tra (ir and nmr) identical with those of lactone **52**. The major material (68%) had the following physical properties: ir 1750 cm^{-1} (broad); nmr δ 1.17 (s, 3), 2.06 (AB quartet, 2), 2.33 (s, 2), 3.60 (s, 3); mass spectrum *m/e* (rel intensity) 170 (M^+, 1), 155 (5), 139 (18), 97 (100). This material was identical with one of the ozonolysis product of enone **35**.

Registry No.—**1**, 32435-95-3; **5**, 32435-96-4; **6**, 32435-97-5; **22**, 32435-98-6; **23**, 32435-99-7; **24**, 32436-00-3; **25**, 32436-01-4; **26**, 32436-02-5; **27**, 32436-03-6; **28**, 13051-32-6; **30**, 32436-05-8; **35**, 32436-06-9; **38**, 32460-84-7; **42**, 32436-07-0; **43**, 32436-08-1; **44**, 32436-09-2; **45**, 32436-10-5; **49**, 32436-11-6; **52**, 32436-12-7; 2,2-dimethyl-4-carbomethoxybutylaldehyde, 4007-81-2; perchloric acid, 7601-90-3; acetic acid, 64-19-7.

Acknowledgment.—The authors are greatly indebted to Dr. Roy Teranishi of the U. S. D. A. Western Regional Research Laboratory, Albany, Calif., for his aid in the separation and glpc analysis done during this study and to James Hubbell for his timely assistance.

Mirestrol. I. Preparation of the Tricyclic Intermediate

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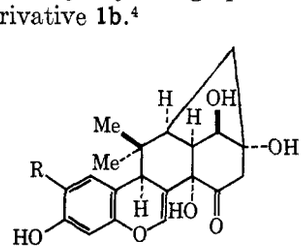
Received July 15, 1971

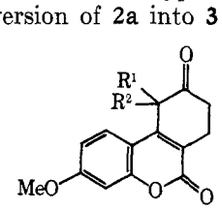
The synthesis of (±)-6aβ,7,8,9,10,10aα-hexahydro-3-methoxy-10,10-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-one (**3**) from 3-(β-carbethoxyethyl)-4-methyl-7-hydroxycoumarin (**12a**) through **12b**, **2a**, **15a**, **16**, **17a**, **18**, **19a**, **19b**, and **20** (Schemes II and III) is described. This multistep transformation involved ring closure to the tricyclic unsaturated lactone **2a** and conversion to the cyclic ether **17a** followed by the introduction of two methyl groups at C-10 to give **20**.

Mirestrol (**1a**) was isolated[1] from the tuber of *Pueraria mirifica* which has been used locally in southeast Asia as a rejuvenating drug. The highly potent estrogenic activity of mirestrol was reported,[1a,2] but a limited supply of the natural resource has restricted extensive physiological studies. The structure of mirestrol was elucidated[3] by X-ray crystallographic studies on the monobromo derivative **1b**.[4]

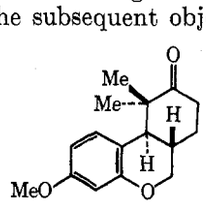


1a, R = H
b, R = Br

This communication deals with the preparation of the A,B,C ring system of mirestrol, which is properly functionalized for eventual conversion into the pentacyclic ring system of the natural product. The tricyclic lactones of type **2** were the first targets and the conversion of **2a** into **3** was the subsequent objective of this study. While all synthetic compounds containing asymmetric carbon are racemic, only one enantiomer is depicted as a matter of convenience.



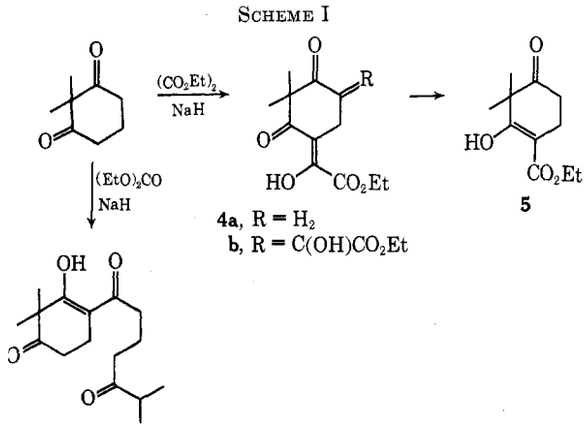
2a, $R^1 = R^2 = H$
b, R^1 = Me, $R^2 = H$
c, $R^1 = R^2$ = Me



3

Preparation of Tricyclic Lactones 2a, 2b, and 2c.—As the most direct approach to obtain **2c**, the Pechmann reaction of resorcinol with **5** was examined. The latter was prepared (Scheme I) by condensation of 2,2-dimethylcyclohexane-1,3-dione[5] and diethyl oxalate to **4a** followed by pyrolysis. A double condensation product **4b** was obtained as a by-product which gave rise to **7** on pyrolysis. Direct carbethoxylation of 2,2-dimethylcyclohexane-1,3-dione with diethyl carbonate in the

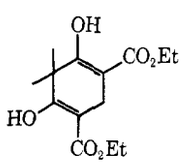
SCHEME I



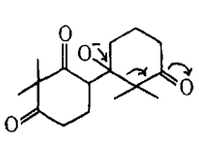
4a, R = H_2
b, R = C(OH)CO_2Et

5

6



7



8

(1) (a) W. Schoeller, M. Dohrn, and W. Hohlweg, *Naturwissenschaften*, **33**, 532 (1940); (b) G. S. Pope, H. M. Grundy, H. E. H. Jones, and S. A. S, Tait, *J. Endocrinol.*, **17**, xv (1958); (c) J. C. Cain, *Nature*, **188**, 774 (1960).

(2) (a) H. E. H. Jones and G. S. Pope, *J. Endocrinol.*, **22**, 303 (1961), and references cited therein; (b) L. Terenius, *Acta Pharmacol. Toxicol.*, **26**, 15 (1968), and references cited therein.

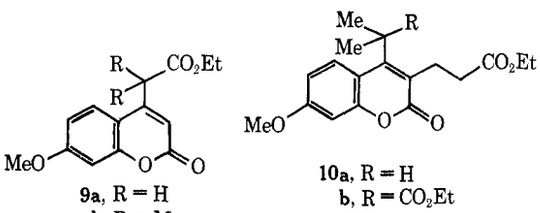
(3) N. E. Taylor, D. C. Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960).

(4) D. G. Bounds and G. S. Pope, *ibid.*, 3696 (1960).

(5) I. N. Nazarov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *Izv. Akad. Nauk SSSR*, **32** (1956); *ibid.*, 325 (1957); *Chem. Abstr.*, **48**, 13667 (1954); **50**, 13847 (1956); **51**, 14597 (1957).

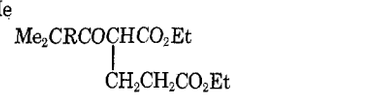
presence of sodium hydride did not produce **5**, but exclusively **6** as the result of an intermolecular aldol condensation followed by an intramolecular retroaldol reaction (see **8**). Unfortunately, **5** did not undergo the Pechmann reaction with resorcinol either under standard conditions[6] or under forcing conditions.[7] It was desirable to achieve introduction of the geminal dimethyl group, as well as formation of ring B and ring C in a single reaction, but it was now realized that the steric interference between the geminal dimethyl group and the aromatic ring had been underestimated.

The Pechmann reaction of resorcinol or its monomethyl ether with open-chain β-keto esters followed by ring closure to **2c** was subsequently examined, in the hope that the open-chain compounds would be flexible enough to reduce steric interference. While **9a**[8] and **9b** were obtained by the boron trifluoride procedure, the condensation of resorcinol monomethyl ether with either **11a**[9] or **11b** did not produce **10a** or **10b** under a variety of conditions.



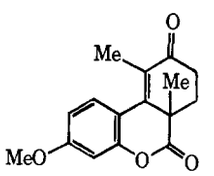
9a, R = H
b, R = Me

10a, R = H
b, R = CO_2Et

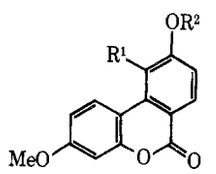


11a, R = H
b, R = CO_2Et

Finally **12a**,[10] the Pechmann reaction product of resorcinol and diethyl 2-acetylglutarate, was chosen as the starting material and was converted into the methyl ether **12b**. The latter could be prepared in one step, though in less satisfactory overall yield, from resorcinol monomethyl ether by the boron trifluoride procedure. The methyl ether **12b** was readily cyclized to **2a** (see Scheme II). It is worth noting that the double bond in **2a** stayed between the aromatic ring and lactone group rather than between the aromatic and ketonic group. Methylation of the potassium

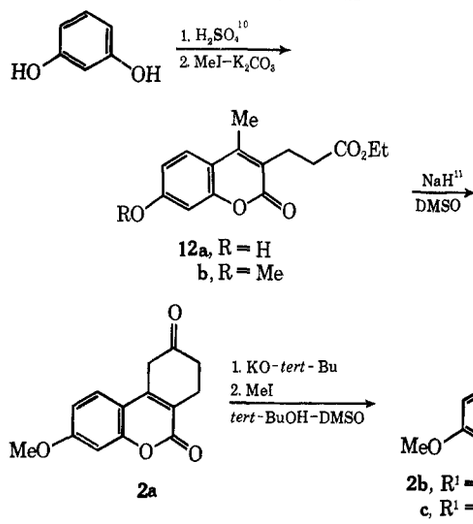


13



14a, $R^1 = R^2 = Me$
b, $R^1 = Me$; $R^2 = H$

SCHEME II



12a, R = H
b, R = Me

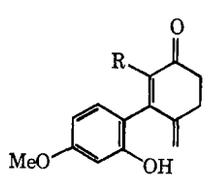
2a

2b, $R^1 = H$; $R^2 = Me$
c, $R^1 = R^2 = Me$

enolate of **2a** give rise to a single product **2b**. The *C*-methyl group exhibited a doublet at τ 8.50 (J = 7.5 Hz) excluding all structural alternatives. The subsequent methylation of **2b** using similar conditions afforded **2c** as the major product (35%), whereas the other C-alkylation product **13**, an O-alkylation–oxidation product **14a**, and an oxidation product **14b** were isolated as minor products. The preferential formation of **2c** over **13** is similar to the alkylation of Hagemann's ester.[12]

Preparation of Tricyclic Ketone 3.—The direct transformation of **2c** to **3** could not be carried out due to steric interference between the C-1 aromatic hydrogen and the geminal dimethyl group. Once the B ring was opened, all attempts to restore the tricyclic system of **3** were unsuccessful. The synthesis of **3** was finally achieved by the transformation of the less hindered **2a** into **17a** (see Scheme III) and subsequent introduction of the geminal dimethyl group.

