and dried by pressing on a porous plate (1.2 g, mp 63–64°). Repeated crystallization of the crude product from hexane, first at −78° and then at −10°, gave 845 mg (0.01%) of pure echinacein as colorless needles: mp 69–70°; ultraviolet maxima (absolute ethanol) at 259, 270, and 279.5 mμ (ε 36,000, 47,000, 38,000); infrared absorption (KBr disk) at 3260 and 3070 (NH), 1668 (α-C=C), 1626 (C=O), 1559 (CONH), 944 (*cis*,-*trans*,*trans*-triene), and 972 cm^{-1} (*trans*-α-C=C).

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.65; H, 10.20; N, 5.65. Found: C, 77.89; H, 10.29; N, 5.62.

The substance was a powerful sialogogue and caused rapid knockdown and high mortality when tested on adult house flies. It polymerized in the air after 1 hr at room temperature and after 2 days in a nitrogen atmosphere at −10° but could be kept unchanged for several months at 5° as a solution in hexane.

Echinacein was obtained in the same manner from the dried roots of *E. pallida*, but the total yield was only 0.001%.

Hydrogenation to N-isobutyllauramide[4] and permanganate oxidation[11] to give succinic, oxalic, and N-isobutyloxamic acids further characterized echinacein as the isobutylamide of 2,6,8,10-dodecatetraenoic acid.

Ultraviolet Stereomutation of Echinacein.—Echinacein (200 mg) was dissolved in 20 ml of hexane, a small crystal of iodine was added, and the solution was exposed to the direct light from an ultraviolet lamp for 2 hr while it was cooled with an electric fan to prevent evaporation. By the end of this period, the mixture had crystallized to a solid, waxy mass. It was melted by warming, 10 ml of hexane was added, and the mixture was heated to boiling on the steam bath and then allowed to cool. The mass of white crystals that separated was filtered off, washed with a little cold hexane, and recrystallized once from this solvent to give 180 mg of small, colorless needles, mp 112–116°.[12] The melting point remained unchanged after a second recrystallization.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.65; H, 10.20; N, 5.65. Found: C, 77.72; H, 10.18; N, 5.59.

The isomer showed ultraviolet maxima at 259, 268, and 278 mμ (ε 38,300, 48,500, and 38,900) and infrared bands at 3250, 3060, 1666, 1623, 1548, 996 (all-*trans*-triene), and 978 cm^{-1}.

Echinacein and its isomeride gave maleic anhydride adducts, mp 99–100° and 149–150°, respectively.

Registry No.—Echinacein, 504-97-2; all-*trans*-triene, 10076-00-3.

Acknowledgment.—The insecticidal tests were conducted by Mr. J. H. Fales, U. S. Department of Agriculture, Beltsville, Md.

(11) M. Jacobson, *J. Am. Chem. Soc.*, **73**, 100 (1951).

(12) Crombie and Tayler[7] reported mp 110–115° for the isomeride of α-sanshool.

Synthesis of Diterpenoid Acids. VI.[1] Conformations of Some Derivatives of Podocarpic Acid

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Received October 4, 1966

For other work,[1] we wanted to use the keto lactone (**1**) as an intermediate to podocarpic acid. We confirmed Bible's[2] result that **1** is transformed into **2a** in 80% yield by catalytic hydrogenation and found that the conversion can also be effected by lithium in liquid ammonia.[3] The thioketal (**4**) was prepared during unsuccessful attempts to remove the ketone at C_7.[6]

Compound **1** was synthesized[2,8] by heating the bromo ketone (**3b**)[9] with collidine. Earlier workers[8,10] suggested that the bromine is α (and thus **3c**). We now propose that the bromine is β and that ring B is distorted to a half-boat form. Our evidence is based mainly on nmr spectra taken in deuteriochloroform solutions and summarized in part A of Table I.

