added 10 ml of an ethereal diazomethane solution. After 3 days in the refrigerator the solvents were removed. The residue (**8**) was recrystallized from ethyl acetate and methanol: mp 117–119° dec; CD curve (1-cm cell) λ_{max} 318 nm (Θ −23400).

Anal. Calcd for $C_{16}H_{22}O_4N_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.35; H, 7.19; N, 9.01.

A solution of 0.094 g of **1a** in 25 ml of ethyl acetate was reduced at atmospheric pressure with prereduced 10% Pd-C. Hydrogen uptake ceased after absorption of 2.6 mol equiv of hydrogen (partial hydrogenolysis). The product was a mixture of four components (tlc) which could not be obtained in crystalline form.

Reduction of Parthemollin with Sodium Borohydride. A.—To a solution of 0.508 g of **1a** in 25 ml of methanol was added with stirring 0.180 g of $NaBH_4$ in 5 ml of methanol at 0°. Stirring was continued for 1 hr, the reaction mixture was acidified with dilute hydrochloric acid, the solvent was removed at reduced pressure, and 10 ml of water was added to the residue. The mixture was extracted with chloroform and the washed and dried extract was evaporated. The solid residue (**2**) was purified by preparative tlc and by recrystallization from ethyl acetate: yield 0.175 g; mp 153–156°; ir 3582, 3480, 1758, 1659, and 1600 cm^{-1}; uv end absorption (ϵ 16,500 at 205 nm).

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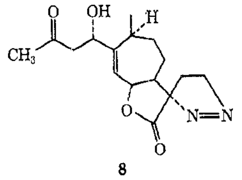
[25] Conformations for both *cis*- and *trans*-fused Dreiding models of parthemollin are possible which appear to satisfy the dihedral angle requirement imposed by the magnitude of the vicinal coupling constant $J_{6,7}$, the allylic coupling constant[26] $J_{2,5}$, and the homoallylic coupling[26] constant $J_{2,6}$. Inspection of these models indicates that regardless of the configuration at C-6, formation of a pyrazoline by reaction of pathemollin with diazomethane should occur primarily, if not excusively, by attack of the reagent from the α side to give **8**. On the basis of a recently deduced relationship[27] between absolute configuration of such pyrazolines and the sign of their Cotton effect, one would expect a strongly negative CD curve for **8**. This was indeed observed, the value [λ_{max} 318 nm (Θ −23,400)] being comparable in sign and magnitude with that reported for coronopilin,[27] damsin,[27] ambrosiol,[28] and psilostachyin C.[28] This provides excellent support for the postulated β orientation of the C-7 side chain.



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[36] Melting points are uncorrected. Rotations were run in chloroform, ultraviolet spectra in 95% ethanol on a Cary Model 14 recording spectrophotometer, infrared spectra in chloroform on a Perkin-Elmer Model 257 grating spectrophotometer, and CD curves in methanol on a Jasco ORD/UV-5 recording spectrophotometer. Petroleum ether was low boiling (30–60°). Analyses were performed by F. Pascher, Bonn, Germany.

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Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.21; H, 8.37; O, 24.46.

B.—Reduction of 0.279 g of **1a** with 0.265 g of $NaBH_4$ in the manner described in the previous paragraph gave a noncrystalline product (**3**) which was purified by preparative tlc: $[\alpha]^{24}\text{D}$ −41.4° (*c* 5.8); ir bands at 3580, 3480, 1760, and 1600 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; O, 23.85. Found: C, 67.09; H, 9.18; O, 23.48.

Dehydroparthemollin (4).—A solution of 0.243 g of **1a** in 25 ml of dry chloroform was stirred with 2.4 g of activated manganese dioxide at room temperature for 4 days and filtered, the precipitate being washed thoroughly with chloroform. The combined filtrate and washings were evaporated at reduced pressure and the residual gum purified by preparative tlc. This gave 0.13 g of **4** and 0.1 g of recovered starting material. The product was recrystallized from ethyl acetate–petroleum ether: mp 95–97°; ir 1760, 1660, and 1600 cm^{-1}; uv λ_{max} 294 and 210 nm (ϵ 16,200 and 17,550).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; O, 24.40. Found: C, 68.22; H, 7.05; O, 24.84.

Anhydroparthemollin (6).—A solution of 0.15 g of **1b** in benzene was chromatographed over a column of basic alumina. The eluate was evaporated and recrystallized from ethyl acetate–petroleum ether to give 0.065 g of **6**: mp 78–80°; ir 1760, 1708, 1665, and 1595 cm^{-1}; uv λ_{max} 277 and 205 nm (ϵ 17,500 and 15,500). The material polymerized on standing.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.05; H, 7.21; O, 19.32.