Lithium aluminum hydride reduction of the ethylene ketal **15a**, which was readily obtained from **2a** in the usual manner, gave **16**. The uv spectrum of **16** showed that the aromatic ring and the double bond were not coplanar. Treatment of **16** with refluxing aqueous acetic acid produced an intractable resin. However, when **16** was refluxed in aqueous acetic acid containing a weak base, both **17a** and **21a** were obtained. Though



21a, R = H
b, R = Me

the uv spectrum suggested that the two rings were noncoplanar, **21a** could be cyclized to **17a** upon treatment with acid–base or with pyridine. The lithium–ammonia reduction of **17a** afforded either **22a** or **23**

(6) Sixteen hours in concentrated sulfuric acid or 3 days in ethanol saturated with hydrogen chloride.

(7) (a) Phosphorus oxychloride in boiling toluene; see R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62**, 1401 (1940). (b) Boron trifluoride in refluxing benzene under the continuous removal of water. A modification of the boron trifluoride procedure was first used by Indian workers; see L. G. Shah, G. D. Shah, and R. C. Shah, *J. Indian Chem. Soc.*, **32**, 302 (1955); *Chem. Abstr.*, **50**, 4927 (1956). (c) After this work had been completed, a novel modification of the Pechmann reaction for a sterically hindered coumarin was published which might be applicable in this case. See G. Büchi and S. M. Weinreb, *J. Amer. Chem. Soc.*, **91**, 5408 (1969).

(8) This compound was previously synthesized in three steps: B. B. Dey, *J. Chem. Soc.*, 1633 (1915).

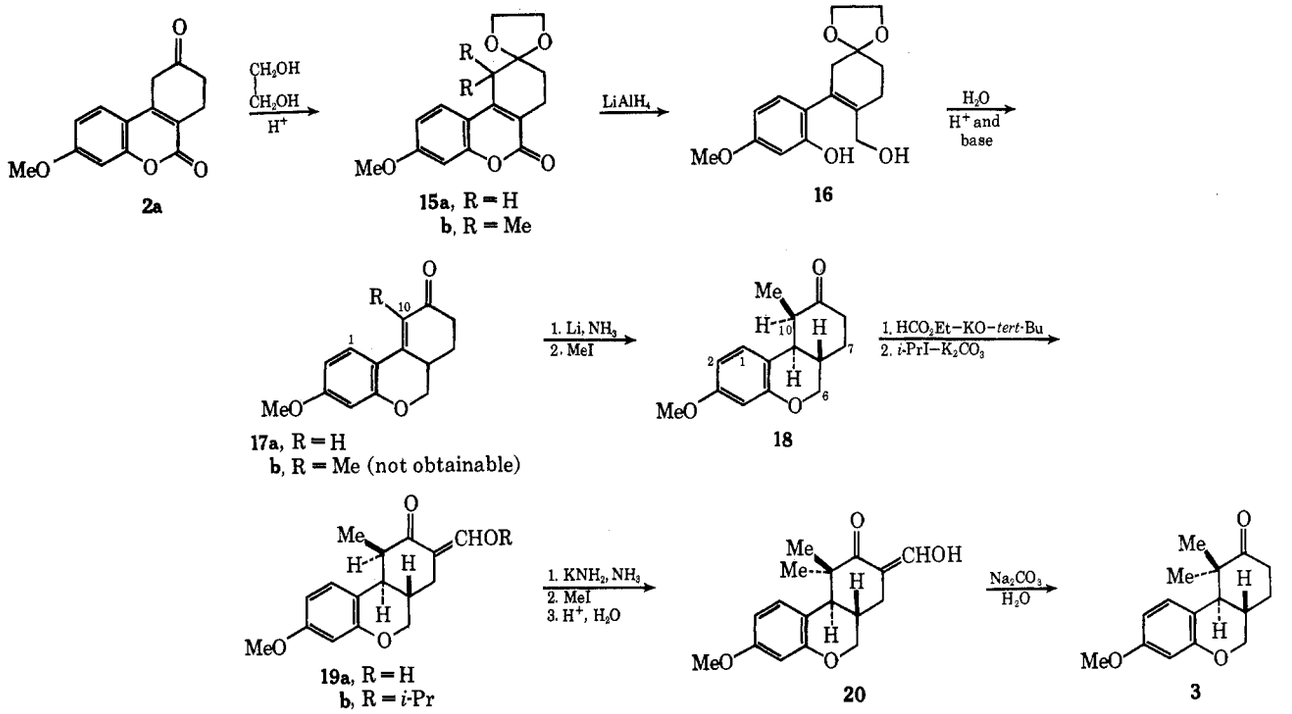
(9) F. Korte, K.-H. Büchel, and L. Schiffer, *Chem. Ber.*, **91**, 763 (1958).

(10) M. M. Shah and R. C. Shah, *Ber.*, **71B**, 2075 (1938).

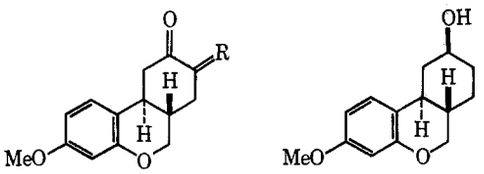
(11) A similar cyclization was recorded in the literature: K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **88**, 2079 (1966).

(12) (a) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893); (b) R. B. Turner, O. Buchart, E. Herzog, R. B. Mofin, A. Riebel, and M. J. Sanders, *J. Amer. Chem. Soc.*, **88**, 1766 (1966).

SCHEME III

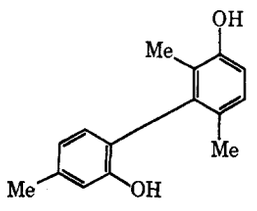


depending upon the reaction conditions. The latter was also obtained by the borohydride reduction of **22a**. Reductive alkylation[13] of **17a** afforded **18**.



The nmr data indicated that the C-10 methyl group of **18** is axial and the B/C ring juncture is trans,[14] as will be discussed later. It is worth emphasizing that the axial methyl group is in the more stable configuration, as it is free from serious steric interaction with the C-1 hydrogen. In agreement with this, **18** was not epimerized upon treatment with either hot hydrochloric acid or hot sodium carbonate solution.

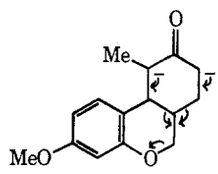
An analogous series of reactions starting from the ketal of **2b** would, in a formal sense, afford **17b** and then **3** by the subsequent reductive alkylation. Actually **17b** could not be isolated, and **21b** and **24** were obtained instead, this result being attributed to serious steric interaction of the C-1 hydrogen and the C-10 methyl in the hypothetical **17b**.



24

Introduction of the C-10 equatorial methyl group in **18** was the most difficult part of this work, due not only to the steric hindrance, but also to a rather unexpected tendency of **22a**, **18**, and **20** to readily undergo fragmentation giving rise to phenolic substances.

The *n*-butylthiomethylene derivative **22c**, obtained *via* **22b** in the well-known manner,[15] gave rise to the red potassium enolate which reacted with methyl iodide under standard conditions.[15] Subsequent alkaline cleavage of the protecting group to generate **18**, however, resulted in phenolic substances. It was later found that **18** itself was readily decomposed in boiling alkali to phenolic products. This behavior might be rationalized by fragmentations as depicted in **25**. Various reagents, both acidic[16] and basic, failed to remove the protecting group without destroying the compound.



25

After the *N*-methylanilinomethylene[17] and trimethylene dithioketal groups[18] had been examined, attention was directed to the isopropoxymethylene group of

(13) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) G. Stork, P. Rosen, and N. L. Goldman, *ibid.*, **83**, 2965 (1961).

(14) The B/C juncture is predicted to be trans based upon theoretical considerations. See ref 13b and G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960); **86**, 1761 (1964).

(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615, 1620 (1962).

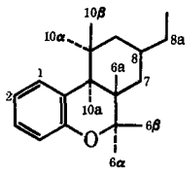
(16) The original authors[15] suggested a possibility of acid hydrolysis of this protecting group to the hydroxymethylene group. This idea could not be expedited in our hands.

(17) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1944).

(18) (a) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. Ives, and R. B. Kelly, *ibid.*, 1131 (1957). (b) For application to saturated ketones, see B. Gaspert, T. G. Halsall, and D. Willis, *ibid.*, 624 (1958).