TABLE I[a]

Compd	C_4 methyl	C_{10} methyl	Ester methoxyl	Ring C methoxyl	C_5 proton	C_6 proton
			(A) $CDCl_3$ Solutions			
2b	76	62	218	224		
3a	75	66	220	229		
3b	92	51	222	230	148 (7)[b]	345 (7)[b]
1	80	67		232	138 (5.5)[b]	293 (5.5)[b]
4	80	77		227	127 (5.5)[b]	324 (5)[b]
			(B) Benzene Solutions			
2b	69	66	199	206		
3a	59	59	197	202		
3b	88	46	194	202	146 (7)[b]	366 (7)[b]
1	55	50		200	88 (6)[b]	266 (5.5)[b]
4	78	54[c]		202	86 (5)[b]	316 (5)[b]

[a] Chemical shifts in cycles per second (cps) from TMS. Spectra were measured on a Varian A-60 machine. [b] Figures in parenthesis are H_5–H_6 coupling constants. [c] This peak is a doublet with less than a 2-cps separation.

The small shift in comparison with steroid models[11] in the position of the C_{10} methyl group on going from **2b** to **3a** suggests that ring B is in a nonchair form. The fact that the 10 methyl in **3a** is not strongly shielded indicates that the methyl is not in the shielding cone of the ketone group; therefore, ring B has a flattened conformation (structure **6**, "sofa" in Chart I)[12] in which atoms 6–10 are approximately coplanar and atom 5 is out of the plane.[13]

Introduction of the bromine causes strong shielding of the C_{10} methyl and deshielding of the C_4 methyl. To account for the former, ring B in **3b** must be a half-boat. The deshielding of the C_4 methyl by the bromine (about that induced by a 1,3 diaxial interaction in a

(1) Part V: A. C. Ghosh, K. Mori, A. C. Rieke, S. K. Roy, and D. M. S. Wheeler, *J. Org. Chem.*, **32**, 722 (1967).

(2) R. H. Bible, personal communication.

(3) *Cf.* metal ammonia cleavage of hindered esters[4] and α-acetoxy ketones.[5]

(4) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 217 (1958).

(5) J. E. Starr, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 299.

(6) Numbering in accord with the system suggested by McCrindle and Overton.[7]

(7) R. McCrindle and K. H. Overton, "Advances in Organic Chemistry, Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, p 47.

(8) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(9) Melting points of 142–144.5° and 123–126° have been reported[2,8] for the bromo ketone. We find that the product of mp 128–130° is **3b** contaminated with a trace of **5**. The compounds are readily separated by preparative thin layer chromatography. Bromination of **3a** with pyridinium bromide perbromide is an effective method of obtaining **3b**.

(10) A. K. Bose, M. S. Manhas, and R. C. Cambie, *J. Org. Chem.*, **30**, 501 (1965).

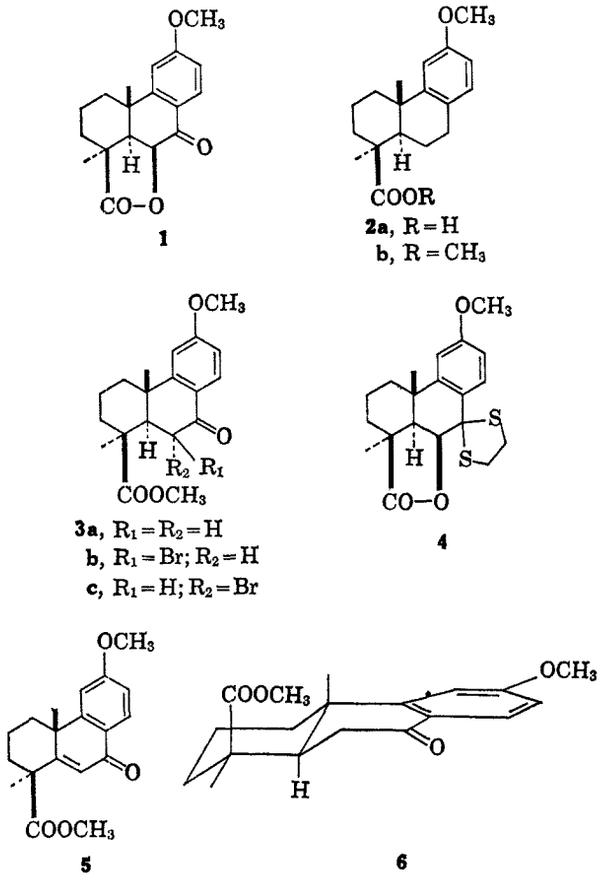
(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden Day, Inc., San Francisco, Calif., 1964, pp 19–21.

(12) E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.*, 167 (1958).

