New Antileukemic Jatrophone Derivatives from *Jatropha gossypiifolia*: Structural and Stereochemical Assignment through Nuclear Magnetic Resonance Spectroscopy[1]

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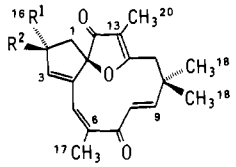
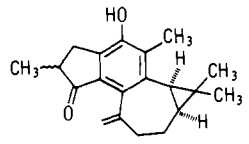
Abstract: Three new antitumor derivatives of the diterpene jatrophone (**1**) have been isolated from roots of *Jatropha gossypiifolia*. The structures and stereochemistry of 2α-hydroxyjatrophone (**4**), 2β-hydroxyjatrophone (**5**), and 2β-hydroxy-5,6-isojatrophone (**10**) were determined from their infrared, ultraviolet, and low-field NMR spectra, in conjunction with detailed high-field ^1H and ^{13}C NMR studies.

Introduction and Background

In 1970 Kupchan and co-workers at the University of Virginia reported the isolation and structure determination of the architecturally novel macrocyclic diterpene jatrophone (**1**).[4,5] This



(1): $R^1 = CH_3$, $R^2 = H$
(2): $R^1 = H$, $R^2 = CH_3$
(3): $R^1 = R^2 = H$
(4): $R^1 = OH$, $R^2 = CH_3$
(5): $R^1 = CH_3$, $R^2 = OH$

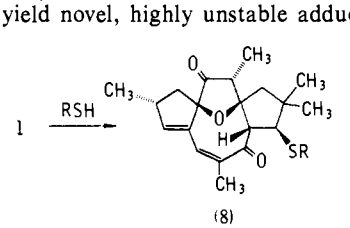


(6): α-CH_3
(7): β-CH_3

compound was obtained as the major cytotoxic and tumor-inhibitory constituent of the roots of *Jatropha gossypiifolia* L. (Euphorbiaceae), a plant used ethnomedicially for the treatment of cancer.[6] Subsequently this plant afforded the biosynthetically related jatropholones A and B (**6** and **7**),[7] several flavonoids,[8,9] and a lignan derivative.[10]

The structure and absolute stereochemistry of jatrophone, initially assigned on the basis of spectroscopic data, were confirmed through aegis of a single-crystal X-ray analysis.[5] More recently the first total synthesis of (±)-jatrophone (**1**), its epimer (**2**),[11] and 2-normethyljatrophone (**3**)[12] were recorded by Smith and co-workers at the University of Pennsylvania.

Concomitant with the isolation and structural studies, Kupchan, in an investigation of the chemistry of jatrophone, obtained several interesting results vis-á-vis the possible chemical mechanism for the observed cytotoxic effects. For example, treatment of **1** with thiols, including the amino acid cysteine, led to conjugate addition at C(9) followed by transannular bond formation between C(8) and C(12) to yield novel, highly unstable adducts such as **8**.



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Sulfhydryl groups present on proteins were found to react in analogous fashion.[5] Similar transannular bond formation was also observed on treatment of **1** with either hydrochloric or hydrobromic acid or on acid-catalyzed ketalization.[4,5] These observations led to the proposal that **1** and related compounds exert their cytotoxic effect by alkylation and thereby inactivate biological macromolecules involved in growth regulation.[5] Important in the context of this report was the suggestion that such reactions are strongly favored by the *Z* configuration of the C(5,6) double bond; this is presumably due to stereoelectronic considerations.

Further fractionation of the biologically active[13] ethyl acetate soluble fraction afforded the Virginia group a second jatrophone derivative, termed hydroxyjatrophone A. The spectral data of this derivative suggested that it possessed a hydroxyl group at C(2).[14] In particular, elemental analysis and high-resolution mass spectrometry established a molecular formula of $C_{20}H_{24}O_4$, while absorptions in the ultraviolet (μ_{max} 281 nm) and infrared (ν_{max} 1675, 1660, and 1605 cm^{-1}) spectra indicated a highly conjugated system similar to that of jatrophone. The proton NMR spectrum of hydroxyjatrophone A was also remarkably similar to that of jatrophone (**1**), except for the lack of a signal corresponding to the proton at C(2). Instead, a clean AB system, ascribed to the methylene protons at C(1), was observed at δ 2.37 amd 2.08 (J_{AB}

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(1) (a) Plant Anticancer Agents. 28. Part 27: Badawi, M. M.; Handa, S. S.; Kinghorn, A. D.; Cordell, G. A.; Farnsworth, N. R. *J. Pharm. Sci.*, submitted for publication. (b) Dedicated to the memory of Professor S. Morris Kupchan.
(2) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980–1985.
(3) Deceased October 19, 1976.
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(13) Tumor-inhibiting activity and cytotoxicity were assayed under the auspices of the National Cancer Institute by the procedures described by: Geran, R. I.; Greenberg, N. H.; McDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *2*, 1.
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Table I. Nuclear Overhauser Enhancement (NOE) Data[a]

com-pound	16-CH_3[b]				17-CH_3[b]		18-CH_3[b]			19-CH_3[b]			20-CH_3[b,c]	5-H[b,d]	
	1-Hα	1-Hβ	2-H	3-H[e]	5-H[e]	9-H	8-H	9-H	11-Hα	8-H	9-H	11-Hβ	11-Hα	9-H	17-CH_3
1			15	12	22	4		13	11	29		10	4		2
2			24	14	23	3		11	7	33		15	4		3
3					19	3		13	7	31		10	7		3
4		15		15	19	3		10	7	26		10	7		3
5	8			9	23	4		10	6	23		7	4		3
10	3			8	24		28		4		10	6	2	9	4

[a] For details of procedure see Experimental Section. Values are expressed in % enhancement relative to irradiated peak (100%) adjusted for the relative number of protons. [b] Irradiated signals, below the irradiated signals are the observed signals. [c] In 10 the 16- and 20-CH_3 groups were not well resolved and were irradiated simultaneously. [d] In 1 and 10 3- and 5-H were observed as a broad singlet and were irradiated simultaneously. [e] In 1 and 10 values were calculated assuming only 3-H or 5-H was enhanced.