TABLE I

NMR SPECTRA OF 18, 19a, 3, AND 20[a]

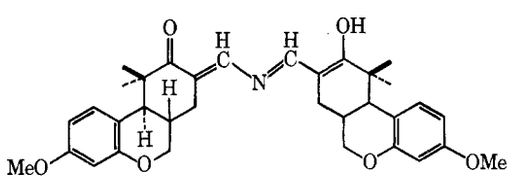


Compd	Solvent	C-1 H (J, Hz)	C-6β H (J, Hz)	C-6α H (J, Hz)	C-10a H (J, Hz)	C-10β Me (J, Hz)	C-10α Me	
18	$CDCl_3$	3.14	5.75	6.30		9.02		Methoxy 6.28
		d	q	t	Overlapped	d		
		(8.5)	(10.5, 3.5)	(10.5)		(7)		
	C_6D_6		6.20	6.78	7.59[c]	9.29		Methoxy 6.70
		Overlapped	q	t	q	d		
			(10.5, 3.5)	(10.5)	(11.5, 4.5)	(7.5)		
						Δ + 0.27[d]		
19a	$CDCl_3$	3.07	5.72	6.28		9.01		Methoxy 6.27
		d	q	t	Overlapped	d		C-8a 1.18, d (1.5)
		(8.5)	(10.5, 3)	(10.5)		J 7		
	C_6H_6	3.35[b]	6.11	6.71	7.66[c]	9.13		Methoxy 6.67
		d	q	t	q	d		C-8a 1.56, d, (1.0)
		(8.5)	(10.5, 3.5)	(10.5)	(11, 5)	(7)		
						Δ + 0.12[d]		
3	$CDCl_3$	2.68[b]	5.86	6.40	7.09[c]	9.08	8.47	Methoxy 6.28
		d	q	t	d	s	s	
		(8.5)	(10.5, 3.5)	(10.5)	(11)			
	C_6D_6	2.80[b]	6.28	6.82	7.56[c]	9.15	8.59	Methoxy 6.69
		d	q	t	d	s	s	
		(9)	(10.5, 4)	(10.5)	(11.5)			
						Δ + 0.07[d]		
20	$CDCl_3$	2.63[b]	5.81	6.34	7.25[c]	9.01	8.32	Methoxy 6.27
		d	q	m	Deformed d	s	s	C-8a 1.31, d, (3)
		(8.5)	(10, 2.5)		(10)			
	C_6D_6	2.77[b]	6.21	6.75	7.65[c]	9.05	8.46	Methoxy 6.69
		d	q	t	d	s	s	C-8a 1.76, d (3)
		(8.5)	(10.5, 3.5)	(10.5)	(11)			
						Δ + 0.04[d]		

[a] The 100-MHz nmr spectra were determined on a Varian HA-100 and chemical shifts are reported in τ values downfield from an internal standard of tetramethylsilane. [b] The long-range coupling with the C-10a proton was observed. [c] The long-range coupling with the C-1 proton was observed. [d] Solvent shift δ ($CDCl_3$) − δ (C_6D_6) or τ (C_6D_6) − τ ($CDCl_3$).

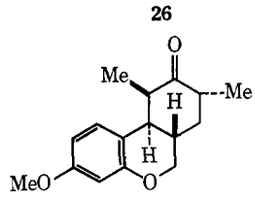
Johnson and Posvic,[19] which, to the best of our knowledge, has only been used by the original authors. This protecting group, being very sensitive to either weak acids or weakly nucleophilic solvents, was easily removed after the alkylation. Under carefully controlled conditions, the isopropoxymethylene group gave satisfactory results. Thus, the hydroxymethylene ketone **19a**, which was readily prepared from **18**, was converted into the isopropoxymethylene ketone **19b** in the usual manner[19] or by simply recrystallizing **18** from isopropyl alcohol. The potassium enolate was generated at room temperature[20] by treatment of **19b** with freshly prepared potassium amide[21] in ether. Alkylation of the enolate with methyl iodide and the subsequent acidic work-up afforded **3** and **20** as the major products and small amounts of **26** and **27**. Cleavage of **20** with boiling sodium carbonate solution gave **3** in quantitative yield.

The nmr spectrum (see Table I) of **20** in deuteriobenzene exhibited a C-10a proton (benzylic) signal at τ 7.65 (d, 1, J = 11 Hz), clearly demonstrating the trans juncture. This doublet was broader than other



racemic and/or meso

26



27

signals, indicating the long-range coupling with the C-1 proton which was confirmed by the decoupling experiment. It is very reasonable to assume that **3**, **18**, **19a**, **19b**, **20**, **22a**, **22b**, **22c**, **26**, and **27** all have the same B/C juncture based upon the way of their preparation. The C-10a proton signals of some of these compounds (Table I, see also Experimental Section) confirmed this view.

It has been mentioned that serious steric interference exists between the C-1 proton and the C-10α (equa-

(19) W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

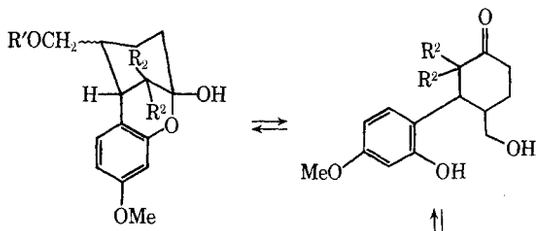
(20) At higher temperature, extensive fragmentation to phenolic substances took place.

(21) Commercial potassium amide did not work at all. Sodium hydride, freshly prepared sodium amide, and potassium *tert*-butoxide were examined, but invariably failed to generate the enolate at room temperature.

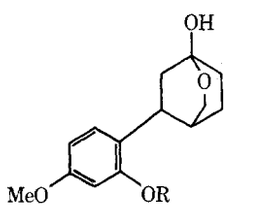
torial) methyl group. In line with this, the C-1 proton signal and the C-10α methyl[22] signal of **3** and **20** appeared at unusually low field because of this steric crowding. The nuclear Overhauser effect confirmed this spacial proximity: irradiation of the methyl signal at τ 8.32 of **20** in deuteriochloroform increased the integration of the C-1 proton at τ 2.63 by as much as 16–20%.

The fact that the C-10 methyl groups of **18** and **19a** are axial (C-10β) could be easily deduced from the chemical shifts as well as from the upfield solvent shifts,[23] that is, positive δ ($CDCl_3$) − δ (C_6D_6) (Table I). Additional evidence was provided by the normal chemical shift of the C-1 proton as well as by the coupling constant (4.5–5 Hz, suggesting the cis relationship) of the C-10a proton and the C-10α proton.

Lithium in ammonia reduction of **15a** followed by acidic work-up afforded an oily product which was best represented by **28a**, though an alternative structure **29a** could not be excluded.

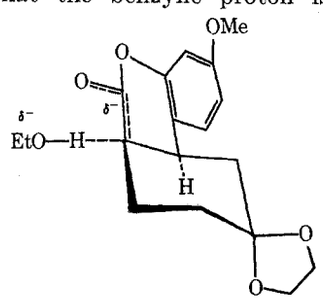


28a, $R^1 = R^2 = H$
b, $R^1 = Ac$; $R^2 = H$
c, $R^1 = H$; $R^2 = Me$

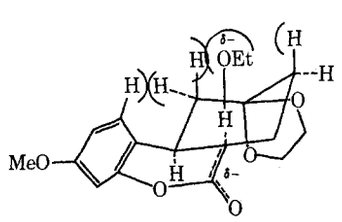


29a, R = H
b, R = Ac

The nmr signal at τ 6.80 (m, 1, $W_{1/2}$ = 12 Hz) suggested that the benzylic proton is equatorial.[24]

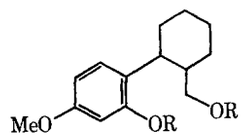


A



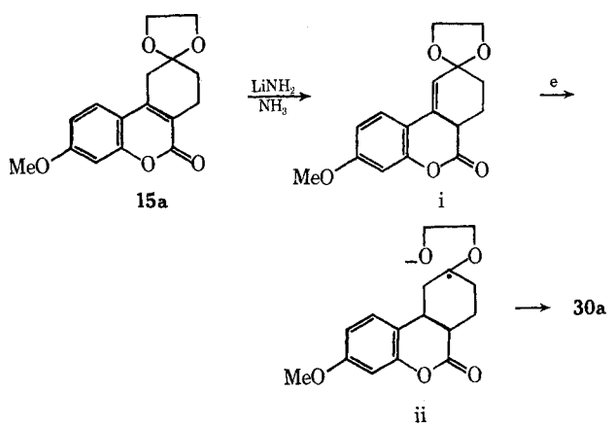
B

When refluxed in acetic acid–water–pyridine, **28a** gave the crystalline monoacetate **28b**. The downfield shift of 0.4 ppm by the $-CH_2O-$ signal of the latter is better rationalized by **28a** → **b** than **29a** → **b**. When nondistilled ammonia was used in the lithium reduction, **28a** was obtained along with a crystalline substance $C_{14}H_{20}O_3$, best formulated as **30a**. The diacetate **30b**, prepared from **30a** by acetic anhydride in pyridine,



30a, R = H
b, R = Ac

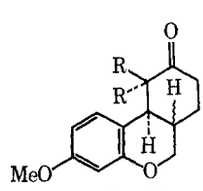
was also crystalline. Wolff–Kishner reduction of **28a** gave **30a**, thus interrelating the two products. The hydrogenolysis of the ethylene ketal group in undistilled ammonia may be due to the presence of lithium amide,[25,26] which would have catalyzed a transient formation of i.



15a i ii **30a**

A similar reduction of **15b** in distilled ammonia gave **28c**, whose nmr signal at τ 7.29 (d, 1, J = 2.5 Hz) indicated that the benzylic proton is equatorial.

Attempted cyclization of **28a** or **28c** to **31a** or **31b** has so far been unsuccessful.



31a, R = H
b, R = Me

Experimental Section

Melting points were determined in open capillary tubes on a Thomas–Hoover Unimelt. All melting and boiling points are uncorrected. The nmr spectra were taken on a Varian A-60 spectrometer with TMS as an internal reference and the data are given in τ values (ppm). Unless otherwise stated, concentrations were carried out *in vacuo* (water pump pressure).

