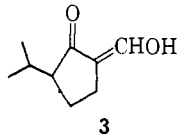
ethyl magnesium bromide followed by isopropyl bromide,[3] was condensed with ethyl formate in the presence of sodium methoxide to give a quantitative yield of the hydroxymethylene ketone **3**, bp 75° (1.5 mm), ν_{max} 3500 (broad), 1735, 1705, 1670, and 1605 cm^{-1}. Reduction of **3** with lithium aluminum hydride in ether furnished the alcohol **4**, bp 94–95° (25 mm), ν_{max} 3450, 1662, and 895 cm^{-1}, in 60% yield.[4] The presence of the exocyclic methylene grouping was substantiated by the nmr spectrum, which showed two signals (1 H each) at δ 4.95 and 5.11, while the proton α to the hydroxyl function gave rise to a multiplet centered at δ 4.2. Treatment of **4** with thionyl chloride in ether afforded a 67% yield of the chloromethyl derivative **5**, bp 36° (0.3 mm), ν_{max} 1645 and 690 cm^{-1}, the nmr spectrum of which showed a singlet at δ 4.12 (2 H, $=CCH_2Cl$) and a broad signal at δ 5.7 (1 H, $-CH=C-$).[5] Hydrogenolysis of **5** with lithium aluminum hydride in isopropyl ether yielded 1-methyl-3-isopropylcyclopent-1-ene (**6**), bp 55° (25 mm), ν_{max} 1650 and 830 cm^{-1}, in 66% yield.[6] The nmr spectrum of **6** showed a multiplet at δ 5.21 (1 H, $-CH=C-$), a singlet at δ 1.63 (3 H, $=C(CH_3)-$), and a pair of doublets centered at δ 1.77 (6 H, $(CH_3)_2CH-$).[7]

Irradiation[8] of a mixture of **6** and 2-cyclopentenone in pentane gave, in addition to the known cyclopentenone photodimers,[9] a 64% yield of two tricyclic ketones in the approximate ratio 1:1. Both ketones showed carbonyl absorption at 1735 cm^{-1} and absence of olefinic protons in their nmr spectra. On the basis of their nmr spectra and by analogy with other photochemical cycloadditions of cyclopentenone which have been shown to yield exclusively *cis,anti,cis* adducts,[9,10] the two ketones are assigned structures **7** and **8**. The angular methyl substituent in **7** appears as a well-defined singlet at δ 1.12 whereas that of **8** is



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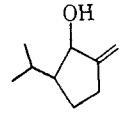

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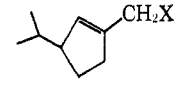
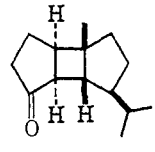
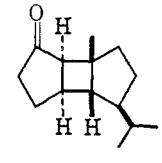


5, X = Cl
6, X = H



7



8

shifted upfield and merges with the signal due to the isopropyl group at δ ~0.9, in agreement with "head-to-tail" and "head-to-head" modes of cycloaddition.[11] Comparison of **7** with the tricyclic ketone obtained by ozonolysis of natural β-bourbonene[1] showed that they were identical, and treatment of **7** with triphenylphosphinemethylene afforded racemic β-bourbonene (**2**) which was indistinguishable from natural material on the basis of infrared and nmr spectra and vapor phase chromatography.[12] In contrast, ketone **8** failed to react with triphenylphosphinemethylene under the same conditions and was markedly less reactive toward carbonyl reagents in general. Brief treatment of synthetic β-bourbonene in ethanol with hydrochloric acid effected isomerization to α-bourbonene (**1**), which had spectral properties corresponding to those reported[1] and was identified by comparison with material obtained by similar acid-catalyzed isomerization of the authentic β isomer.

Acknowledgment. We wish to thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research.

(3) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(4) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 939 (1953).
(5) F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *ibid.*, **77**, 4182 (1955).
(6) R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948); L. F. Hatch and J. J. D'Amico, *ibid.*, **73**, 4393 (1951).
(7) The isopropyl substituent in each of the compounds **3–6**, as well as 2-isopropylcyclopentanone, shows magnetically nonequivalent methyl groups (see H. J. Jakobsen, P. Madsen, and S. O. Lawesson, *Tetrahedron*, **22**, 1851 (1966)).
(8) A Hanovia 450-w high-pressure mercury lamp was used with a Pyrex filter. The photolysis was carried out by adding successive portions of cyclopentenone until most of the olefin **6** was consumed, and then filtering off the crystalline cyclopentenone dimers.
(9) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344 (1962).
(10) P. E. Eaton, *ibid.*, **84**, 2454 (1962).
(11) Confirmation of the stereochemistry of 7 is being sought through X-ray analysis of its thiosemicarbazone.
(12) We are indebted to Professor F. Šorm for samples of authentic β-bourbonene and the tricyclic ketone derived from it.