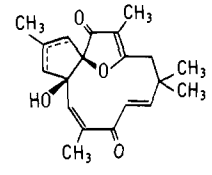
= 13.8 Hz). More significant, however, was the appearance of a singlet methyl resonance at δ 1.38 replacing the doublet at δ 1.09 assigned to the C(16) secondary methyl group of jatrophone. Finally, a facile reaction of hydroxyjatrophone A and trichloroacetyl isocyanate afforded a carbamate derivative. The ^1H NMR spectrum of this derivative displayed a resonance at δ 8.36 for the NH group while the resonances due to the C(1) methylene and C(3) olefinic protons adjacent to the tertiary hydroxyl group had undergone significant downfield shifts relative to the underivatized system.

(i) Reinvestigation of *Jatropha gossypiifolia* L.: Isolation of Hydroxyjatrophone B and C. In 1981 the Illinois group was asked by the National Cancer Institute to reisolate a quantity of jatrophone for additional, more substantial anticancer testing. In the course of this effort, the opportunity was taken to study further hydroxyjatrophone A. In the event, careful separation of the biologically active fractions using the KB system,[13] led to the isolation and identification of two additional jatrophone derivatives (vide infra).

In retrospect the original isolation procedure for jatrophone, described by Kupchan,[5] was quite laborious, involving several solvent partitions. Since in fact jatrophone had been isolated from a hexane soluble fraction, it was suggested that an initial hexane extraction followed by chloroform would yield jatrophone and related compounds without the need for solvent partition. In practice, jatrophone was almost completely separated via such a protocol; furthermore jatrophone, obtained from the hexane extract, could be purified easily by column chromatography. The hexane extract also yielded two new hydroxyjatrophones, B and C, whereas hydroxyjatrophone A, isolated originally by the Virginia group, was found in the chloroform extract.

Hydroxyjatrophone B analyzed for $C_{20}H_{24}O_4$ by high-resolution mass spectrometry. The ultraviolet maximum at 285 nm and strong infrared absorptions at 1670 and 1626 cm^{-1} were again analogous to those of jatrophone. An additional infrared absorption at 3450 cm^{-1} indicated that this too was a hydroxy derivative. The low-field (100 MHz) proton NMR spectrum was also quite similar to that of jatrophone, the only significant difference being a singlet now appearing at δ 1.39 assigned to the 16-CH_3. Taken together these observations suggested that hydroxyjatrophone B was the C(2) diastereomer of A.

Hydroxyjatrophone C, also derived from the hexane extract, was crystalline, in contrast to A and B, which were amorphous. High-resolution mass spectrometry indicated a molecular formula of $C_{20}H_{24}O_4$. The ultraviolet and infrared spectra were again similar to that of jatrophone (**1**) except for hydroxyl absorption observed at 3430 cm^{-1}. All three hydroxyjatrophones exhibit specific rotations that were similar in direction and magnitude to that exhibited by jatrophone. This result indicates that the relative configuration at the furanone oxygen is the same, i.e., β, for each system. Furthermore, the proton NMR spectrum of C corresponded well with the data established for the jatrophone system, although some important differences were noted. In particular, the signals assigned to the C(3) and C(5) olefinic protons were shifted downfield (~0.3 ppm), as was the C-(17)-methyl resonance (~0.07 ppm). Most dramatic, however, was the change in chemical shift of the resonance assigned to the C(16) methyl, which was now observed at δ 1.70. Such a chemical shift is typical of a vinylic methyl group. With resonances attributable to the C(3) (or C(1)) and C(5) olefinic protons still in evidence and a hydroxyl group to be inserted, it was initially throught that hydroxyjatrophone C was a 4β-hydroxy derivative (**9**), in which the double bond could be placed at either C(1,2) or C(2,3).



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During the course of the isolation and preliminary structural studies considerable effort was expended to obtain crystals of the 2-hydroxyjatrophones suitable for X-ray crystallographic analysis. These efforts included the preparation of several derivatives of hydroxyjatropone A by the Virginia group. When none of these attempts proved successful, it became clear that structural and stereochemical assignments for the hydroxyjatrophone derivatives would of necessity be based on chemical and spectroscopic evidence. It was at this juncture that high-field (250 MHz) NMR studies were initiated at the University of Pennsylvania. In particular, extensive double-resonance experiments were performed that allowed virtually complete assignments of ^1H and ^{13}C NMR spectra of all six natural and synthetic jatrophones. These results form a basis for the structural assignments of hydroxyjatrophones A, B, and C.

(ii) Analysis of the High-Field ^1H NMR Spectra of Hydroxyjatrophones A, B, and C. The 100-MHz proton NMR spectrum of jatrophone (**1**) was originally assigned by Kupchan and coworkers,[5] although not completely, on the basis of chemical shift, multiplicity, and routine decoupling experiments. In particular the assignments of the AB (or ABC) systems of C(1) and C(11) and the geminal methyl groups C(18) and C(19) were not resolved. It was assumed that completion of these assignments would aid in the assignment of structure to the related derivatives. Toward this end a detailed study, via nuclear Overhauser enhancement difference spectra (NOEDS),[15,16] was initiated that eventually encompassed all six jatrophones derivatives. The results of this study are shown in Table I. The magnitude of the observed enhancements were not optimized; rather the irradiating power level was adjusted in order to maximize selectivity for the particular resonance irradiated.

For jatrophones (**1**) the C(11) AB system assignments were secured by irradiation of the singlet at δ 1.74 [C(20) methyl] and observing the enhancement of the doublet at δ 2.86. The latter could then be assigned to the C(11) α-proton and the doublet at δ 2.40 to the C(11) β-proton. The doublet at δ 2.86 was also