(22) The downfield shift of the C-10α methyl group may be partially due to deshielding by the aromatic ring.

(23) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 169; (b) R. S. Matthews, P. K. Hyer, and E. A. Folkers, *Chem. Commun.*, 38 (1970).

(24) The aromatic ring and hydroxymethyl group in **28a** and **28c** are more likely to be cis than trans, considering the transition states of protonation (by ethanol) leading to cis (**A**) and trans (**B**) isomers.

(25) Traces of iron present in undistilled ammonia catalyze the formation of the alkaline metal amide or the metal alkoxide; for instance, see C. R. Hauser and W. H. Peterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1964).

(26) The undistilled ammonia contains traces of iron. See H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

2,2-Dimethyl-4-ethoxalylcyclohexane-1,3-dione (4a). A.—To a suspension of 4.3 g of 56% sodium hydride mineral oil in 250 ml of anhydrous ether was added a mixture of 14.0 g of 2,2-dimethylcyclohexane-1,3-dione[5] and 29 g of diethyl oxalate. The mixture was stirred under reflux for 3 hr. In case the reaction did not start after 30 min of refluxing, 2 drops of ethanol were added as an initiator. The reaction mixture was cooled with an ice bath, neutralized with aqueous acetic acid, and extracted with ether. The ethereal extract was washed with bicarbonate solution containing sodium chloride. The bicarbonate washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was distilled. The fraction boiling at 120–145° (0.5–1.0 mm) was collected (7.9 g) and redistilled, giving 6.7 g (29%) of **4a**: bp 120–121° (0.25 mm); uv max (MeOH) 312 mμ (ε 10,600); ir ($CHCl_3$) 1734, 1726, 1623, 1577 cm^{-1}; nmr ($CDCl_3$) τ 8.58 (s, 6), 7.22 (m, 4, H-5 and -6), 2.61 (s, 1, enolic H).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.74; H, 6.51.

The neutral fraction gave 6.5 g of ethyl 4-keto-5-methylhexane-1-carboxylate:[27] bp 65–67° (0.25 mm); ir ($CHCl_3$) 1733 (ester), 1710 cm^{-1} (ketone); nmr ($CDCl_3$) τ 8.90 (d, 6, J = 7 Hz).

B.—To a solution of 88.8 g of 2,2-dimethylcyclohexane-1,3-dione[5] and 200 g of diethyl oxalate in 300 ml of anhydrous ether was added 27.5 g of 56% sodium hydride in mineral oil. The mixture was refluxed gently (39–42°) for 2 hr and worked up as described above. The bicarbonate-soluble fraction gave 24.7 g (16.3%) of **4a** boiling at 125° (0.4–0.5 mm) and 10 g of higher boiling [130–180° (0.8 mm)] material which was mostly **4b**. The latter was decarbonylated without purification.

2,2-Dimethyl-4-(2-methyl-3,7-heptanedione)cyclohexane-1,3-dione (6).—A suspension of 8.6 g of 56% sodium hydride mineral oil in 150 ml of benzene containing 40 g of diethyl carbonate was heated to 90°, to which a solution of 14.6 g of 2,2-dimethylcyclohexane-1,3-dione[5] in 100 ml of benzene was added during 1 hr. The mixture was stirred at 85–90° for an additional 1.5 hr, cooled, neutralized with 15 ml of acetic acid, decomposed with 150 ml of water, and extracted with ether. The ethereal extract was washed with bicarbonate solution, dried on sodium sulfate, and concentrated to an oily residue, which was distilled through a 20-cm column, giving 11.0 g (80%) of **6**: bp 168–170° (0.5 mm); uv max (MeOH) 288 mμ (ε 8480); ir ($CHCl_3$) 1720 (ketones), 1560–1640 cm^{-1} (enolic β-diketone); nmr ($CDCl_3$) τ 8.91 (d, 6, J = 7 Hz), 8.67 (s, 6), 7.40 (s, 4, H-5 and -6, this peak was transformed to m in pyridine), 1.96 (s, 1, enolic H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.62. Found: C, 68.85; H, 8.93.

2,2-Dimethyl-4-carbethoxycyclohexane-1,3-dione (5).—**4a** (15 g) was distilled in the presence of 0.5 g of soft glass powder and a trace (less than 1 mg) of iron powder at a bath temperature of 180°. The fraction (7.4 g) boiling at 135–145° (12 mm) was redistilled through a 20-cm column, giving pure **5**: bp 93° (0.5 mm); uv max (MeOH) 254.5 mμ (ε 9340); ir ($CHCl_3$) 1723 (ketone), 1653 (ester), 1613 cm^{-1} (enolic C=C); nmr ($CDCl_3$) τ 8.65 (s, 6), 7.43 (s, 4, H-5 and -6), −2.6 (s, 1, enolic H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.50; H, 7.76.

2,2-Dimethyl-4,6-dicarbethoxycyclohexane-1,3-dione (7).—The higher boiling fraction (**4b**) obtained in the preparation of **4a** was distilled in the presence of soft glass powder. The distillate, containing long needles, was filtered and the crystals were purified by recrystallization from cyclohexane and sublimation at 100° (0.05 mm) to give **7**: mp 159–161°; uv max (MeOH) 242 mμ (ε 18,480); ir ($CHCl_3$) 2560–3570 (broad, enolic OH), 1681, 1652, 1612, 1241 cm^{-1} (strongest band); nmr ($CDCl_3$) τ 8.65 (t, 6, J = 7.5 Hz), 8.53 (s, 6), 6.94 (s, 2, H-4), 5.69 (q, 4, J = 7.5 Hz), −2.6 (s, 2, enolic H).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.07; H, 7.26.

Ethyl 7-Methoxycoumarin-4-acetate (9a).—A solution of 3.7 g of resorcinol monomethyl ether, 6.0 g of diethyl acetonedicarboxylate, and 4.2 g of boron trifluoride etherate in 30 ml of benzene was refluxed for 3 hr under continuous water separation. Most of the water (totally 0.5 ml) was separated during the first 1 hr. The reaction mixture was poured into bicarbonate solution, stirred for 2 hr, and extracted with additional benzene. The benzene extract was washed with water, dried over sodium sulfate, and concentrated. Crystallization of the residue from 25 ml of benzene–cyclohexane (1:1) yielded 4.3 g (55%) of **9a**: mp 101.5–103° (lit.[8] mp 101.5–103°); uv max (MeOH) 220 mμ (ε 17,400), 323.5 (14,130).

Ethyl 7-Methoxycoumarin-4-(2-isobutyrate) (9b).—A solution of 7.4 g of resorcinol monomethyl ether, 8.7 g of diethyl 2,2-dimethyl-3-ketoglutarate,[28,29] and 4.2 g of boron trifluoride etherate in 30 ml of benzene was refluxed for 16 hr under continuous water separation. Totally 0.6 ml of water was separated. The reaction mixture was poured into bicarbonate solution, stirred for 2 hr, and extracted with benzene. The benzene solution was washed with 2% aqueous potassium hydroxide, washed with water, dried over sodium sulfate, and concentrated. The material remaining was recrystallized from benzene–cyclohexane (1:1) to give 1.0 g (11%) of **9b**: mp 171.5°; uv max (MeOH) 220 mμ (ε 19,250), 322 (13,600); ir ($CHCl_3$) 1725 (broad), 1616 cm^{-1}; nmr ($CDCl_3$) τ 8.37 (s, 6, gem dimethyl), 6.13 (s, 3, methoxy), 3.69 (s, 1, H-3).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.01; H, 6.17.

Diethyl 2,2-Dimethyl-3-oxo-4-carbethoxyheptane-1,7-dioate (11b).—To a solution of 3 g of potassium *tert*-butoxide in 18 ml of ethanol was added 92 g of diethyl 2,2-dimethyl-3-ketoglutarate,[28,29] and the solution was heated to 85°. Ethyl acrylate (40 g) was then added and the mixture was stirred at 85–90° for 4 hr. After cooling, the reaction mixture was poured into iced dilute sulfuric acid and extracted with ether. The ethereal extract was washed with bicarbonate solution, dried over sodium sulfate, concentrated, and distilled, giving 106 g (80%) of **11b**: bp 131–132° (0.2 mm); ir ($CHCl_3$) 1721–1755 cm^{-1} (C=O, broad); nmr ($CDCl_3$) τ 8.58 (s, 3), 8.55 (s, 3).

Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.37; H, 7.96.

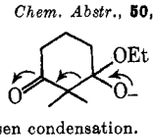
Ethyl 7-Methoxy-4-methylcoumarin-3-propionate (12b). A.—To a solution of 300 g of ethyl 7-hydroxy-4-methylcoumarin-3-propionate (**12a**)[10] and 425 g of methyl iodide in 1 l. of acetone was added 240 g of potassium carbonate and the mixture was stirred under reflux for 3.5 hr. An additional 280 g of potassium carbonate and 240 g of methyl iodide were added and the mixture was refluxed for another 4 hr. The reaction mixture was filtered to remove inorganic substances and the filtrate was concentrated and then dissolved in ether. The ethereal solution was washed with aqueous alkali, washed with water, dried over potassium carbonate, and concentrated to 500 ml. Colorless needles were collected and washed with ether, giving 282.7 g of **12b**, mp 74–75.5°. The second crop (25.8 g, mp 72–73.5°) was obtained on concentration of the mother liquor. Occasionally, the product did not crystallize, in which case it could be distilled to give colorless oil, bp 195–197° (0.08 mm). The oily material showed identical spectral data with the crystalline one and crystallized upon seeding: uv max (MeOH) 322 mμ (ε 17,820); ir ($CHCl_3$) 1711 (broad), 1610 cm^{-1} (C=C); nmr ($CDCl_3$) τ 7.58 (s, 3, CMe), 7.23 (AB type m, 4, methylenes), 6.14 (s, 3, OMe).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.38; H, 6.09.

