Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.12; H, 8.56.

2-(*cis,cis*-2,6-Dihydroxycyclohexyl)propenoic Acid Lactone (14). A solution of lactone **13** (240 mg, 1.0 mmol) in 4.0 ml of dry THF was added slowly over a period of 1 hr to a cooled (−78°) solution of LDA under nitrogen. LDA was prepared from diisopropylamine (131 mg, 1.30 mmol) and *n*-butyllithium (0.81 ml of 1.6 *M* solution in hexane) in THF (3.5 ml) cooled to −78°. After enolate formation was complete, the reaction mixture was warmed to −30° and formaldehyde was passed into the reaction vessel via a stream of nitrogen (flow rate 200 ml/min) by heating paraformaldehyde (450 mg, 15.0 mmol) at 155° until depolymerization was complete. Stirring was continued for an additional 1.5 hr. The reaction was quenched by the addition of saturated aqueous ammonium chloride. The solvent was removed under reduced pressure on a rotary evaporator and the remaining residue was dissolved in methylene chloride (40 ml). The organic solution was washed with water and saturated brine. Evaporation of the solvent in vacuo gave an oil (381 mg) which was chromatographed on silica gel (13 g). Benzene–ether (15:1) eluted pure hydroxymethylated lactone (200 mg, 74%). In addition 30 mg of starting lactone was recovered.

A solution of the above pure hydroxymethylated lactones (189 mg, 0.7 mmol) and methanesulfonyl chloride (96.6 mg, 0.84 mmol) in dry pyridine (3.0 ml) was stirred at 3° for 16 hr. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate. The organic solution was washed with brine and dried (magnesium sulfate). Removal of the solvent afforded 250 mg (100%) of mesylate which was homogeneous by TLC analysis.

A solution of the crude mesylate (244 mg, 0.7 mmol) in 4.0 ml of dry pyridine was heated at 135° (bath temperature) under nitrogen. After 6 hr, the solvent was evaporated in vacuo (high vacuum pump). The residue was dissolved in methylene chloride and was washed with saturated brine. After drying and removal of the solvent, there was obtained 126 mg of an oil which was chromatographed on silica gel (6 g). Benzene–ether (20:1) eluted the THP ether of lactone **14** (40 mg, 23%). Benzene–ether (15:1) eluted the oxygenated α-methylene lactone **14** (71 mg, 60%): ir (film) 3450, 1760, 1668 cm^{-1}; NMR ($CDCl_3$) 6.24 (d, J = 2 Hz, 1 H, $=CH_2$), 5.92 (d, J = 2 Hz, 1 H, $=CH_2$), 4.62 (m, 1 H, CHOCO–), 4.08 (m, 1 H, –CHOH), 3.22 (m, 1 H, –CHC=)]. An analytical sample was prepared by distillation [115° (bath temperature) (0.35 mmHg)].

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.26.

A solution of the THP ether of lactone **14** (40 mg, 0.16 mmol) in 2.0 ml of methanol containing *p*-toluenesulfonic acid (1.0 mg) was stirred at room temperature for 6 hr. The reaction was quenched with pyridine (2 drops). The solvent was evaporated in vacuo, affording 29 mg of an oil which was through a short column of silica gel. Elution with benzene–ether (1:1) yielded pure oxygenated α-methylene lactone **14** (27 mg, 100%).

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (RO1 CA 13689-03) from the National Cancer Institute and in part by Eli Lilly and Co. We thank F. Okuniewicz for mass spectral data and Ljiljana Marinovic for experimental assistance.

Registry No.—**4,** 26054-46-6; **5,** 54911-58-9; **6,** 54911-59-0; **7,** 54911-60-3; **8,** 54911-61-4; **10,** 34896-02-1; **11,** 54911-62-5; **12,** 54911-63-6; **13,** 54911-64-7; **14,** 54911-65-8; 2-hydroxy-5-tetrahydropyranyloxycyclopentylacetic acid α-methylhydroxy lactone, 54911-66-9; 2-hydroxy-5-tetrahydropyranyloxycyclopentylacetic acid α-methylhydroxymesylate lactone, 54911-67-0; 2-hydroxy-6-tetrahydropyranyloxycyclohexylacetic acid α-methylhydroxy lactone, 54911-68-1; 2-hydroxy-6-tetrahydropyranyloxycyclohexylacetic acid α-methylhydroxymesylate lactone, 54911-69-2.