(13) Wenkert and his co-workers[14] reached similar conclusions on the basis of a more complete study. They use the term "half-boat" to describe the normal conformation of ring B. However, it is clear from their discussion of totarol that they, like us, distinguish between nonchair conformations in which the 7-keto shields or does not shield the C_{10} methyl group.

(14) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

CHART I



steroid[11]) indicates that these groups are about 2.6 A apart. This is best accounted for if ring A is chair and the bromine at 6 is β. As the coupling constant between the C_5 and C_6 protons is 7 cps, the dihedral angle between these protons is either about 20° (which fits our suggested structure) or 140° (which fits for the bromine α if the ring B is half-boat but not if it is a chair.) However, the second possibility explains neither the strong deshielding on the C_4 methyl, nor the positive ORD shift on bromination.[10] The increase in the turning up of the carbonyl group in **3b** compared with **3a** is easily explained if the bromine is β; interactions involving the bromine, the C_4 carbomethoxy, and the C_{10} methyl are decreased by going from the sofa into the half-boat form. The nmr spectra of the lactone (**1**) and the thioketal (**4**) are in accord with our conclusions. Compared with **3b**, formation of the lactone decreases the coupling constant between the protons at 5 and 6 by opening the dihedral angle slightly. In turn, the shielding of the C_{10} methyl by the ketone is decreased and the oxygen at 6 is closer to the C_{10} methyl. Thus the signal for the C_{10} methyl is at a lower field than in the bromo compound. In addition, the formation of the lactone probably forces ring A into a twist form, which lessens the deshielding of the C_4 methyl by increasing the distance between that group and the oxygen at 6. In the thioketal (**4**), one of the sulfur atoms will be close to the C_{10} methyl deshielding it, so that the signals for the two methyl groups appear close to each other. The spectrum of **3b** shows no significant change[15] when taken at −60°; this indicates that we are not dealing with easily interconvertible conformers.

The ultraviolet spectra of **3a**, **3b**, and **1** are given in Table II. The difference in the conformation of ring

TABLE II
ULTRAVIOLET SPECTRA OF ETHANOL SOLUTIONS

Compd	λ, mμ	ε	λ, mμ	ε
3a	280	9,100	225	8200
3b	298	10,700	235	8500
1	295	10,700	232	8200

B in **3a** and **3b** (which affects the steric relation between the ketone and the ring) may well have more effect on the spectrum than the stereochemistry of the halogen. Thus it seems inadvisable to attempt to use the normal shifts found on halogenation in the n–π^*[16] (peaks in **3a** and **3b** estimated from ORD data[10] to be at 346 and 360 mμ, respectively) ketone peak and the π–π^*[17] bands of α-tetralones. However, the similarity in the spectra of **3b** and **1** indicates that these compounds must, as we suggest, have similar stereochemistries.

We also report in part B of Table I, the main nmr peaks shown by the compounds in benzene solution.[18] Applying the rules proposed by McCrindle and Williams,[20–23] we also conclude that the carbomethoxy groups in **2a**, **3a**, and **3b** exist preferentially in a conformation in which the oxygen of the carbonyl group points in the direction of the C_6-axial bond; that is, the carbonyl is turned through 180° from the position it must adopt in the lactone (**1**).[24] If the carbomethoxy group in **2b** has the conformation we suggest, the result of going from deuteriochloroform to benzene will be to shield the C_4 methyl (observed, 7 cps) and deshield slightly the C_{10} methyl (observed, 4 cps). With the keto ester (**3a**) the effect of the benzene complexing with the carbomethoxy is the same as with the ester (**2b**). However, complexing with the keto group produces a shielding effect on both methyls. As expected, the solvent shielding effect is greater with the C_4 methyl. With the keto lactone (**1**) and the thioketal lactone (**4**) the C_4 carbonyl is twisted almost 180° from its favored conformation in the esters. In both compounds, the C_{10} methyl is behind, and the C_4 methyl is almost in the reference plane of the lactone carbonyl. Thus, in **4** the C_4 methyl is slightly shielded and the C_{10} methyl is strongly shielded by the solvent change. In the keto lactone, the effect of the ketone group leads to a shield-

(15) The ester methoxyl peak has started to split at −60° (less than 2 cps between peaks). Presumably the conformational interchange of this group is inhibited at this temperature. This point will be investigated further.