B.—A solution of 3.7 g of resorcinol monomethyl ether, 6.9 g of diethyl α-acetoglutarate, and 4.2 g of boron trifluoride etherate in 40 ml of benzene was refluxed for 9 hr under continuous water separation. The reaction mixture was worked up in the usual manner (see preparation **9b**) to give 3.5 g (41%) of **12b**, bp 205–210° (0.5 mm). This product crystallized upon seeding and exhibited identical spectra with the specimen prepared by procedure A.

2-(2-Hydroxy-4-methoxyphenyl)-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2a).—To a solution of 100 g of **12b** in 400 ml of dimethyl sulfoxide was added 15 g of 56% sodium hydride mineral oil and the solution was stirred for 2 hr without external heating. The dark brown solution was neutralized with 25 ml of acetic acid and decomposed with 500 ml of water to produce a voluminous precipitate. The crystals were filtered with suction, then washed with water followed by ether. The yellowish needles (67.4 g, 80.2%), mp 222–224°, were recrystal-

(27) S. Eskola, A. Auvienen, A. Hirvines, T. Rinne, and R. Waris, *Suom. Kemistilehti*, **27B**, 88 (1954); *Chem. Abstr.*, **50**, 5559 (1956). Undoubtedly



formed by the reversed Claisen condensation.

(28) W. H. Perkin, Jr., and A. E. Smith, *J. Chem. Soc.*, **83** 12 (1903).

(29) L. I. Smith and W. W. Prichard, *J. Org. Chem.*, **4**, 348 (1939).

lized from 1 l. of dioxane giving 51.8 g of **2a**: mp 228.5°; uv max (MeOH) 319 mμ (ε 16,240); ir ($CHCl_3$) 1720 (C=O), 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.75; H, 4.69.

2-(2-Hydroxy-4-methoxyphenyl)-3-methyl-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2b).—To a solution of 26.3 g of **2a** and 13.5 g of potassium *tert*-butoxide in 250 ml of dimethyl sulfoxide and 60 ml of *tert*-butyl alcohol was added 100 ml of methyl iodide. The solution was heated to gentle reflux for 15 min, evacuated to remove excess methyl iodide, poured into 500 ml of ice–water, and refrigerated overnight. Yellow crystals were collected, washed with water, triturated with 250 ml of acetone, and filtered to remove 3.8 g of recovered starting material. The acetone filtrate was concentrated and the residue was recrystallized from methanol to give 17.1 g of pale yellow **2b**: mp 135°; uv max (MeOH) 322 mμ (ε 15,000); ir ($CHCl_3$) 1720 (C=O), 1614 cm^{-1} (C=C); nmr ($CDCl_3$) τ 8.50 (d, 3, J = 7.5 Hz, *C*-Me), 6.30 (q, 1, J = 7.5 Hz), 6.11 (s, 3, OMe).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.54; H, 5.54.

Upon heating the methanol solution, this material was partially converted into the dimethyl ketal: mp 159° (recrystallized from acetone); uv max (MeOH) 319.5 mμ (ε 16,430); ir ($CHCl_3$) 1712, 1611 cm^{-1}; nmr ($CDCl_3$) τ 8.72 (d, 3, J = 7.5 Hz, *C*-Me), 6.76 (s, 3, acetal OMe), 6.65 (s, 3, acetal OMe), 6.13 (s, 3, phenolic OMe).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; OMe, 30.60. Found: C, 67.14; H, 6.61; OMe, 29.89.

2-(2-Hydroxy-4-methoxyphenyl)-3,3-dimethyl-4-oxo-1-cyclohexene-1-carboxylic Acid Lactone (2c), 13, 14a, and 14b.—To a solution of 5.2 g of **2b** in 70 ml of dimethyl sulfoxide was added 2.4 g of potassium *tert*-butoxide and the mixture was stirred for 15 min to dissolve the starting material. A mixture of 15 ml of *tert*-butyl alcohol and 20 ml of methyl iodide was added. The resulting solution was stirred for 30 min at room temperature, heated to gentle reflux for 20 min, cooled, poured into ice water, and finally extracted with ether. The ethereal extract was washed twice with 3% potassium hydroxide solution, washed with water, and dried over potassium carbonate. After evaporation of the solvent, recrystallization of the residue from chloroform–ether gave 1.9 g of **2c**: mp 186.5–188°; uv max (MeOH) 321 mμ (ε 15,000) ir ($CHCl_3$) 1723, 1626, 1610 cm^{-1}; nmr ($CDCl_3$) τ 8.27 (s, 6, gem dimethyl), 7.14 (m, 4, methylenes), 6.12 (s, 3, OMe).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.40; H, 5.82.

The mother liquor (2.5 g) was adsorbed on 175 g of silica gel, washed with benzene, and eluted with 5% ethyl acetate–benzene and then with 10% ethyl acetate–benzene. The 5% ethyl acetate fractions gave successively **14a**, **13**, and **2c** (0.4 g). The 10% ethyl acetate fractions gave **14b**. Recrystallization from benzene–cyclohexane afforded pure **14a**: mp 189°; uv max (MeOH) 260, 287, 299, 325 mμ (ε 53,500, 12,500, 12,500, 6200); ir (KBr) 1741 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; methoxy, 22.96. Found: C, 70.85; H, 5.07; methoxy 22.00.

Recrystallization from benzene afforded pure **13**: mp 156.5°; uv max (MeOH) 229 mμ (ε 18,200), 317 (10,200); ir ($CHCl_3$) 1770 (lactone), 1678 (ketone), 1621 cm^{-1} (C=C); nmr ($CDCl_3$) τ 8.58 (s, 3), 7.91 (s, 3), 6.10 (s, 3).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.98; H, 5.86. Found: C, 70.57; H, 5.92.

Recrystallization from benzene afforded pure **14b**: mp 257.5°; uv max (MeOH) 260.5, 287.5, 299.5, 326 mμ (ε 53,300, 12,500, 12,600, 6830); ir (KBr) 3245 (OH), 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.39; H, 4.74.

7,8,9,10-Tetrahydro-3-methoxyspiro(6*H*-dibenzo[*b*,*d*]pyran-9,2′-[1,3]dioxolan)-6-one (15a).—A suspension of 150 g of **2a** and 1 g of *p*-toluenesulfonic acid in a mixture of 230 ml of ethylene glycol and 1.5 l. of benzene was refluxed for 8 hr under continuous water separation. The reaction mixture was washed with potassium carbonate solution, dried over sodium sulfate, and concentrated at atmospheric pressure to 600 ml. Stout, transparent crystals of mp 145.5° were obtained (130.5 g). The second crop (21.0 g) was obtained upon concentration to 200 ml: uv max (MeOH) 319 mμ (ε 17,300); ir ($CHCl_3$) 1717 (C=O), 1613 cm^{-1} (C=C); nmr ($CDCl_3$) τ 8.07 (t, 2, J = 6.5 Hz, H-8), 7.20 (t, 2, J = 6.5 Hz, H-7), 7.05 (s, 2, H-10), 6.14 (s, 3), 5.92 (s, 4, ethylenedioxy).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.76; H, 5.64.

7,8,9,10-Tetrahydro-3-methoxy-10,10-dimethylspiro(6*H*-dibenzo[*b*,*d*]pyran-9,2′-[1,3]dioxolan)-6-one (15b).—A suspension of 18 g of **2c** and 0.5 of *p*-toluenesulfonic acid in 50 ml of ethylene glycol and 500 ml of benzene was refluxed for 48 hr. Work-up in the usual manner furnished 18.7 g of **15b**: mp 179–180°; uv max (MeOH) 319 mμ (ε 14,600); ir ($CHCl_3$) 1725 (C=O), 1626 cm^{-1} (C=C); nmr ($CDCl_3$) τ 8.42 (s, 6, gem dimethyl), 8.09 (t, 2, J = 6.5 Hz, H-8), 7.25 (t, 2, J = 6.5 Hz, H-7), 6.14 (s, 3), 5.92 (s, 4, ethylene ketal).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.16; H, 6.37.

2-(2-Hydroxy-4-methoxyphenyl)-4-ethylenedioxy-1-cyclohexene-1-methanol (16).—A suspension of 20.0 g of **15a** and 7.0 g of lithium aluminum hydride in 1 l. of ether was refluxed for 12 hr. To the ice-cooled reaction mixture was added, under nitrogen, a solution of 20 ml of 95.5% sulfuric acid and 6 ml of acetic acid in 500 ml of water to decompose excess hydride, and the reaction mixture was extracted with ether. The ethereal extract was washed with water, washed with bicarbonate, dried over sodium sulfate, and concentrated, giving glassy **16** in quantitative yield: uv max (MeOH) 281.5 mμ (ε 2980); ir ($CHCl_3$) 3675 (OH), 3480 (OH), 1628 cm^{-1} (C=C); nmr ($CDCl_3$) τ 6.23 (s, 3, OMe), 6.05 (broad s, 2, $-CH_2O-$), 5.99 (s, 4, methylenedioxy). This material was used in the next step without purification.

6,6a,7,8-Tetrahydro-3-methoxy-9*H*-dibenzo[*b*,*d*]pyran-9-one (17a) and 3-(2-Hydroxy-4-methoxyphenyl)-4-methylene-2-cyclohexen-1-one (21a). A.—The crude diol **16**, prepared from 10 g of **15a**, was dissolved in a mixture of 250 ml of acetic acid, 200 ml of water, and 50 ml of pyridine and refluxed for 29 hr. The reaction mixture was concentrated, diluted with water, and extracted with ether. The ethereal extract was washed successively with water, cold dilute potassium hydroxide solution, and water and dried over sodium sulfate. The alkaline washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate. After removal of the solvent, the neutral fraction was dissolved in the minimum amount of chloroform and crystallized by addition of ether to yield 1.9 g of **17a**: mp 126°; uv max (MeOH) 247.5, 303, 346 mμ (ε 6900, 12,000, 20,100); ir ($CHCl_3$) 1666 (C=O), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) τ 6.27 (q, 1, J = 10.5 and 12 Hz, H-6α), 6.19 (s, 3, OMe), 5.63 (q, 1, J = 10.5 and 5 Hz, H-6β) 2.45 (d, 1, H-1).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.02; H, 6.18.