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(11) We have observed that tetrahydropyranyl ethers can be efficiently cleaved in pyridine with either methanesulfonic acid (i) or *p*-toluenesulfonic acid (ii). For example, treatment of **13** with i (2.0 equiv) in pyridine for 6 hr at 135° results in a 91% yield of **12.** Utilization of ii under identical conditions affords **12** in 82% yield. Heating in pyridine for 6 hr at 135° without added i or ii results in complete recovery of starting material. We have also found that **13** can be quantitatively cleaved with a catalytic amount of pyridinium *p*-toluenesulfonate in absolute ethanol at 55° for 3 hr.
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Reaction of Benzoins with Hexamethylphosphoric Triamide. A Convenient Synthesis of 2,3,5,6-Tetraarylpyridines[1]

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Received February 11, 1975

In the course of our investigation[2] on the reaction between hexamethylphosphoric triamide (HMPT) and benzyl alcohols to give *N,N*-dimethylbenzylamines, we treated benzoin (**1a**) with HMPT in an attempt to prepare the corresponding α-dimethylaminodeoxybenzoin (**2**). After a 30-min reflux, the solution was subjected to a water work-up and an 18% yield of 2,3,5,6-tetraphenylpyridine (**3a**) was isolated (Scheme I). The identity of the product was verified by comparison with a sample prepared by the published method.[3]

The reaction of benzoin with ammonium acetate in acetic acid to give 2,3,5,6-tetraphenylpyrazine is well known,[4a] but the conversion of benzoins to substituted pyridines requires the incorporation at the 4 position of one additional carbon atom whose source is not immediately apparent, although a related reaction of simple ketones has been the

Scheme I

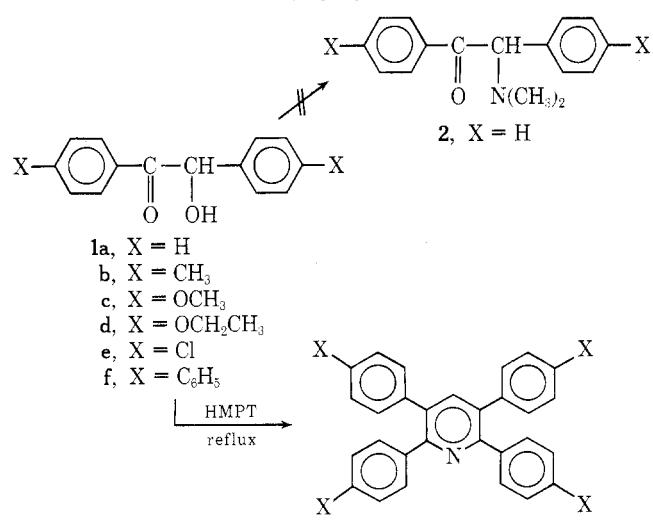


Table I
Tetraarylpyridines (3) from the Reaction of Benzoins with Refluxing HMPT

Benzoin	Reflux time, min	Product	Yield, %	Mp, °C	Anal., % Calcd	Anal., % Found
1a	30	3a	18	238–239[a]		
1b	40	3b	18	278	C, 90.2; H, 6.6; N, 3.2	C, 90.1; H, 6.7; N, 3.2
1c	60	3c	10	259–260	C, 78.7; H, 5.7; N, 2.8	C, 78.9; H, 5.9; N, 3.1
1d	60	3d	19	250	C, 79.4; H, 6.6; N, 2.5	C, 79.2; H, 6.6; N, 2.7
1e	15	3c	16	285–286	C, 66.8; H, 3.3; N, 2.7	C, 66.9; H, 3.3; N, 2.8
1f	30	3f	18	>350	C, 92.5; H, 5.4; N, 2.0	C, 92.3; H, 5.2; N, 2.3

[a] Lit.[5] mp 240–241°.

subject of some speculation.[4b] In any case, an investigation of the scope of the reaction seemed appropriate, since a convenient synthesis of these tetraarylpyridines is not available.