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Table II. ^{1}H NMR Chemical Shift Data[a]

proton	compound 1	2	3[b]	4	5	10[b]
1-Hα	2.16 dd (13.7, 5.9)	2.52 dd (14.0, 5.9)	2.30 dt (12.2, 2.8)	2.37 d (13.8)	2.33 d (14.0)	2.42 d (14.3)
1-Hβ	1.84 dd (13.7, 5.5)	1.65 d (14.0)	1.92 dd (12.2, 6.2)	2.08 d (13.8)	1.99 d (14.0)	2.22 d (14.3)
2-H	2.95 m	2.80 m	2.24, 2.29 dm (16.4), dm (16.4)			
3-H	5.81 m	5.87 m	5.83 m	5.80 m	5.82 m	6.10 m
5-H	5.81 m	5.75 m	5.69 m	5.71 m	5.72 m	6.10 m
8-H	5.99 d (16.2)	5.99 d (16.2)	5.89 d (16.3)	5.94 d (16.4)	5.98 d (16.2)	5.97 d (16.5)
9-H	6.45 d (16.2)	6.41 d (16.2)	6.37 d (16.3)	6.36 d (16.4)	6.44 d (16.2)	6.54 d (16.5)
11-Hα	2.86 d (14.7)	2.84 d (14.7)	2.79 d (14.9)	2.81 d (15.0)	2.85 d (14.7)	2.76 d (13.2)
11-Hβ	2.40 d (14.7)	2.43 d (14.7)	2.31 dq (14.9, 0.9)	2.41 d (15.0)	2.41 d (14.7)	2.48 d (13.2)
16-CH_3	1.09 d (6.9)	1.07 d (7.0)		1.38	1.39	1.70
17-CH_3	1.87 d (1.6)	1.87 d (1.8)	1.78 d (1.5)	1.83 d (1.5)	1.85 d (1.5)	1.92
18-CH_3	1.24	1.21	1.15	1.17	1.21	1.31
19-CH_3	1.36	1.37	1.26	1.32	1.32	1.18
20-CH_3	1.74 d (0.7)	1.71	1.65 d (0.9)	1.66	1.70	1.68 d (0.7)

[a] Spectra were obtained for deuteriochloroform solutions at 250 MHz on a Bruker WM-250 spectrometer. Chemical shifts are reported in δ relative to tetramethylsilane. Multiplicities (d, doublet; dd, doublet of doublets; m, multiplet; singlet if not specified) and coupling constants (Hz), in parentheses, are given below each value. [b] Chemical shifts and coupling constants were determined from the normal one-dimensional and two-dimensional *J*-resolved spectra.

enhanced when the singlet at δ 1.24 was irradiated, thus indicating a cis-vicinal orientation with the C(18) methyl. Similarly, a cis-vicinal relationship between the C(19) methyl (δ 1.36) and the C(11) β-proton (δ 2.40) was demonstrated. These latter experiments also provided considerable insight into the solution conformation of **1**. In this regard the crystal conformation of **1** as determined by Kupchan[5] was shown to have the C(8,9) olefin in a transoid, nearly coplanar conformation relative to the C(7) carbonyl. This conformation places the C(19) methyl very near to the C(8) proton and to a lesser degree the C(18) methyl near the C(9) proton. An alternative cisoid conformation, readily accessible in Dreiding models of **1** by rotation about the C(7,8) and C(9,10) bonds, reverses the methyl–olefin proton relationships. That the former conformation is found in solution as well as in the crystal is strikingly revealed by enhancements observed for the respective olefinic protons upon irradiation of the geminal methyl groups. Irradiation of the singlet assigned to the C(17) methyl produced an enhancement of the broad singlet at δ 5.81 attributable to both the C(3) and C(5) olefinic protons. This enhancement, however, is probably due solely to the C(5) proton, in that in other jatrophones where these resonances were fully resolved, only the C(5) proton signal was enhanced. The same signal was enhanced when the C(16)-methyl doublet was irradiated, although here the enhancement is attributable to the C(3) proton. No enhancement of the C(1)-methylene protons was observed in this experiment. This result was surprising since an NOEDS may reveal enhancements as small as 1% or less.[15,16] Nonetheless an assignment of the C(1)-methylene AB system could be made on the basis of chemical shift and the observed effect of the C(2)-methyl substituent on these protons. That is, the C(1) α-proton should be deshielded relative to C(1) β-proton due to its proximity to ($\sim$2.3 Å) and position near the plane of the furanone carbonyl. Furthermore, the doublet of doublets at δ 2.16 is upfield by δ 0.36 relative to the corresponding signal in **2**. The latter presumably reflects the anisotropic shielding of the cis-vicinal C(2)-methyl group. The upfield doublet of doublets at δ 1.84 of **1** is similarly shifted upfield in **2** to δ 1.65, reflecting the change in stereochemistry at C(2). Due to the rigidity of the cyclopentene ring in **1** and **2**, conformational changes resulting from the C(2) stereochemistry are probably not significant in regard to these comparisons of chemical shift.

The overall similarity of the proton NMR spectra of **1**, **2**, and **3** allowed ready assignment of the latter spectra in a similar manner. The magnitude and distribution of nuclear Overhauser enhancements further indicated nearly identical conformations for all three molecules. Of interest is the absence of enhancement of the C(1)-methylene protons of **2** upon irradiation of the C(16)-methyl doublet. The C(1)- and C(2)-methylene groups in **3** presented a complex pattern of resonances, which was not readily resolved by simple decoupling techniques. Use of two-dimensional ^{1}H J-resolved spectroscopy,[15,16] however, allowed these protons to be assigned as indicated in Table II. The contour, projection, and cross-section plots for a portion of the two-dimensional ^{1}H *J*-resolved spectrum of **3** are shown in Figure 1. The individual multiplets attributable to the C(1)- and C(2)-methylene protons are clearly revealed in the cross-section plots. The C(1) α- and β-proton resonances may be assigned to δ 2.30 and 1.92, respectively, by using the chemical shift considerations previously described for **1**. The individual resonances for the C(2)-methylene protons, which exhibit surprisingly simple coupling patterns, could not be assigned with confidence. In addition the spectrum revealed several small couplings. These included the allylic C(20)-methyl–C(11)-proton coupling, which was previously observed, in the normal one-dimensional spectra, only in the spectrum of **1**.