The phenolic fraction was concentrated and the residue was recrystallized from benzene to give 1.45 g of **21a**: mp 116.5–117.5°; uv max (MeOH) 276 mμ (ε 11,500);[30] ir ($CHCl_3$) 1667 (C=O), 1622 cm^{-1} (C=C); nmr ($CDCl_3$) τ 7.26 (m, 4, A_2B_2 type), 6.21 (s, 3, OMe), 4.80 (broad s, 1, vinylic), 4.53 (broad s, 1, vinylic, 3.81 (s, 1, olefinic).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.13; H, 5.96.

B.—A heterogeneous mixture consisting of **16** (prepared from 26.6 g of **15a**), 750 ml of acetic acid, 600 ml of water, 150 ml of pyrrolidine, and 800 ml of toluene was refluxed for 20 hr. The organic layer was separated. The aqueous layer was refluxed again with 800 ml of fresh toluene for 20 hr. Both toluene solutions were combined, washed successively with water, dilute hydrochloric acid, water, dilute alkali, and water, dried over sodium sulfate, and concentrated, giving 16.7 g (78%) of **17a**.

C.—The dihydroxy compound **16**, prepared from 10 g of **15a**, was dissolved in a mixture of 20 g of potassium hydroxide, 250 ml of acetic acid, and 200 ml of water and refluxed for 30 hr. Work-up in the usual manner gave 1.9 g of **17a** and 1.2 g of **21a**.

Transformation of 21a to 17a.—A solution of 1 g of **21a** and 2 g of pyridine hydrochloride in 30 ml of pyridine was refluxed for 5 hr. The reaction mixture was poured into ice water, and after the usual work-up (see procedure A for preparation of **17a**) gave 0.2 g of **17a**.

A solution of 1 g of **21a** and 3 ml of acetic acid in pyridine was refluxed for 5 hr. Work-up in the usual manner afforded 0.25 g of **17a**.

2-Methyl-3-(2-hydroxy-4-methoxyphenyl)-4-methylene-2-cyclohexen-1-one (21b) and 2-Hydroxy-4-methoxy-2′,6′-dimethyl-3′-hydroxybiphenyl (24).—A suspension of 4.6 g of the dimethyl

(30) The uv maximum is in good accordance with the calculated value assuming that the benzene ring is not coplanar: 215 + 30 + 12 + 18 + 5 = 280.

ketal of **2b** and 2.0 g of lithium aluminum hydride in 400 ml of ether was refluxed for 7 hr, cooled, and decomposed with a solution of 20 ml of 95.5% sulfuric acid and 3 ml of acetic acid in 500 ml of water. The ether extract was washed with water, washed with bicarbonate solution, dried over sodium sulfate, and concentrated to a colorless glass. The glass was dissolved in a mixture of 250 ml of acetic acid, 200 ml of water, and 20 g of potassium hydroxide and refluxed for 45 hr. The reaction mixture was worked up in the usual manner (see experiment for **17a** and **21a**). The neutral fraction contained only a trace of material and gave no hypothetical compound **17b**. The phenolic fraction (3.4 g) was chromatographed on 272 g of silica gel starting with benzene and continuing with increasing amounts of ethyl acetate. The biphenyl product was eluted quickly with 10% ethyl acetate–benzene and recrystallized from chloroform–benzene to give 86 mg of **24**: mp 126.5°; uv max (MeOH) 281.5 mμ (ε 6100); ir ($CHCl_3$) 3635 (OH), 3570 cm^{-1} (OH); nmr ($CDCl_3$) τ 8.03 (s, 6, CMe), 6.17 (s, 3, OMe).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.84; H, 6.57.

The ketonic substance was eluted slowly with the same solvent and recrystallized from benzene to afford 703 mg of **21b**: mp 142.5–144°; uv max (MeOH) 280 mμ (ε 14,400); ir ($CHCl_3$) 3595 (OH), 3340 (OH), 1680 (C=O), 1630 (C=C), 915 cm^{-1} (C=CH_2); nmr ($CDCl_3$) τ 8.29 (s, 3, *C*-Me), 7.25 (m, 4, A_2B_2 type), 6.18 (s, 3, OMe), 5.10 (broad s, 1, vinylic), 4.70 (broad s, 1, vinylic).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.57; H, 6.56.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-6*H*-dibenzo[*b*,*d*]pyran-9-one (22a).—To a suspension of 2.3 g of **17a** in 100 ml of ether and 250 ml of ammonia was added 0.5 g of lithium wire. The mixture was stirred under reflux for 1 hr, cooled with Dry Ice–acetone, decomposed with 6 g of ammonium chloride (added in one portion), and set aside to evaporate ammonia. The residue was taken up in ether, and the solution was washed thoroughly with water, dried over sodium sulfate, and concentrated. Recrystallization of the residue from chloroform–ether separated 1.7 g of **22a**: mp 129–130.5°; uv max (MeOH) 281.5 mμ (ε 3160), 287.5 mμ (ε 2720); ir ($CHCl_3$) 1721 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.93 (q, 1, $J_{6a,10a}$ = 12.5, $J_{10a,10\beta}$ = 3 Hz, $J_{10a,10\alpha}$ = small, benzylic H-10a), 6.24 (s, 3, OMe), 6.20 (t, 1, J = 10.5 Hz, H-6α), 5.67 (q, 1, $J_{6\alpha,6\beta}$ = 10.5, $J_{6\beta,6a}$ = 3.5 Hz, H-6β), 3.04 (d, 1, H-1).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.18; H, 6.86.

6a,7,8,9,10a-Hexahydro-3-methoxy-6*H*-dibenzo[*b*,*d*]pyran-9-ol (23). A.—The reaction conditions were the same as for **22a** (see above) except that the ammonium chloride was added portionwise. The residue was recrystallized from chloroform–ether, giving **23**: mp 104–105;[31] uv max (MeOH) 281.5 mμ (ε 2940), 287.5 (2730); ir ($CHCl_3$) 3700 (OH), 3532 cm^{-1} (OH); nmr ($CDCl_3$) τ 6.28 (m, 1, H-9), 6.28 (t, 1, J = 10.5 Hz, H-6α), 6.26 (s, 3, OMe), 5.80 (q, 1, J = 10 and 3.5 Hz, H-6β), 2.96 (broad d, 1, J = 8.5 Hz, H-1).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.70; H, 7.84.

B.—The identical substance was obtained by sodium borohydride reduction of **22a** in methanol.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-10-methyl-6*H*-dibenzo-[*b*,*d*]pyran-9-one (18). A. Reductive Methylation of 17a.—To a suspension of 13.8 g of **17a** in 200 ml of ether and 300 ml of ammonia was added 1 g of lithium wire. After 25 min at reflux temperature the blue color disappeared. A piece of lithium was added and the mixture was stirred for 20 min (still blue), cooled with a Dry Ice–acetone bath, and treated with 20 ml of methyl iodide. The cooling bath was removed, and the mixture was stirred for 4 hr under reflux, set aside overnight to evaporate ammonia, and then taken up with ether. The ethereal extract was treated with potassium hydroxide solution, water, and 5% hydrochloric acid, and filtered to remove the precipitate. The filtrate was washed with water, dried over potassium carbonate, and concentrated at atmospheric pressure to about 15 ml. Colorless needles (5.4–7 g) of mp 92° were obtained which were used for the next step without further purification. Pure **18** was obtained by recrystallization from chloroform–ether: mp 95°; uv max (MeOH) 282.5 mμ (ε 3040), 288 (2790); ir ($CHCl_3$) 1712 cm^{-1} (C=O); nmr ($CDCl_3$) τ 9.00 (d, 3, J = 7 Hz, Me-10β), 6.27 (t, 1, J = 10.5 Hz, H-6α), 6.23 (s, 3, OMe), 5.70 (q, 1, J = 10.5 and 3.5 Hz, H-6β), 3.07 (d, 1, H-1).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.88; H, 7.30.

B. Recovery from 19a.—A solution of 300 mg of **19a** in 50 ml of 20% aqueous sodium carbonate was refluxed for 2 hr, cooled, and extracted with ether. After evaporation the residue was recrystallized from ether to afford 200 mg of **18**, mp 93°. The mixture melting point with an authentic sample was 93–94°.

Fragmentation and Equilibrium of 18.—When 300 mg of **18** in a mixture of 25 ml of diethylene glycol and 25 ml of 25% potassium hydroxide solution was refluxed for 7 hr, the majority of the material was transformed into phenolic substances, presumably owing to fragmentation (see **25**).

A suspension of 300 mg of **18** in 50 ml of 20% sodium carbonate was refluxed for 24 hr. The oil crystallized (mp 85°, mixture melting point with the starting material 93°) on cooling and was recrystallized from chloroform–ether to give the pure starting material, mp 95°.