The reaction of substituted benzoins with refluxing HMPT proved to be quite general. A variety of 4,4′-disubstituted benzoins (1) underwent the conversion to the corresponding tetraarylpyridines (3) smoothly in yields ranging from 10 to 19%, as shown in Table I. One merely heats the benzoin in an excess of HMPT until the pot temperature just exceeds 245°. The solution at this point is usually a clear dark orange. After the work-up, the crude reaction product weighs about 50% more than the starting benzoin. Infrared examination of this product indicates the presence of the product pyridine, some unreacted benzoin (<10%), and organophosphorus compounds, although a detailed characterization of the components of this mixture has not been carried out. Tetraphenylpyrazine was not found in the crude reaction product from benzoin by comparison with the spectrum of an authentic sample.[4] Treatment of the crude reaction product with ethanol results in the rapid precipitation of the tetraarylpyridine, which is easily isolated by filtration.

If the reaction mixture is heated much above 245°, considerable darkening occurs, and the yield of tetraarylpyridine is diminished. A shorter reflux period results in much unreacted benzoin with organophosphorus compounds being the major products detectable by infrared.

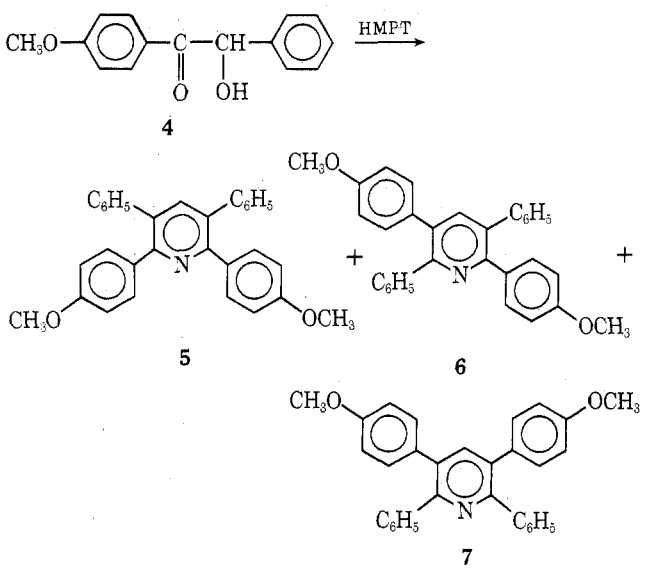
α-Pyridoin, tropolone, and α-hydroxyacetophenone all failed to give isolable products. These latter compounds are apparently sensitive to hot HMPT and decompose well below the reflux temperature. 2-Hydroxycyclohexanone reacted rapidly with refluxing HMPT, affording 2-dimethylaminocyclohexanone in 59% yield.

The reaction between 4-methoxybenzoin (4) and HMPT (45-min reflux) gave a 16% yield of product which after two recrystallizations from ethanol–benzene had a melting point of 178–194°. Its spectral properties and elemental analysis were consistent with a di(*p*-methoxyphenyl)diphenylpyridine, but its melting point suggested that it was a mixture, possibly arising as shown in Scheme II. Column chromatography (neutral alumina) of the mixture afforded three sharp-melting fractions, as well as small amounts of lower melting intermediate fractions. The melting points of the three fractions (in order of elution) follow: A, 212–214°; B, 220–221°; C, 197–198°.

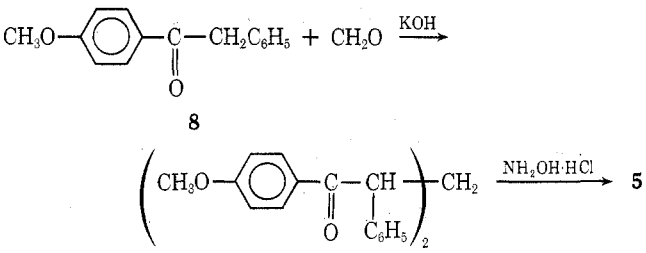
In order to clarify these results, we undertook the synthesis of authentic **5** by an unambiguous route employing as the starting material benzyl *p*-methoxyphenyl ketone (8). The procedure was adapted from the published synthesis of **3a**[3] (Scheme III). The melting point of **5** proved to be 203–204°, and its ir and NMR spectra were virtually identical with those of the unchromatographed products of Scheme II.