As previously outlined, two of the newly isolated 2-hydroxyjatrophone derivatives (A and B) exhibited proton NMR spectra that were virtually identical with each other as well as quite similar to the spectrum of **1**, with the only apparent differences attributable to the presence of the hydroxy substituent at C(2). Further evidence for the proposed structures (i.e., **4** and **5**) was obtained in the NOEDS. In particular, irradiation of the C(17), C(18), C(19), and C(20) methyls in A and B produced enhancements essentially identical with those observed for **1**, **2**, and **3**. A significant difference was the enhancement of the C(1)-methylene protons upon irradiation of the C(16) methyl. In the first derivative, A, irradiation of the C(16) methyl produced an enhancement of the upfield doublet (δ 2.18). The same ex-

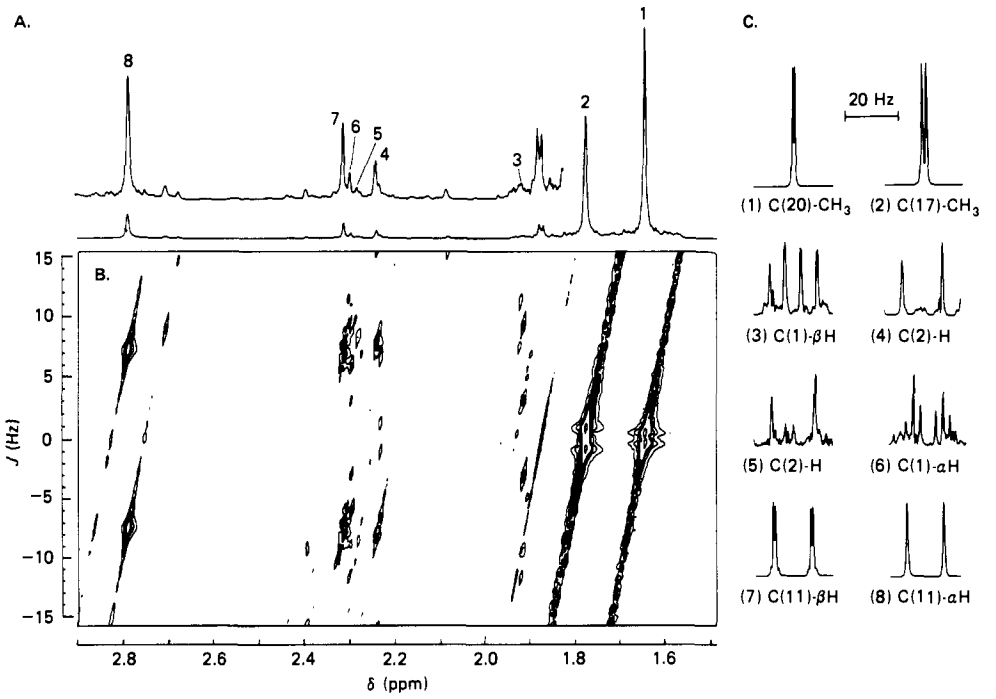
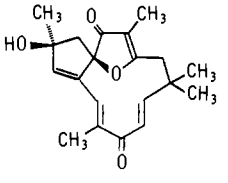


Figure 1. Two-dimensional ^1H J-resolved spectrum of 2-normethyljatrophone (**3**). Shown are the (A) projection, (B) contour, and (C) cross-section plots for the portion of the spectrum indicated. The two methyl resonances at highest field are not shown.

periment produced an enhancement of the downfield doublet (δ 2.33) in the case of hydroxyjatrophone **B**. These results indicated that the relative chemical shifts of the C(1) α- and β-protons were identical in both A and B. Furthermore, since the absolute chemical shifts were similar in A and B, it was apparent that the anisotropic shielding effects of the C(2)-hydroxy and C(2)-methyl substituents were approximately the same. The AB system could then be assigned in the same manner as **1**, that is, the downfield doublet to C(1) α and the upfield doublet to C(1) β. Thus for hydroxyjatrophone A in which a cis-vicinal relation of the C(16) methyl and C(1) β-proton was demonstrated, the stereochemistry is as indicated in **4**. Likewise for the hydroxyjatrophone B structure **5** is assigned.

Several aspects of the spectral properties of hydroxyjatrophone C (vide supra) differentiated it from the other natural and synthetic jatrophones and led to structure **9** as the initial assignment. This derivative, in contrast to **4** and **5** was crystalline, thereby permitting X-ray crystallographic analysis. Unfortunately the analysis was not successful in that due to the small size of the crystals and the consequent paucity of reflections, the structure could not be refined to a satisfactory level (R = 0.14).[17] Nonetheless the connectivity of the structure appeared certain and was shown to be **10**, although certain bond distances and angles were



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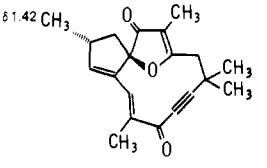
in doubt. Clearly **10** was quite different from the initially proposed structure **9**. Like **4** and **5** it was a C(2)-hydroxy derivative, the major difference being the E geometry of the C(5,6) double bond. In all the other derivatives (**1**–**5**) the C(5,6) bond is Z. Although unusual, upon reexamination of the spectra with the addition of the NOEDS results, there appeared to be considerable spectroscopic evidence to support this structure.

First the chemical shift of the C(16)-methyl group, which appeared to be too far downfield simply to be α to a hydroxy group, required rationalization. As an aside, the C(16)-methyl group was assigned to the resonance at δ 1.70 and the C(20)-methyl to δ 1.68 on the basis of the two-dimensional ^1H J-resolved spectrum of **10**, which revealed the latter as a doublet (J = 0.7 Hz) apparently due to an allylic coupling with one of the C(11)-methylene protons. Examination of Dreiding-type models of **10** and **5** did not show a significant difference in the environments of the C-(16)-methyl groups. Nonetheless an analogous shift difference was observed for the two intermediates **11** and **12**, prepared in



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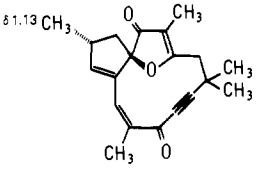

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the course of the total synthesis of **1**;[11] the latter provided a good empirical foundation for the observation in **10**. The structure of **11** was determined by analogy to its 2-normethyl analogue[11,12] for which a single-crystal X-ray structure was obtained, while **12** was prepared from **11** by isomerization (I_2/acetic acid). The C(16) methyl in **11** appears at δ 1.42 and in **12** at δ 1.13. The observed shift difference is virtually identical both in direction and magnitude with that of **10** and **5**. It may also be noted that the isomerization of **10** to **5** was attempted under the same conditions. No change in **10**, however, was observed over several days.[18] An additional observation, that of an allylic coupling (1.5–1.8 Hz), was found in the spectrum of **12** in the doublet assigned to the C(17) methyl. This coupling is identical with observations made for **1**–**5**. Compounds **10** and **11**, however, do not exhibit a similar coupling pattern in their spectra.