A suspension of 1 g of **18** in 100 ml of 10% hydrochloric acid was refluxed for 30 min. The starting material was recovered unchanged.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-6*H*-dibenzo[*b*,*d*]pyran-9-one (22b).—To a solution of 2.3 g of **22a** and 2.0 g of ethyl formate in 30 ml of benzene was added 2.3 g of potassium *tert*-butoxide. The mixture was stirred at room temperature under nitrogen for 5 hr, set aside overnight, and decomposed with ice water. The aqueous layer was washed with ether, acidified with hydrochloric acid to pH 3, and refrigerated. The crystals were collected, washed with water, dried, and recrystallized from benzene to give 2.3 g of **22b**: mp 156–156.5°; uv max (MeOH) 289 mμ (ε 9300), 313 (14,300); ir ($CHCl_3$) 2855 (broad, OH), 1656 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.23 (s, 3, OMe), 6.20 (t, 1, J = 10.5 Hz, H-6α), 5.67 (q, 1, J = 10.5 and 3 Hz, H-6β), 2.96 (d, 1, J = 8.5 Hz, H-1), 1.22 (s, 1, H-8a).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.43; H, 6.23.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-10-methyl-6*H*-dibenz[*b*,*d*]pyran-9-one (19a).—This substance was prepared in the usual manner (see preparation of **22b**) and recrystallized from benzene–cyclohexane: mp 126°; uv max (MeOH) 282.5 mμ (ε 11,200), 288.5 (11,100); ir ($CHCl_3$) 2775 (broad, OH), 1646 cm^{-1} (broad, C=O); nmr ($CDCl_3$) τ 9.00 (d, 3, J = 7 Hz, Me-10β), 6.27 (t, 1, J = 10.5 Hz, H-6α), 6.22 (s, 3, OMe), 5.69 (q, 1, J = 10.5 and 3 Hz, H-6β), 3.00 d, 1, J = 8.5 Hz, H-1), 1.32 (s, 1, H-8a).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.13; H, 6.62.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-*n*-butylthiomethylene-6*H*-dibenzo[*b*,*d*]pyran-9-one (22c).—A solution of 2.6 g of **22b**, 1.1 g of *n*-butylmercaptan, and 40 mg of *p*-toluenesulfonic acid in 40 ml of benzene was refluxed for 2 hr under continuous water separation. The reaction mixture was diluted with benzene, washed with bicarbonate and then with salt solution, dried over sodium sulfate, and concentrated. The residue was recrystallized from benzene–cyclohexane to yield 2.6 g of **22c**: mp 142.5–143°; uv max (MeOH) 312 mμ (ε 19,000); ir ($CHCl_3$) 1664 (C=O), 1546 cm^{-1} (C=C); nmr ($CDCl_3$) τ 9.05 (t, 3, J = 6 Hz, CMe), 6.24 (s, 3, OMe), 6.19 (t, 1, J = 10 Hz, H-6α), 5.63 (q, 1, J = 10.5 and 3 Hz, H-6β), 2.96 (d, 1, J = 8.5 Hz, H-1), 2.20 (m, 1, $W_{1/2}$ = 4.5 Hz, H-8a).

Anal. Calcd for $C_{19}H_{24}SO_3$: C, 68.64; H, 7.28; S, 9.64. Found: C, 68.47; H, 7.24; S, 9.77.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-isopropyloxymethylene-10-methyl-6*H*-dibenzo[*b*,*d*]pyran-9-one (19b).—A mixture of 2.7 g of **19a**, 2.7 g of potassium carbonate, and 3.4 g of 2-iodopropane in 50 ml of methyl ethyl ketone was refluxed for 6 hr. After cooling, ice water was added, and the mixture was extracted with ether. The ethereal extract was washed twice with cold potassium hydroxide solution, washed with water, dried over potassium carbonate, and concentrated under nitrogen. The material which remained was crystallized from cyclohexane–Skelly A to give 2.3 g of **19b**: mp 135°; uv max (MeOH) 281.5 mμ (ε 18,900); ir ($CHCl_3$) 1670 (C=O), 1582 cm^{-1} (C=C); nmr ($CDCl_3$) τ 9.07 (d, 3, J = 7 Hz, Me-10β), 8.67 (d, 6, J = 6 Hz, isopropyl), 6.28 (t, 1, J = 10 Hz, H-6α), 6.25 (s, 3 OMe), 5.80 (m, 1, H-6β, overlapped with OC**H**Me_2), 3.04 (d, 1, J = 8 Hz, H-1), 2.47 (t, 1, J = 1.5 Hz, H-8a).

(31) Some preparations melted at 118.5°. The mixture melting point of 105 and 118.5° specimens was 118.5°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.05; H, 7.71.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-8-hydroxymethylene-10,10-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-one (20). A.—This entire operation was carried out under a nitrogen stream. To 250 ml of ammonia containing a few pieces of ferric nitrate was added 10 g of potassium in several portions. After the blue color disappeared, the reflux condenser (Dry Ice–acetone) was removed and 250 ml of anhydrous ether was added to the ammonia solution with vigorous stirring. The bulk of the ammonia was evaporated on an acetone–water bath (0–25°) under continuous stirring. More anhydrous ether (250 ml) was added to the potassium amide suspension and a slow stream of nitrogen was bubbled overnight through the suspension to remove traces of ammonia. The volume of the suspension was then adjusted to 500 ml with anhydrous ether (about 250 ml was needed). To the cool (0–5°) and vigorously stirred potassium amide suspension was added a solution of 20 g of **19b** in 125 ml of dioxane and a rapid stream of nitrogen was passed through to remove ammonia as soon as it was formed. The mixture was warmed and stirred vigorously at 22–25° for 20 min. The deep red solution was cooled to 0° and 145 g of methyl iodide was added during 5 min. The reaction mixture was stirred at 0–5° for 30 min and then at room temperature for 3 hr, while a moderate stream of nitrogen was being introduced to evaporate methylamine as soon as it was formed. The reaction mixture was cooled, decomposed with 250 ml of water, and filtered to remove a yellow, crystalline substance (1.5 g) and the filtrate was taken up in ether. The ethereal extract was washed with cold dilute hydrochloric acid, washed with 2% salt solution, dried over sodium sulfate, and concentrated, and the residue was dissolved in a mixture of 75 ml of water and 250 ml of tetrahydrofuran. This solution was acidified with concentrated hydrochloric acid, set aside for 24 hr, poured into cold water, and extracted with ether. The ethereal solution was washed with iced 2% potassium hydroxide, followed by 2% salt solution, and dried over sodium sulfate. The cold alkaline washing was acidified and extracted with ether. The ether extract was washed with 2% salt solution, dried over sodium sulfate, and concentrated. The product which remained was recrystallized from ethyl acetate to give 9.55 g (52%) of **20**: mp 155°; uv max (MeOH) 288.5 mμ (ε 10,500); ir ($CHCl_3$) 1621, 1584, 1511 cm^{-1}; nmr ($CDCl_3$) τ 8.98 (s, 3, Me-10β), 8.29 (s, 3, Me-10α), 7.21 (m, 1, H-10a), 6.32 (t, 1, J = 10.5 Hz, H-6α), 6.24 (s, 3, OMe), 5.77 (q, 1, J = 10 and 2.5 Hz, H-6β), 2.55 (d, 1, H-1), 1.27 (d, 1, J = 3 Hz, H-8a).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.62; H, 6.91.

The yellow crystalline product which separated from the original reaction mixture was repeatedly recrystallized from warm chloroform–dioxane to give **26**: mp 287° dec; uv max (MeOH) 281.5 mμ (ε 8900), 384 (46,000); ir ($CHCl_3$) 1667, 1642, 1617, 1573, 1505 cm^{-1}, nmr ($CDCl_3$) τ 9.09 (s, 3, Me-10β), 9.04 (s, 3, Me-10β), 8.42 (s, 3, Me-10α), 8.32 s, 3, Me-10α), 6.21 (s, 6, OMe).

Anal. Calcd for $C_{34}H_{39}O_6N$: C, 73.22; H, 7.05; N, 2.51. Found: C, 73.16; H, 7.20; N, 2.57.

The neutral fraction was adsorbed on SilicAR CC-7 and the column was eluted with benzene. The earlier fractions contained complex mixtures of trimethylated compounds which were not fully characterized. Further elution with benzene produced a crystalline product which was triturated with cold ether and then recrystallized from benzene–hexane to afford colorless crystals of **27**: mp 122–123°; ir ($CHCl_3$) 1714, 1622, 1581, 1509, 1168 cm^{-1}; uv max (MeOH) 282, 288 mμ (ε 3300, 2980); nmr ($CDCl_3$) τ 3.08 (d, 1, J = 8 Hz), 6.25 (s, 3), 8.90 (d, 2, J = 6.5 Hz), 9.00 (d, 2, J = 7 Hz).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.74.

6a,7,8,9,10,10a-Hexahydro-3-methoxy-10,10-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-one (3). A.—A solution of 2.5 g of **20** in 250 ml of 20% aqueous sodium carbonate was refluxed for 2 hr, cooled, and extracted with ether. The ethereal extract was dried over sodium sulfate and concentrated and the residual material was recrystallized from chloroform–ether to deposit 2.1 g of **3**: mp 94°; uv max (MeOH) 282 mμ (3490), 288 (3120); ir ($CHCl_3$) 1719 cm^{-1} (C=O); nmr ($CDCl_3$) τ 9.05 (s, 3, Me-10β), 8.45 (s, 3, Me-10α), 7.05 (d, 1, J = 11 Hz, H-10a), 6.37 (t, 1, J = 10.5 Hz, H-6α), 6.25 (s, 3, OMe), 5.83 (q, 1, J = 10.5 and 3.5 Hz, H-6β), 2.62 (d, 1, J = 10 Hz, H-1).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.99.

B.—A suspension of 9.7 g of crude **26** in 200 ml of toluene and 200 ml of 10% hydrochloric acid was refluxed for 24 hr. The toluene layer was washed and separated into enolic and neutral fractions in the usual manner. The enolic fraction gave 4.0 g of **20**, mp 147.5–150°. The neutral fraction (3.2 g) was chromatographed to give 1.5 g of **3**.