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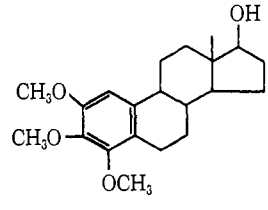
Analgesic Efficacy of Poly(alkoxy)estratrienes

Sir:

It was reported recently[1] that a new series of polyalkoxyestratrienes, as typified by *d*-2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol (1), were potent analgesics when tested in mice, rats, cats, and dogs using morphine and meperidine as controls. In the course of subsequent laboratory work, we have been unable to reproduce the previously reported pharmacological results.



I

Our results, wherein I has been compared with morphine sulfate in several of the more commonly used analgesia screens, are given in Table I.[2] As Table I indicates, compound I was only weakly analgesic when tested in the mouse and rat. In the foot-clamp and tail-clip procedures, no satisfactory dose-response relationship could be established. In dogs, no significant differences from controls could be elicited with I in doses of 5 and 10 mg/kg (intravenous,

(1) (a) L. R. Axelrod, P. N. Rao, and D. H. Baeder, *J. Am. Chem. Soc.*, **88**, 856 (1966); (b) L. R. Axelrod and D. H. Baeder, *Proc. Soc. Exptl. Biol. Med.*, **121**, 1184 (1966).
(2) The results obtained with I are typical for all members of the series which were screened. In addition, we are aware of results comparable to ours which have been obtained independently in five other laboratories.

Table I. Comparison of Analgesia. Morphine Sulfate *vs.* I

Method	AD_{50} (mg/kg)[a] Morphine sulfate	I
Rat tail flick[b]	5.8	No effect (0.25–8.0)[g]
	2.2	50 (0.5–50.0)
Mouse tail electroshock[c,d]	1.2	~60 (32–64)
Mouse hot plate[e]	1.7	50 (5.0–50.0)
Mouse foot clamp[f]	1.1	No effect (64.0–128.0)
Mouse tail clip[f]	8.2	Could not estimate (0.5–100.0)

[a] AD_{50} = analgesic dose in 50% of the animals (as calculated by graphical means). Morphine sulfate administered intravenously as a water solution. Compound I administered intraveneously as a propylene glycol solution. Sodium chloride (0.9%) and propylene glycol solutions were administered as negative controls. Satisfactory AD_{50} values were also obtained for codeine phosphate, *d*-propoxyphene, and sodium salicylate. [b] Tested essentially by the method of F. E. D'Amour and D. L. Smith, *J. Pharmacol.*, **72**, 74 (1941). [c] P. L. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961). [d] Intraperitoneal administration. [e] Method of G. Woolfe and A. D. Maconald, *J. Pharmacol.*, **98**, 121 (1950), as modified by N. B. Eddy and D. Leimbach, *ibid.*, **107**, 385 (1953). [f] C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954). [g] Values in parentheses represent the range of dosesa dministered in milligrams per kilogram.

propylene glycol solution) or with other members of the series in doses up to 50 mg/kg (intravenous, water solution). On the other hand, morphine sulfate in doses of from 1 to 5 mg/kg showed some degree of analgesia in all dogs tested. Crossover studies between morphine sulfate and I in some of the dogs compensated for individual variations in response to the painful stimuli employed.

(3) The authors gratefully acknowledge the skillful assistance of Miss Nancy Hess, Dr. Anthony Valenti, Dr. Robert E. Havranek, and Messrs. Mills T. Kneller, John P. McDermott, Hugo J. Selinger, and Robert E. Allen, and also Mrs. Mary M. Boyce, Mr. Thompson N. Berdeen, Jr., and Mr. Frederick J. Snyder, throughout the course of this research program.