Mixture melting points of authentic **5** with the chromatographic fractions A, B, and C gave the following results: A + **5**, mmp 180–200°; B + **5**, mmp 175–190°; C + **5**, mmp 198–203°. These results suggest that fraction C is identical with authentic **5** and that the product of the reaction of 4-methoxybenzoin with HMPT is indeed the mixture of compounds shown in Scheme II.

Scheme II



Scheme III



It appears, therefore, that the reaction proceeds through a symmetrical intermediate, and that for synthetic purposes, the reaction will give unambiguous products only when the starting benzoin is symmetrically substituted. Based on the fact that the dimethylamino group substitutes for hydroxyl in 2-hydroxycyclohexanone and in benzyl alcohols,[2] and on the fact that enamines are known to be produced by the reaction of ketones with HMPT,[6] we are led to suggest that the symmetrical intermediate is an enediamine such as $ArC(NMe_2)=C(NMe)_2Ar$.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were recorded on a

Jeolco Model C-60 spectrometer with Me_4Si as internal standard. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, Calif. Commercial HMPT was distilled before use, bp 120–122° (21 mm). Other compounds not described below were commercially available and were used without further purification.

Benzoins (1). Conventional procedures[7] were employed for the synthesis of the benzoins listed in Table I as well as 4-methoxybenzoin (4). 4,4′-Dichlorobenzoin could not be crystallized and was oxidized with nitric acid to the corresponding benzil.[8] Reduction of this benzil with sodium dithionite[9] afforded the expected 4,4′-dichlorobenzoin.

2,3,5,6-Tetraarylpyridines (3). General Procedure. The benzoin (0.05 mol) was refluxed with 35 ml of HMPT until the pot temperature just exceeded 245° (15–60 min as shown in Table I). After cooling, the clear, dark orange reaction mixture was poured into 150 ml of cold water and the resulting mixture was saturated with sodium chloride. This mixture was extracted three times with benzene. The benzene solution was washed twice with brine, dried (anhydrous sodium sulfate), and reduced in volume on a rotary evaporator, leaving a residue of oil and crystals. Ethanol (100 ml) was added to the residue and the solution was heated briefly on a steam bath. Crystallization followed upon cooling. The product was recrystallized from ethanol–benzene. For example, benzoin (**1a**, 10.6 g, 0.05 mol) treated as above affords 15.05 g of crude reaction product as a dark orange oil. The ir spectrum (film) of the oil shows bands at 5.96 (benzoin C=O), 7.04 (tetraphenylpyridine), and 7.6–8.0 μ (organophosphorus P=O). Addition of ethanol at room temperature followed by standing for several hours afforded 1.73 g (18%) of **3a** as a light yellow solid. Recrystallization from ethanol–benzene gave white product of the reported melting point.

Reaction of 2-Hydroxycyclohexanone with HMPT. 2-Hydroxycyclohexanone (0.05 mol) was refluxed with 35 ml of HMPT. Ten minutes after the onset of reflux, a volatile material had formed which was distilled from the reaction vessel. Water (200 ml) was added to the reaction vessel and distillation was continued until no more organic material steam distilled. The distillate was extracted with ether, the ethereal solution was dried (anhydrous sodium sulfate), and the ether was evaporated, affording 2-dimethylaminocyclohexanone in 59% yield. The ir and NMR spectra of the product were identical with those of an authentic sample. The picrate melted at 110–113° (lit.[10] mp 113–114°).

Reaction of 4-Methoxybenzoin (4) with HMPT. 4-Methoxybenzoin (**4**) was refluxed with HMPT and worked up in the same manner as described above. The product, after two recrystallizations from ethanol–benzene, had mp 178–194°. The ir and NMR spectra of the product were virtually identical with those of authentic **5**.

Anal. Calcd for $C_{31}H_{25}O_2N_2$: C, 84.0; H, 5.6; N, 3.1. Found: C, 83.7; H, 5.7; N, 3.1.

The product was chromatographed on neutral alumina. Petroleum ether–benzene (3:7) as eluent gave fractions A and B, and petroleum ether–benzene (1:4) gave fraction C. Small amounts of intermediate materials having depressed melting points were also obtained.

1,3-Di(*p*-methoxybenzoyl)-1,3-diphenylpropane (9). This compound was prepared by the method used by Carpenter[3] for an analogous compound. Thus, benzyl *p*-methoxyphenyl ketone[11] (**8**) was treated with aqueous formaldehyde and potassium hydroxide in ethanol at room temperature to give crude **9** in 63% yield. The product was recrystallized twice from ethanol: mp 150–151°; ir (film) 5.99 and 6.26 μ.