(16) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(17) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(18) Narayanan and Venkatasubramanian[19] have recently described some empirical rules for deducing the stereochemistry of diterpenoid acids from shifts in nmr peaks on changing solvents from chloroform to benzene and pyridine.

(19) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Letters*, 3639 (1965).

(20) J. D. Connolly and R. McCrindle, *Chem. Ind.* (London), 379 (1965).

(21) J. D. Connolly and R. McCrindle, *ibid.*, 2066 (1965).

(22) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1641 (1965).

(23) D. H. Williams and D. A. Wilson, *J. Chem. Soc.*, B, 144 (1966).

(24) Wenkert[14] and Tahara[25a] have already pointed out that the carbomethoxy group is oriented so that the angular methyl group is within the shielding cone of the carbonyl group, but this would also be the case if the carbonyl oxygen pointed toward C_3. This conformation, the "tangential" conformation, has been proposed for axial carboxyl groups by Sicher[25b] and Wepster,[25c] and their co-workers.

(25) (a) A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965); (b) J. Sicher, M. Tichý, and F. Šipoš, *Collection Czech. Chem. Commun.*, **31**, 2238 (1966); *Tetrahedron Letters*, 1393 (1966); (c) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *ibid.*, 1401 (1966).

ing of the C_4 methyl and both carbonyls will cause a shielding of the C_{10} group. Change of solvent leads to strong shielding of both methyl groups. With the bromo compound (**3b**), the change of solvent leads to a slight shielding of both methyl groups. This may be due to the fact that in this compound the 7-ketone group is turned upward more than in any other compound in the series so that the C_{10} methyl group is close to its reference plane. However, the proximity of a highly polar substituent can alter the effect of the ketone group.[23] The shifts of the C_5 and C_6 protons on changing from deuteriochloroform to benzene may be similarly analyzed.

The behavior of the bromo ketone (**3b**) with base[8] deserves some comment. Contrary to the normal situation, increasing the hindrance in the base (from hydroxide to pyridine to collidine) increases the amount of substitution to give **1** and decreases the amount of elimination to **5**. The reason for this anomaly is not clear. However, with the stereochemistry (**3b**) the mechanism of the elimination poses no problem;[8] the dihedral angle between the bromine and hydrogen is about 140°. The formation of the lactone (**1**) must involve displacement of the bromine by the collidine followed by attack of the ester group on the 6 position. Using our ideas on the conformation of the ester group, we suggest that the carbonyl oxygen attacks the 6 position.[8] The methyl group of the ester must be removed as methyl collidinium bromide.

Experimental Section[26]

Methyl O-Methyl-6β-bromo-7-oxopodocarpate (3b).—The bromo ketone (**3b**) was prepared from podocarpic acid by a three-step synthesis.[2] The bromination of **3a** was done with N-bromosuccinimide in carbon tetrachloride[2,8,10] or with pyridinium bromide perbromide in tetrahydrofuran. The former conditions gave better yields though the product was sometimes contaminated with a by-product (see below). The bromo ketone after crystallization from aqueous methanol had mp 135–137° (single spot on thin layer chromatography) (lit.[2] 142–144.5° and 121–125.5° in one preparation; 141–142°[10] and 123–126°[8]); ν_{max} 2950, 1729, 1684, 1604, 1575, 1487, 1466, 1383, 1324, 1274, 1254, 1215, 1154, 1129, 1077, 1062, 1036, 1007, 981, 952, 924, and 877 cm^{-1}. The bromo ketone (**3b**) had $\nu_{max}^{CCl_4}$ (in carbonyl region) 1732, 1691, and 1603 cm^{-1}; the keto ester (**3a**) had $\nu_{max}^{CCl_4}$ (in carbonyl region) 1733, 1685, and 1603 cm^{-1}. Other physical data for **3b** are given in Tables I and II.

Sometimes we isolated from the bromination (with N-bromosuccinimide) material with mp 128–130°, or slightly lower. This material had the same infrared spectrum as **3b** but, in addition, had a shoulder at 1660 cm^{-1}. Thin layer chromatography on silicic acid (solvent system ethyl acetate 10%–benzene 90%) showed this material to be a mixture which on preparative thin layer chromatography was separated into **3b** and **5**.