Further support for the C(5,6)-E geometry can be found in the NOEDS. Molecular models as well as the preliminary X-ray structure of **10** indicate that the C(5) and C(9) olefinic protons are proximate. Irradiation of the C(5) proton produced a 9% enhancement of the C(9) proton. Similar experiments performed on each of the other five derivatives produced no analogous enhancement. The relative stereochemistry at C(2) in **5** and **10** was also shown to be the same (i.e., β-hydroxy) by irradiating the

C(16) methyl in **10** and observing an enhancement of the downfield doublet (δ 2.42) of the C(1)-methylene AB system. This result supports the stereochemistry indicated by the X-ray crystallographic analysis.[17]

Using the NOEDS results to assign the geminal methyl resonances in the same manner as for **1–5**, that is relating the C(20) methyl to the C(11) methylene and then C(18,19) methyls to the C(11) methylene, revealed that the geminal methyl groups had reversed their relative chemical shifts. In **1–5** the C(19) methyl is found to resonate downfield of the C(18) methyl whereas in **10** the converse holds. Again turning to molecular models, the relative positions of these methyl groups with respect to the C(8,9) olefin appear to be the dominant factor. The methyl that is found near to and in the plane of the olefin is observed to be deshielded and thus downfield. The orientation of the methyl groups in **10** with respect to the C(8,9) olefinic protons has also been reversed relative to **1–5**. The latter is clearly shown in the NOEDS results.

The results described above not only allow assignment of structure **10** to hydroxyjatrophone C, but also corroborate the stereochemical assignments made for **4** and **5**. The extensive NOEDS study further provides insight as to the solution conformations of all six derivatives.

At this point it should be noted that lanthanide-induced-shift (LIS) experiments[19] were considered as a possible approach to assignment of C(2)-hydroxy stereochemistry. Indeed such experiments were carried out, using a series of concentrations of europium complex [Eu(fod)$_3$], with respect to **4** and **5** (molar ratios: 0.0–0.5); values for the LIS were obtained from the linear regression of the observed shifts vs. molar ratio. The results obtained, however, were ambiguous in that in both **4** and **5** the C(1) α-proton was shifted to a greater degree than that of the C(1) β-proton. Observed shifts for protons distant from the hydroxyl were similar in both isomers. Presumably the polyfunctional nature of **4** and **5** combined with the sterically hindered environment around the teriary alcohol contributes to obscure the mode of lanthanide substrate complexation.

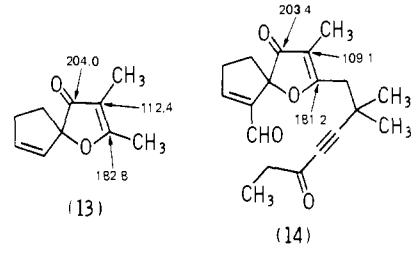
(iii) Analysis of the High-Field ^{13}C NMR Spectra of Hydroxyjatrophone A, B, and C. With proton spectral assignments complete the carbon NMR spectra were examined. Here assignment of virtually all of the carbon resonances was accomplished in a straighforward manner through a combination of chemical shift, off-resonance decoupled multiplicities, and double-resonance techniques; these assignments are shown in Table III. Complete spectra were obtained for each compound except for **2** for which the amount of material available was insufficient to observe quaternary carbons. Complete assignments for compounds **3**, **4**, and **10** were made independently and were consistent throughout except for certain resonances in the spectrum of **10**, which could be rationalized as due to the structural differences in carbon skeleton and substitution. The spectra of the remaining compounds **1**, **2**, and **5** were assigned primarily by analogy to **3** and **4**. Where ambiguities remained specific experiments were performed.

Table III. ^{13}C NMR Chemical Shift Data[a]

carbon (mult)[b]	compound[c] 1	2	3	4	5	10
1 (t)	42.45	40.68[d]	33.49	49.35	48.34	47.71
2 (v)	38.30	38.66	30.42	81.18	80.56	82.41
3 (d)	123.70	123.81	123.15	122.82	122.29	139.60
4 (s)	137.13		137.82	137.34	140.08	137.13
5 (d)	147.03	146.58	140.62	147.61	145.78	136.30
6 (s)	141.75		141.55	142.81	142.73	142.60
7 (s)	201.84		201.05	201.25	200.78	201.88
8 (d)	128.71	129.04	128.24	128.70	128.58	128.45
9 (d)	158.71	158.72	158.74	159.14	159.43	157.95
10 (s)	36.59	36.59	36.25	36.74	36.74	40.66
11 (t)	41.25	40.98[d]	40.98	41.27	41.47	43.21
12 (s)	183.13		182.77	183.90	182.98	184.97
13 (s)	112.36		112.01	112.38	112.76	113.11
14 (s)	203.78		203.73	203.22	202.98	203.56
15 (s)	99.75		98.85	97.67	97.76	97.82
16 (q)	18.93	20.23[e]		26.92	25.66	28.81
17 (q)	20.68	20.74[e]	20.37	20.74	20.86	12.87
18 (q)	30.38	30.35	30.00	30.18	30.33	26.27
19 (q)	26.89	26.79	26.50	26.74	26.89	30.25
20 (q)	6.04	6.05	5.66	5.86	5.98	6.99

[a] Spectra were obtained for deuteriochloroform solutions at 62.9 MHz on a Bruker WP-250 spectrometer, except for 2 the spectrum of which was obtained on a JEOL FX-270 spectrometer. Shifts are given in ppm (δ) downfield from tetramethylsilane. [b] Multiplicities were determined from the off-resonance decoupled spectra; s, singlet; d, doublet; t, triplet; q, quartet; v, varies with substitution at C-2. Multiplicities could not be determined for 2. [c] Complete assignments for 3, 4, and 10 were obtained by using double resonance techniques and for 1, 2, and 5 by analogy; ambiguous assignments were resolved by double-resonance experiments. [d,e] Assignments may be reversed.