3-(2-Hydroxy-4-methoxyphenyl)-4-hydroxymethyl-1-cyclohexanone Hemiketal (28a).—To a suspension of 5.8 g of **15a** in 350 ml of distilled ammonia was added 1.0 g of lithium wire. After stirring under reflux for 3 hr the reaction mixture was cooled with Dry Ice–acetone and 12 g of ammonium chloride (or 38 ml of ethanol) was added. After evaporation of ammonia the residue was taken up with ether, washed with water, and extracted with dilute potassium hydroxide solution. The alkaline washing was acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed, dried over sodium sulfate, and concentrated. The product (3.0 g of colorless glass) was chromatographed on 200 g of silica gel using benzene with increasing amounts of ethyl acetate. The major fraction was eluted with 30% ethyl acetate to give 1.5 g of **28a**: ir ($CHCl_3$) 3635 (OH), 3580 (OH), 3425 cm^{-1} (OH); nmr ($CDCl_3$) τ 6.80 (m, 1, $W_{1/2}$ = 12 Hz, benzylic H), 6.65 (d, 2, J = 7.5 Hz, $-CH_2O-$), 6.27 (s, 3, OMe).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.20; H, 7.60.

3-(2-Hydroxy-4-methoxyphenyl)-4-acetoxymethyl-1-cyclohexanone Hemiketal (28b).—A solution of 13.2 g of **28a** in a mixture of 100 ml of acetic acid, 80 ml of water, and 20 ml of pyridine was refluxed for 45 hr, cooled, and extracted with ether. The ethereal extract was washed successively with water, dilute hydrochloride acid, water, and bicarbonate solution, and dried over potassium carbonate. Concentration of the dried extract gave 4.4 g of crystalline substance which was recrystallized from benzene to afford **28b**: mp 113–113.5°; uv max (MeOH) 281 mμ (ε 3360), 287 mμ (ε 3100); ir ($CHCl_3$) 3480 (OH), 3445 (OH), 1735 cm^{-1} (ester); nmr ($CDCl_3$) τ 7.90 (s, 3, acetyl), 6.24 (s, 3, OMe), 6.88 (m, 1, $W_{1/2}$ = 11 Hz).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.46; H, 6.99.

2,2-Dimethyl-3-(2-hydroxy-4-methoxyphenyl)-4-hydroxymethyl-1-cyclohexanone Hemiketal (28c).—A suspension of 3.2 g of **15b** in 350 ml of ammonia was reduced with 2 g of lithium and worked up as described for **28a**. The product gave a major spot on tlc (silica gel, ethyl acetate) accompanied by two minor spots. Purification of this material was not attempted. However, spectral similarity to **28a** led to the tentative structure **28c**: uv max (MeOH) 281 mμ (ε 3970), 287 (3650); ir ($CHCl_3$) 3650 (OH), 3280 cm^{-1} (OH); nmr ($CDCl_3$) τ 9.08 (s, 3, CMe), 8.72 (s, 3, CMe), 7.29 (d, 1, J = 2.5 Hz, benzylic H), 6.67 (d, 2, J = 7 Hz, $-CH_2O-$), 6.23 (s, 3, OMe).

2-(2-Hydroxy-4-methoxyphenyl)cyclohexane-1-methanol (30a). A.—A suspension of 5.8 g of **15a** in 300 ml of ether and 400 ml of undistilled ammonia was reduced with 3.0 g of lithium, then treated with 33 ml of ethanol and worked up as described for **28a**. The phenolic fraction (5.6 g) gave rise to a crystalline mass which was triturated with 50% methanol, filtered, and recrystallized from acetone–benzene to yield 1.4 g of **30a**: mp 140–141.5°; uv max (MeOH) 280.5 mμ (ε 2920), 286.5 (2480); ir ($CHCl_3$) 3650 (OH), 3300 cm^{-1} (OH); nmr (DMSO-d_6) τ 6.52 (s, 3, OMe).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.37.

B.—A solution of 0.8 g of **28b** and 1.0 ml of hydrazine hydrate in 30 ml of diethylene glycol was set aside for 2 days, then heated to 180–190° in the presence of 1.5 g of potassium hydroxide for 3 hr. The reaction mixture was poured into 500 ml of water, acidified with hydrochloric acid, and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated. The residue was recrystallized from acetone–benzene to give 0.5 g of **30a**, mp 142–143° (no depression upon admixture with **30a** obtained by procedure A).

C.—Hemiketal (**28a**) was reduced in an analogous manner to give **30a**, mp 142–143°.

2-(2-Acetoxy-4-methoxyphenyl)cyclohexane-1-methanol Acetate (30b).—The dihydroxy compound **30a** was acetylated with acetic anhydride and pyridine in the usual manner to obtain **30b**: mp 71°; ir ($CHCl_3$) 1766 (aromatic acetoxy), 1736 cm^{-1} (aliphatic acetoxy); nmr ($CDCl_3$) τ 8.13 (s, 3, acetoxy), 7.68 (s, 3,

acetoxy), 7.68 (s, 3, acetoxy), 6.23 (q, 1, J = 11 and 9 Hz, one of $-CH_2O-$), 5.95 (q, 1, J = 11 and 5.5 Hz, one of $-CH_2O-$).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.36; H, 7.40.

Registry No.—**1a**, 2618-41-9; **2a**, 31582-01-1; **2b**, 32632-37-4; **2b** dimethyl ketal, 32632-38-5; **2c**, 31582-04-4; **3**,32632-40-9; **4a**,32670-67-0; **5**,32670-68-1; **6**, 32632-41-0; **7**, 32632-42-1; **9a**, 32632-43-2; **9b**, 32632-44-3; **11b**, 32632-45-4; **12b**, 31582-00-0; **13**, 32670-69-2; **14a**, 32632-47-6; **14b**, 32632-48-7; **15a**, 31582-08-8; **15b**, 31582-09-9; **16**, 32632-51-2; **17a**, 32632-52-3; **18**, 32632-53-4; **19a**, 32632-54-5; **19b**, 32632-55-6; **20**, 32632-56-7; **21a**, 31582-11-3; **21b**, 32632-58-9; **22a**, 32632-59-0; **22b**, 32632-60-3; **22c**, 32632-61-4; **23**, 32632-62-5; **24**, 32632-63-6; **26**, 32632-64-7; **27**, 32632-65-8; **28a**, 32632-66-9; **28b**, 32670-70-5; **28c**, 32632-67-0; **30a**, 32632-68-1; **30b**, 32632-69-2.

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Mirestrol. II.[1] A Synthesis of a New Tricyclic System

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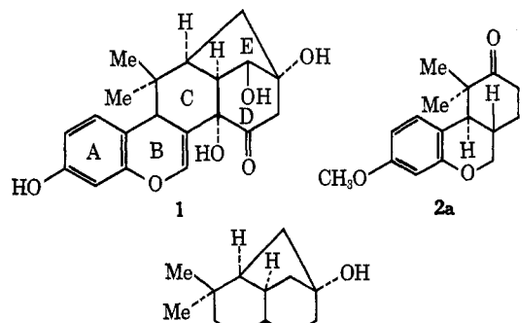
As a model experiment to construct the C,D,E ring system of mirestrol (**1**), the unequivocal synthesis of (±)-2β,4β-ethano-4,5,6,7,8α,9α-hexahydro-7,7-dimethylindan-2α-ol-11-one (**2b**) from 2,2-dimethylcyclohexanone is described in Schemes I and II. This sequence involved elaboration of the starting material to the γ-keto ester **4b**, followed by introduction of an acetonyl side chain to obtain **6b**. The latter underwent an aldol condensation to the unsaturated bicyclic keto acid **7**, which was reduced catalytically to the *cis*-hydrindanone **18a**. Conversion of **18a** to the diketone **23a** and the subsequent intramolecular aldol ring closure gave the desired ketol **2b**.

As a part of our effort to synthesize mirestrol (**1**)[2] and related substances from the tricyclic ketone **2a**,[1] we explored an unambiguous synthesis of the new tricyclic ring system incorporated in the C,D,E rings of the natural product. To determine the feasibility of constructing such a ring system, we chose to convert a



1

2a

2b

simple analog of compound **2a** into the ketol **2b**, and the successful synthesis of the latter compound is the subject of this paper. Although all synthetic compounds containing a chiral carbon atom are racemic, only one enantiomer is depicted for convenience.

2,2-Dimethylcyclohexanone, an obvious model for **2a**, was transformed by conventional methods (see Scheme I) into 6,6-dimethylcyclohexanone-3-carboxylic acid (**4a**), which was identical with the authentic specimen[3] prepared from camphoric anhydride by a series of known procedures.[3a]

Our next objective, the formation of the five-membered ring, was initiated by alkylation of the methyl ester **4b** with methallyl iodide[4] in the presence of potassium *tert*-butoxide to afford a mixture of *trans*- and *cis*-2-methallyl-3-carbomethoxy-6,6-dimethylcyclohexanone (**5**) (see also **8a** and **9a**) in about a 3:1 ratio. Since further treatment of this mixture with sodium methoxide in refluxing methanol did not significantly alter the ratio of the isomers, the major product (lower boiling[5]) was suspected to be the more stable trans compound **8a**. This assumption was supported by conformational analysis, which indicated that **9a** is 0.55 kcal[6] less stable than **8a**. The mixture **5** was partially separated by distillation and more effective purification was achieved by preparative thin layer chromatography (see Experimental Section). The nmr spectrum of the more abundant isomer possessed a broad multiplet at τ 6.83 representing the hydrogen attached to C-2; the observed half-height width of 22 Hz is consistent with a diaxial coupling of H-2 and H-3, and the major epimer was designated trans as in **8a**. The cis isomer **9a** was obtained as a low-melting solid whose nmr displayed a

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(6) The conformational energy (1.1 kcal) of the axial carbomethoxy group was divided by two. See E. L. Eliel, N. L. Allinger, J. S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 441.