Oxidation of Parthemollin to α-Methylglutaric Acid.—A solution of 1.0 g of **1a** in 100 ml of ethyl acetate was ozonized at 0° for 1 hr. After addition of 20 ml of water the mixture was warmed on the water bath for 0.5 hr. The solvents were removed at reduced pressure. The residue was taken up in 100 ml of 5% sulfuric acid and a solution of 5 g of $KMnO_4$ in 120 ml of water was added dropwise in 4 hr. The precipitate of manganese dioxide was reduced with sulfur dioxide solution in water. The clear solution was concentrated to 20 ml of at reduced pressure and extracted with ether. The washed and dried ether extract was evaporated and the residual gum was chromatographed over acid-washed alumina. Elution with chloroform–methanol (9:1) gave 0.35 g of gum which was dissolved in acetone and mixed with cyclohexylamine. The precipitated cyclohexylamine salt was recrystallized from ethanol–acetone and then melted at 168–171°. Decomposition of the salt with dilute hydrochloric acid, extraction with ether, washing, drying, and evaporation of the ether extract yielded 0.21 g of (*S*)-(+)-α-methylglutaric acid which was recrystallized from ethyl acetate–petroleum ether, mp 80–82°, $[\alpha]^{24}\text{D}$ +21.6° (ethanol, *c* 5.3). The melting point was undepressed on admixture of an authentic sample of mp 78–80°, $[\alpha]^{24}\text{D}$ +18° (*c* 1.24) and their ir spectra (Nujol) were superimposable.

Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.25; H, 6.90.

Preparation of 9, 10, and 11.—A solution of 0.310 g of **1a** and 0.8 ml of ethanedithiol in 10, ml of ether was mixed with 1.2 ml of boron trifluoride etherate and allowed to stand at room temperature. After 15 min concentrated aqueous potassium carbonate solution was added and the product was extracted with ether. Evaporation of the washed and dried extract gave crystalline **9**: mp 128–131°; $[\alpha]^{25}\text{D}$ −61.7° (*c* 2.02); ir 3410, 1750, and 1653 cm^{-1}.

A solution of 0.15 g of **9** in 10 ml of methanol–dioxane (1:1) were reduced with $NaBH_4$ as described in the preparation of **3**. The noncrystalline product **10** was purified by preparative tlc: $[\alpha]^{24}\text{D}$ −34.0° (*c* 5.62); ir 3420 and 1762 cm^{-1}.

A solution of 0.10 g of **10** in 10 ml of tetrahydrofuran was added dropwise with stirring to a slurry of 0.240 g of $LiAlH_4$ at 0°. Stirring was continued overnight at room temperature. Excess reducing agent was decomposed by addition of ethyl acetate. The mixture was acidified and the solvents were removed. The residue was taken up in chloroform. The washed and dried extract was evaporated and the noncrystalline product **11** was purified by preparative tlc, wt 30 mg, $[\alpha]^{24}\text{D}$ −13.7° (*c* 2.9).

Reaction of 1a with Phenylbutyric Anhydride.—The method of ref 22 was employed, using 211 mg (6.8×10^{-4} mol) of α-phenylbutyric anhydride and 61 mg (2.27×10^{-4} mol) of **1a**. The recovered α-phenylbutyric acid weighed 133 mg (constant weight after drying *in vacuo*, pure on tlc), $\alpha^{24}_{546.1}$ −0.064° (5 ml of benzene, 4-ml tube, measured on a Bendix Type 143A automatic polarimeter), $[\alpha]^{24}_{546.1}$ −5.97°. This corresponded to an optical yield of 25–30% ($[\alpha]\text{D}$ of α-phenylbutyric acid is ±96.5°, but a specimen of optically pure acid for determination of the rotation at the $Hg_{546.1}$ line was not available).

Registry No.—**1a**, 23264-32-6; **1b**, 23264-33-7; **2**, 23264-34-8; **3**, 23263-98-1; **4**, 23263-99-2; **6**, 23282-28-2; **7**, 1115-82-8; **8**, 23264-01-9; **9**, 23264-02-0; **10**, 23264-03-1; **11**, 23264-04-2.

The Absolute Configuration of α-*t*-Butylphenylacetic Acid and Some Derivatives[1]

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The absolute configurations of α-isopropylphenylacetic acid and α-*t*-butylphenylacetic acid have been established as *R*-(−) by relating them chemically to (*S*)-(+)-hydratropic acid through (*R*)-(−)-2-methyl-3-phenylbutane (**2**) and (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**). (+)-*t*-Butylphenylcarbinol (**16**) and (+)-β-*t*-butyl-β-phenylpropionic acid (**13**) have been related to α-*t*-butylphenylacetic acid (**9**) and shown to have the *R* configuration. These experiments resolve the uncertainties concerning the configurations of these compounds. The method of configurational correlation of these and related compounds is outlined in formulas **1–16**.

There has been considerable controversy concerning the absolute configuration of α-isopropylphenylacetic acid[2-4] (**3**). Červinka and Hub[2] reported a method for correlating configurations of α-substituted phenylacetic acids, which involved the reaction of an excess of the racemic acid with the chiral amine (*S*)-(+)-1-phenyl-2-methylaminopropane, and measuring the optical rotation of the recovered, unreacted acid. They concluded that the α-alkylphenylacetic acids which they tested[5] had the absolute *S*-(+) configuration with the exception of α-isopropylphenylacetic acid which had the *S*-(−) configuration. These experiments were repeated by Halpern and Westley[3] who failed to confirm this latter exception and concluded that all these α-substituted phenylacetic acids had the *S*-(+) configuration including the α-isopropyl derivative. We

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(5) The alkyl groups included methyl, ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *n*-hexyl, iso-propyl, iso-butyl, benzyl, and allyl.