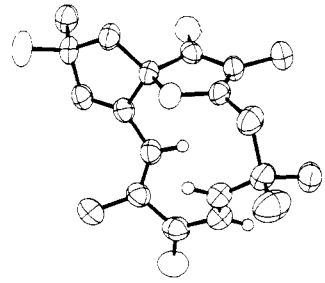
The process of assigning the ^{13}C-NMR spectrum of **4** is illustrative. Here several resonances could be assigned on the basis of chemical shift and multiplicity. Two carbonyl resonances (δ 201.25 and 203.22) were observed. The resonance at lower field was assigned to the furanone carbonyl [C(14)] by comparison with two related compounds, **13** and **14**, in which corresponding carbons resonate at δ 204.0 and 203.4, respectively. Consequently the higher field resonance is assigned to C(7). The singlet at δ 97.67 is similarly assigned to the spiro carbon C(15) while the singlet at δ 81.2 may be assigned to the hydroxyl-bearing C(2) carbon. The furanone olefin carbons [C(12,13)] are assigned to singlets at δ 112.4 and 183.9, respectively, by analogy to **13** and **14** in



which similar carbons are observed at δ 112.4, 109.1 and δ 182.8, 181.2. Only one singlet is present at high field and therefore is associated with C(10).

Assignment of protonated carbons was accomplished by correlation of the carbon and proton spectra using both low-power selected-frequency decoupling (LPSFD)[20] and low-power single-frequency off-resonance decoupling (LPSFORD)[21] techniques. In this way carbons 1, 3, 5, 8, 9, 11, and 16–20 could be assigned

(17) Unpublished results of P. Carroll and V. Santiopietro (University of Pennsylvania). Subsequent to the completion of this manuscript a second crystal was obtained and a successful X-ray analysis was performed (final R value = 0.049), which confirmed the preliminary crystal structure. An ORTEP drawing of hydroxyjatrophone C (**10**) is illustrated below. A full account of these results will be reported elsewhere as part of a larger study of the crystal structures of jatrophone derivatives and synthetic analogues.



(18) This experiment was carried out by Dr. S. R. Schow, University of Pennsylvania.

(19) Gansow, O. A.; Willcott, M. R.; Lenkinski, R. E. *J. Am. Chem. Soc.* **1971**, *93*, 4295.

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Table IV. Antineoplastic Activity of Jatrophone and Derivatives[13]

compound		test system: P-388		test system: KB
name	NSC no.	in vivo T/c, mg/kg	in vitro ED_{50}, μg/mL	in vitro ED_{50}, μg/mL
jatrophone (1)	135037	145, 12.0	0.01	0.000087
2α-hydroxyjatrophone (4)	266490	125, 6.0	0.03	0.16
2β-hydroxyjatrophone (5)	353455	132, 10.0	0.06	0.07
2β-hydroxy-5,6-isojatrophone (10)	353456	inactive	2.2	0.03

as indicated. Remaining to be assigned were the olefinic carbons C(4) and C(6). These resonances were distinguished by a long-range LPSFD experiment. In particular, examination of the completely coupled carbon spectrum reveals the line widths of the peaks at δ 142.8 and 137.3 to be 9.2 and 8.0 Hz, respectively. When the spectrum is obtained with concurrent irradiation of the C(17)-methyl protons the relative magnitude of the line widths are reversed as well as the peak heights; i.e., the signal at δ 141.6 increases in height and decreases in line width relative to the peak at δ 137.8. This result reflects the elimination of two-bond coupling between the C(6) (δ 141.6) and the C(17)-methyl protons.

A quite similar process was applied to **3** and **10**, permitting unambiguous assignments to be made as indicated in Table III. A near one-to-one correspondence of peaks for the spectra of **1**, **3**, and **4** permitted assignment of most of the spectrum of **1**. The similarity of C(1) and C(11) resonances, however, required LPSFD experiments to differentiate between them. Assignment of the spectrum of **5** was accomplished by comparison to the spectrum of **4**.

Several differences noted in the spectrum of **10** are consistent with the structural assignment. The largest shifts relative to the corresponding carbons in **1**–**5** are found, as might be expected, for the olefinic carbons C(3–6), as well as the C(17) methyl, which is shifted upfield by approximately 8 ppm. The chemical shift of C(16) methyl is δ 28.81, the furthest downfield of the six derivatives, as is the case in the proton spectra. The C(16)-methyl resonance in **2** is shifted 1.3 ppm downfield of the corresponding peak in the spectrum of **1**. This shift is identical with the shift difference for C(16) in **4** and **5**. In both pairs the β-methyl group is shifted downfield by the same amount (ca. 1.3 ppm) relative to the compound with an α-methyl.

(iv) Antineoplastic Properties of the Hydroxyjatrophones. The new isolates, 2α-hydroxyjatrophone (**4**, NSC 266490), 2β-hydroxyjatrophone, (**5**, NSC 353455), and 2β-hydroxy-5,6-isojatrophone (**10**, NSC 353456), were evaluated for their antineoplastic activity in the P-388 lymphocytic leukemia test system both in vivo and in vitro, as well as for the Eagle's carcinoma of the nasopharynx test system (KB) in vitro.[13] The results are summarized in Table IV. Each of the isolates were considerably less active in the KB test system than was jatrophone (**1**), but both hydroxyjatrophones **4** and **5** displayed comparable activity relative to **1** in the P-388 test system in vivo and in vitro. Interestingly, 2β-hydroxy-5,6-isojatrophone (**10**) was substantially less cytotoxic in the P-388 test system in vitro than **1** and was inactive in this system in vivo. Possibly the inability of **9** to undergo concommitant nucleophilic attack at C(9), with cyclization,[5] of C(8) to C(12), due to the conformational changes induced by the C(5,6)-*E* double bond accounts for the observed reduced cytotoxicity.

Experimental Section

General. Melting points were determined by means of a Kofler hot plate and are uncorrected. The UV spectra were obtained with a Beckman, Model DB-G, grating spectrophotometer. IR spectra were determined with a Beckman, Model IR 18-A, spectrophotometer. Proton NMR spectra were recorded in $CDCl_3$ with a Varian T-60A instrument having Nicolet FT-7 Fourier transform attachment (University of Illinois), with a Varian XL-100 spectrometer (University of Virginia), or with a Bruker WM-250 spectrometer (University of Pennsylvania). Carbon-13 NMR specta were recorded in $CDCl_3$ with a Bruker WM-250 instrument operating at 62.9 MHz. Tetramethylsilane was used as an internal standard and chemical shifts are reported in δ units. Low-resolution mass spectra were obtained with a Varian MAT 112 double-focusing instrument operating at 70 eV and high-resolution mass spectra with an AEI MS902 double-focusing instrument operating at 70 eV. Optical rotations were measured with a JASCO J-40A spectrophotometer.