Anal. Calcd for $C_{31}H_{28}O_4$: C, 80.2; H, 6.0. Found: C, 80.3; H, 6.1.

2,6-Di(*p*-methoxyphenyl)-3,5-diphenylpyridine (5). This compound was prepared by the method used by Carpenter[3] for an analogous compound. Thus, **9** (1.0 g) and hydroxylamine hydrochloride (0.35 g) were dissolved in 40 ml of absolute ethanol and heated in a closed tube at 150° for 21 hr. Upon cooling, the mixture yielded 0.29 g of crude **5** which was recrystallized from benzene–ethanol: mp 203–204°; ir (film) 6.23 and 6.35 μ; NMR (CCl_4) δ 4.04 (s, 6, CH_3O), 7.02 (d, 4, J = 9 Hz), 7.61 (m, 11), 7.86 (d, 4, J = 9 Hz).

Anal. Calcd for $C_{31}H_{25}O_2N_2$: C, 84.0; H, 5.6; N, 3.1. Found: C, 84.0; H, 5.7; N, 3.1.

Registry No.—**1a**, 119-53-9; **1b**, 1218-89-9; **1c**, 119-52-8; **1d**, 53458-15-4; **1e**, 4254-20-0; **1f**, 5623-25-6; **3a**, 24301-97-1; **3b**, 54932-37-5; **3c**, 54932-38-6; **3d**, 54932-39-7; **3e**, 54932-40-0; **3f**, 54932-41-1; **4**, 4254-17-5; **5**, 54932-42-2; **8**, 1023-17-2; **9**, 54932-43-3; 2-hydroxycyclohexanone, 533-60-8; hexamethylphosphoric triamide, 680-31-9; 2-dimethylaminocyclohexanone, 6970-60-1; 2-dimethylaminocyclohexanone piciate, 54932-44-4.

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Identification of C-22 Epimers in Steroids by Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1a]

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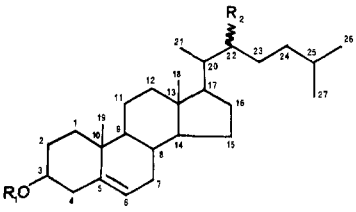
Received December 16, 1974

A recent communication reported a ^1H NMR analytical method to identify (20*R*,22*R*)- and (20*R*,22*S*)-dihydroxy steroidal isomers.[2] However, the same study indicated that ^1H NMR spectroscopy failed to differentiate (22*R*)- and (22*S*)-hydroxy cholesterols.[2]

We wish to report the utility of ^{13}C NMR in this case and provide an easy method to determine the absolute configuration at C-22 of steroids substituted at this center and having the cholestane side chain.

Noise and single frequency decoupled ^{13}C NMR spectra were recorded for the (22*R*)- and (22*S*)-substituted cholesterol derivatives[3,4] **2–7** and for cholesteryl benzoate **1**. Application of chemical shift rules[5] as well as previous analysis of the ^{13}C NMR spectrum of cholesterol[6] led to the signal assignments shown in Table I.

Compared to the respective resonance positions in the spectrum of **1**, C-22, C-20, and C-23 are deshielded while C-17, C-21, and C-24 are shielded in all the compounds studied. These chemical shift variations are easily understood from the qualitative point of view as a consequence of α, β, and γ effects.[5,7] However, inspection of Table I indicates that the magnitude of the β effects is totally different for the 22*S* and 22*R* compounds. Considering the spectra of **2, 3, 5,** and **6,** the average β effect on C-20 is 4.1 and 6.8 ppm in the *S* and *R* series, respectively. On the chemical shift of C-23 an even more pronounced difference is observed between the two series. The β effect in this case is



1 R_1=COC_6H_5 ; R_2= H
2 R_1=COC_6H_5 ; R_2=OH (22S)
3 R_1= H ; R_2=NH_2(22S)
4 R_1=COC_6H_5 ; R_2=N_3 (22S)
5 R_1=COC_6H_5 ; R_2=OH (22R)
6 R_1=H ; R_2=NH_2(22R)
7 R_1=COC_6H_5 ; R_2=N_3 (22R)