Lactone of O-Methyl-6β-hydroxy-7-oxopodocarpic Acid (1).—This was prepared by boiling **3b** with collidine.[8] The product after crystallization from aqueous methanol had mp 195–197° (ν_{max} 3050, 2975, 2945, 1781, 1694, 1603, 1568, 1482, 1456, 1386, 1336, 1311, 1264, 1218, 1170, 1106, 1060, 1026, 1009, 944, 877, 852, and 815 cm^{-1}) identified as **1** by comparison (melting point, mixture melting point, and infrared spectrum) with a sample supplied by Dr. Bible. Other physical data are in Tables I and II.

Attempts to improve the yield of **1** by heating **3b** with aqueous sodium hydroxide or pyridine led to increased amounts of unsaturated ketone **5**.

Attempts to convert **1** into the lactone of O-methyl-6β-hydroxypodocarpic acid by the Clemmensen or Wolff-Kishner reduction failed.

(26) See part II[27] for general details. Unless otherwise specified, infrared spectra were taken in CH_2Cl_2 solutions. Melting points are uncorrected.

(27) S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).

Thioketal of the Keto Lactone (1).—Dry hydrogen chloride was passed slowly through a cooled solution of the keto lactone (**1**, 494 mg) in ethanedithiol (10 ml) for 2 hr.[28] Solid potassium carbonate was added (a little more was added after foaming had stopped). Ether (70 ml) was added and the ethereal solution was washed with water, then repeatedly with dilute, aqueous potassium hydroxide until the dithiol odor had gone, and finally with water, and was dried (Na_2SO_4). Removal of solvent gave a residue which on crystallization from aqueous methanol had mp 135–140° (202 mg), raised to mp 150–152.5° when crystallized from ether–petroleum ether (bp 30–60°). For analysis the compound had mp 158–159°; ν_{max} 3050, 1774, 1608, 1569, 1481, 1381, 1291, 1240, 1217, 1183, 1112, 1065, 1046, 1020, 1008, 966, 940, 925, 882, 863, 845, 811, and 779 cm^{-1}. For nmr data see Table I.

Anal. Calcd for $C_{20}H_{24}O_3S_2$: C, 63.82; H, 6.43; O, 12.75; S, 17.00. Found: C, 63.69; H, 6.54; O, 12.91; S, 17.23.

O-Methylpodocarpic Acid (2a).[29]—A solution of the keto lactone (**1**, 500 mg) in ethyl acetate (50 ml) and concentrated sulfuric acid (1 ml) was hydrogenated in the presence of palladized charcoal (200 mg). Three moles of hydrogen was absorbed. The catalyst was filtered off and the filtrate was washed with dilute, aqueous sodium hydrogen carbonate and was dried (Na_2SO_4). Removal of the solvent gave O-methylpodocarpic acid (**2a**), mp 154–156° (390 mg), identified by comparison (melting point, mixture melting point, and infrared spectrum) with authentic **2a**, prepared by lithium in ammonia cleavage of methyl O-methylpodocarpate.[4]

A similar result (but in poorer yield) was obtained when **1** was reduced with lithium in liquid ammonia.

Registry No.—**1**, 10037-24-8; **2b**, 10037-26-0; **3a**, 901-36-0; **3b**, 10060-22-7; **4**, 10037-25-9.

Acknowledgments.—We wish to acknowledge the support of U. S. Public Health Service Grant CA 05796 made by the National Cancer Institute. We are most grateful to Dr. R. H. Bible for details of his unpublished work and for a gift of Rimu resin.

(28) V. Schwarz, V. Černý, and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 1851 (1959).

(29) This experiment was tried after we had been informed by Bible[2] that "hydrogenation of **1** over Pd–C in ethanol gave an 80% yield of O-methylpodocarpic acid."

Intramolecular Transesterifications. Syntheses of α-Hydroxybenzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides and 3-Phenacylcoumarins

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Received December 15, 1966

Recently 3-phenacylcoumarin was prepared in a moderate yield by the reaction of β-benzoylpropionic acid and 2-hydroxybenzaldehyde in the presence of a sulfur trioxide–dimethylformamide complex.[1] It is conceivable that this reaction involves a cyclodehydration of β-benzoylpropionic acid to γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, which in turn would be alkylated at the α-methylene carbon of the lactone skeleton. Subsequent elimination of water would give rise to the

(1) E. Baltazzi and E. A. Davis, *Chem. Ind.* (London), 1653 (1962).