Plant Material. The plant material (PR-4444) was collected in the Province of Los Santos, Panama, in 1975, and identified as the roots of *Jatropha gossypiifolia* L. (Euphorbiaceae) by the Economic Botany Laboratory, Science and Education Administration, BARC, USDA, Beltsville, MD. A voucher specimen documenting the collection is deposited in the Herbarium of the National Arboretum, USDA, Beltsville, MD.

Extraction and Preliminary Fractionation. Air-dried and milled roots of *Jatropha gossypiifolia* (25 kg) were thoroughly extracted, successively, with light petroleum and $CHCl_3$. Concentration of the extracts in vacuo afforded residues A and B weighing 130 and 275 g, respectively.

Bioassay of the Crude Extracts. Fractions A and B displayed ED_{50} 0.12 μg/mL and 0.074 μg/mL, respectively, in the P-388 leukemia test system in vitro and ED_{50} 1.2 μg/mL and 0.46 μg/mL, respectively, in the KB test system in vitro.[13]

Chromatographic Separation of the Light Petroleum Extract. The light petroleum extract (130 g) was chromatographed on a column of silica gel (2000 g, mesh 70–230) packed in light petroleum. Elution of the column with light petroleum–$CHCl_3$ mixtures, $CHCl_3$, and finally $CHCl_3$–MeOH mixtures resulted in 11 fractions. The fraction (6.5 g) eluted with $CHCl_3$ was rechromatographed on Woelm neutral alumina (120 g), eluting with light petroleum–chloroform (6:1) to afford a fraction (3.6 g) that on crystallization from hexane afforded jatrophone (**1**, 2.31 g, 0.009%) as white needles, mp 152–3 °C. The last fraction from the silica gel column eluted with 10% MeOH–$CHCl_3$ (15.1 g, ED_{50} 0.37 μg/mL, 0.24 μg/mL in KB and P-388 in vitro, respectively) was chromatographed on a column of neutral alumina (300 g). Elution with $CHCl_3$ and $CHCl_3$–MeOH mixtures afforded 10 fractions. Rechromatography of the second fraction (1.4 g) (ED_{50} 0.21 μg/mL and 0.04 μg/mL in KB and P-388 in vitro, respectively) eluted with $CHCl_3$ on a column of neutral alumina (50 g) afforded four fractions. Preparative layer chromatography of the fraction (0.22 g) on silica gel, eluting twice with diethyl ether, furnished two pure fractions.

2β-Hydroxyjatrophone (5). The more polar fraction on extraction with diethyl ether and concentration in vacuo yielded 2β-hydroxyjatrophone (**5**) as a colorless gum (0.140 g, 0.0005%): R_f 0.26 (diethyl ether); $[\alpha]^{26}_D$ +233° (*c* 0.83, $CHCl_3$); UV (MeOH) λ 283 nm (log ε 4.16), 225 nm (sh, log ε 4.17); IR (NaCl) ν 3450, 2965, 2930, 2875, 1670, 1626, 1430, 1405, 1382, 1220, 1168, 1125, 1077, 980, 760 cm^{-1}; mass spectrum, *m/z* (relative intensity) 328 (M^+, 9%), 311 (8), 310 (27), 285 (6), 271 (7), 255 (22), 243 (10), 205 (23), 204 (13), 202 (15), 191 (29), 189 (19), 173 (13), 160 (21), 147 (13), 145 (13), 125 (20), 105 (18), 91 (28), 83 (27), 82 (93), 77 (20), 53 (88), 43 (100), 28 (39). Mass measurement, $C_{20}H_{24}O_4$ requires 328.1674; found 328.1669.

2β-Hydroxy-5,6-isojatrophone (10). The less polar fraction from the preparative plate on crystallization from diethyl ether/light petroleum (1:3) afforded white crystals of 2β-hydroxy-5,6-isojatrophone (0.048 g, 0.0002%): mp 218–219 °C; R_f 0.30 (diethyl ether); $[\alpha]^{26}_D$ +314.2° (*c* 0.4, $CHCl_3$); UV (MeOH) δ 280 nm (log ε 4.08); IR (KBr) ν 3430, 2958, 2935, 1659, 1647, 1615, 1437, 1407, 1372, 1363, 1314, 1260, 1215, 1200, 1167, 1150, 1137, 1079, 1070, 1052, 1003, 994, 972, 942, 872, 748, 635 cm^{-1}; mass spectrum, *m/z* (relative intensity) 328 (M^+, 100%), 313 (25), 311 (11), 320 (47), 295 (17), 285 (23), 271 (12), 267 (30), 255 (17), 253 (14), 247 (12), 243 (25), 239 (20), 229 (19), 227 (20), 213 (36), 201 (17), 189 (27), 187 (18), 173 (15), 161 (26), 147 (12), 133 (11), 128 (10), 125 (17), 95 (15), 91 (28), 81 (45), 77 (18), 53 (74), 41 (42). Mass measurement, $C_{20}H_{24}O_4$ requires 328.1674; found 328.1679.

Chromatographic Separation of the $CHCl_3$ Extract and the Isolation of 2α-Hydroxyjatrophone (4). The $CHCl_3$ extract (100 g) was chromatographed on a column of silica gel (2000 g, mesh 70–230) eluting with $CHCl_3$ and $CHCl_3$–MeOH mixtures. The fraction eluted with $CHCl_3$–3% MeOH on concentration furnished a brown gum (8.3 g, ED_{50} 0.31 μg/mL and 0.53 μg/mL in KB and P-388 in vitro, respectively), which was rechromatographed on a column of neutral alumina (200 g). The $CHCl_3$–25% light petroleum eluate on concentration yielded a pale brown gum (0.420 g, ED_{50} 0.07 μg/mL and 0.13 μg/mL in KB and P-388 in vitro, respectively), which was dissolved in $CHCl_3$ (25 mL) and decolorized by passage through a column of activated charcoal (0.2 g). A portion of the residue (0.2 g) was then separated preparatively on silica gel eluting five times with diethyl ether–8% CH_3CN. The UV-visible band was separated with $CHCl_3$–4% MeOH to afford pure 2α-hydroxyjatrophone (**4**) as a colorless gum (0.095 g, 0.001%): R_f 0.45

($CHCl_3$–6% MeOH); $[\alpha]^{25}_D$ +231.6° (c 1.5, $CHCl_3$); UV (MeOH) λ 283 (log ε 4.16) and 225 nm (sh, log ε 4.17); IR (NaCl) ν 3415, 2930, 2890, 2825, 1690, 1658, 1627, 1411, 1381, 1329, 1234, 1125, 1077, 1050, 935, 842 cm^{-1}; mass spectrum, m/z (relative intensity) 328 (M^+, 5%), 310 (3), 295 (2), 285 (4), 271 (5), 267 (3), 255 (10), 230 (9), 205 (301), 204 (23), 191 (15), 189 (14), 147 (8), 125 (13), 105 (12), 91 (24), 85 (26), 83 (41), 81 (77), 53 (92), 43 (100), 28 (38). Mass measurement, $C_{20}H_{24}O_4$ requires 328.1674; found 328.1665.