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Stereospecific Transannular Cycloaddition to a 1,6-Cyclodecadiene[1]

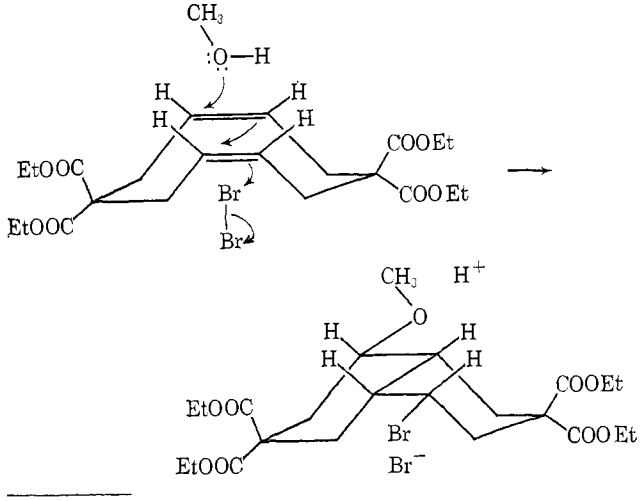
Sir:

The reaction of *cis*-1,4-dichloro-2-butene with diethyl malonate and 2 equiv of sodium ethoxide has been reported to form diethyl 3-cyclopentene-1,1-dicarboxylate, diethyl 2-vinylcyclopropane-1,1-dicarboxylate, and a small amount of a crystalline solid which was thought to be a bi- or tricyclic derivative on the basis of lack of reaction with bromine in ether or with potassium permanganate in acetone.[2]

In the present investigation, the crystalline solid, mp 161–162°, has been identified as tetraethyl *cis,cis*-3,8-cyclodecadiene-1,1,6,6-tetracarboxylate on the basis of analytical data and particularly the nuclear magnetic resonance spectrum.[3] The presence of two double bonds was confirmed by catalytic hydrogenation in acidic solution to produce the saturated cyclodecane derivative, mp 145–146°.[4]

Although the 1,6-cyclodecadiene derivative does not add bromine in carbon tetrachloride, it does react with bromine in methanol at room temperature to form a derivative, mp 129–130°, in high yields (>90%). The analyses and nmr spectrum of the product[5] indicate that it is a bicyclo-disubstituted derivative formed by a transannular cycloaddition reaction.

Since the product is formed in high yields, it was of considerable interest to determine by X-ray crystallographic studies the structure of the product, which could be a substituted bicyclo[4.4.0]- or -[5.3.0]decane formed by a stereospecific cycloaddition. The crystals of the product are monoclinic, space group $P2_1/c$, with the following unit-cell dimensions: a = 13.56, b = 16.92, c = 12.25 A, β = 97.16°, and there are 4 molecules/unit cell. Integrated intensities of 2411 independent nonzero reflections were measured using a scintillation counter, with Cu Kα radiation, and the structure was solved by Patterson and Fourier methods. Several cycles of least-squares refinement have been carried out, and the agreement index, R, is 14% at this stage. A complete report of the crystallographic investigation will be made when refinement has been completed. These crystallographic studies have demonstrated that the addition occurs with the formation of the decahydronaphthalene derivative and that the reaction is stereospecific to form tetraethyl 4-bromo-8-methoxydecahydronaphthalene-2,2,6,6-tetracarboxylate with the bromo and methoxy groups in a *cis* position relative to the *cis*-fused rings, as indicated by



Found: C, 62.12; H, 7.83; mol wt, 418. The nmr spectrum consisted of four olefinic protons, a broad singlet at τ 4.50–4.85; the protons of four carbethoxy groups, a quartet centered at τ 5.78 and a triplet centered at τ 8.70 with a mutual coupling of 7 cps; and an eight-proton multiplet at τ 6.98–7.82 which simplified into an AB pattern (J = 15 cps) when the olefinic protons were decoupled.

(4) *Anal.* Calcd for $C_{22}H_{36}O_8$: C, 61.66; H, 8.47. Found: C, 61.81; H, 8.34. The nmr spectrum taken in $CDCl_3$ consisted of the protons of four carbethoxy groups, a quartet centered at τ 5.90 and a triplet centered at τ 8.78 with a mutual coupling of 7 cps; and two broad singlets of eight protons each centered at τ 7.95 and 8.56.

(5) *Anal.* Calcd for $C_{23}H_{35}O_9Br$: C, 51.59; H, 6.59; Br, 14.9. Found: C, 51.73; H, 6.68; Br, 15.3. The nmr spectrum shows absorptions for four carbethoxy groups consisting of two overlapping quartets centered at τ 5.78 and 5.80 and a triplet centered at τ 8.74 with a mutual coupling of 7 cps; one methoxy group, a singlet at τ 6.65; one proton α to oxygen, a broad band from τ 6.35 to 6.60; one proton α to bromine, a broad band from τ 5.4 to 5.6 (partially obscured by the absorption of the ethoxy methylenes); and a broad ten-proton band at τ 7.00–8.35.

(1) Taken in part from the Ph.D. Dissertation of R. M. G., University of Texas, Aug 1965.

(2) K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

(3) *Anal.* Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60; mol wt, 424.