Trichloroacetyl Carbamate of Hydroxyjatrophone A. To a solution of 2α-hydroxyjatrophone (3 mg) in $CDCl_3$ (0.2 mL) was added one drop of trichloroacetyl isocyanate and the solution was subjected to NMR measurement. After evaporation of the solvent, the crystalline residue was recrystallized from acetone to afford 3 mg of product, mp 156.2–156.3 °C: IR (KBr) 2.95, 5.52, 5.88, 6.00, 6.18, 6.6, 8.55, 12.0 μ; NMR ($CDCl_3$, 100 MHz) δ 8.36 (1 H, s, NH), 6.46 (1 H, d, J = 16 Hz, 9–H), 6.07 (1 H, m, 3–H), 6.00 (1 H, d, J = 16 Hz, 8–H), 5.79 (1 H, m, 5–H), 2.91 (1H, d, J = 15.4 Hz, 11–Hα), 2.76 (1 H, d, J = 14 Hz, 1–H), 2.51 (1 H, d, J = 15.4 Hz, 11–Hβ), 2.47 (1 H, d, J = 14 Hz, 1–H), 1.92 (3 H, d, J = 2 Hz, 17–CH_3), 1.74 (6 H, s, 16–CH_3), 1.38 (3 H, s, 19–CH_3), 1.25 (3 H, s, 18–CH_3); mass spectrum, m/e 310 (M^+ – $CCl_3CONHCOOH$), 295, 282, 267, 239, 226, 211, 186, 150, 128, 115, 91.

Nuclear Overhauser Enhancement Difference Spectra (NOEDS). The procedure employed was similar to that described by Hall and Sanders.[15,16] Samples of the jatrophones (2–25 mg) were dissolved in deuteriochloroform, degassed by five freeze–thaw cycles at 10^{-3} torr, and then sealed under vacuum.

Spectra were obtained at 250 MHz with 8K data points. Ten transients were taken with irradiation at the on-resonance frequency, the memory was negated, ten more transients were collected with irradiation at the off-resonance frequency, and memory was again negated. The first two transients in each set were not accumulated to allow equilibration. The sequence was repeated 8 to 256 times until satisfactory signal to noise levels were obtained. The decoupler power level was adjusted until a single resonance was irradiated.

From the difference spectrum the magnitude of the NOE could be determined from the absolute values of the integration of the enhanced resonance and the irradiated resonance, which was assumed to be 100%.

Two-Dimensional J-Resolved Spectra. The spectra were obtained at 200 MHz on an IBM WM-200 spectrometer following a procedure similar to that described by Hall and Sanders.[15,16] A spectral width of 500 Hz covering the high-field region of the spectrum was examined over 2K data points (digital resolution of 0.24 Hz). Data processing using software provided by Bruker was performed on 128 specta of 16 transients each with t incremented by 16 ms, which each time gave an F_1 width of 31.0 Hz with resolution of 0.12 Hz.

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Registry No. 4, 85152-62-1; **4** trichloroacetyl carbamate, 85152-63-2; **5**, 85201-31-6; **10**, 85201-83-8.

Mechanisms of Elimination Reactions. 36. Stereochemistry and Transition-State Structure in Eliminations from Primary Alkyltrimethylammonium Salts[1,2]

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Abstract: A study of stereochemistry of elimination in E2 reactions of $R_1R_2CHCHDNMe_3^+$ reveals that syn elimination can become the major reaction path when R_1 and R_2 are both bulky groups such as aryl or branched alkyl. With OH^-/50% Me_2SO–H_2O at 80 °C, the percent of syn is 68.5 for R_1 = Ph, R_2 = *i*-Pr; 61.9 for R_1 = Ph, R_2 = *p*-MeOPh; 26.5 for R_1 = Ph, R_2 = CH_3. With *n*-BuO^-/50% Me_2SO–*n*-BuOH, the percent of syn runs 61.5 for R_1 = Ph, R_2 = *i*-Pr; 12 for R_1 = *n*-Bu, R_2 = Me; and <5 for R_1 = *n*-Bu, R_2 = D. The results can be rationalized by a simple conformational argument in which steric interactions between bulky β-substituents and the leaving trimethylammonio group destabilize the transition state for anti elimination. Primary β-tritium, secondary α-tritium, and primary α-^{14}C isotope effects were determined on the (2,2-diphenylethyl)trimethylammonium ion and compared with similar data on the (2-phenylethyl)trimethylammonium ion, which eliminates by an exclusively anti mechanism. The extent of proton transfer in the transition state seems not to differ widely between the two systems, but the extent of C–N cleavage appears less in the 2,2-diphenylethyl system. Hammett ρ values are smaller in the 2,2-diphenylethyl system, though their interpretation presents ambiguities.

Our initial aim in these studies was to compare transition-state structure and the propensity for tunneling in eliminations from 2-arylethyl and 2,2-diarylethyl derivatives.[4] When we studied the quaternary ammonium salts in these and related systems however, we became increasingly convinced that simple differences in transition-state structure were not sufficient to explain the differences in the results. We then set out to examine the stereochemistry of elimination using appropriate stereospecifically deuterated derivatives. Prior studies with 2-phenylethyl-*1,2-d*$_2$-trimethylammonium[5] and 1-decyl-*1,2-d*$_2$-trimethylammonium[6] ions revealed little or no syn elimination from primary alkyltrimethylammonium ions in protic solvents. No work with β-branched primary alkyl derivatives had been reported, however.[7]

(1) This work was supported by the National Science Foundation.
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