The same substance was also obtained from acetylation of **2f** with a mixture of acetic anhydride and boron trifluoride in methylene chloride at room temperature in 67% yield and by treatment of **2f** with boron trifluoride in quantitative yield (Chart V).

Registry No.—**2a**, 15273-07-1; **2b**, 15273-22-0; **2c**, 15273-08-2; **2d**, 15273-09-3; **2e**, 15273-10-6; **2f**, 15273-11-7; **3**, 15233-12-8; **4**, 15350-49-9; **5**, 15273-14-0; **6**, 15273-13-9; **7**, 15273-15-1; $(Acac)_2Cu$, 13395-16-9; $(Acac)_2Co$, 14024-48-7; $(Acac)_2Ni$, 14024-60-3; $(Acac)_3Fe$, 14024-18-1; $(Acac)_3Co$, 13681-88-4; $(Acac)_3Cr$, 13681-82-8.

Acknowledgments.—The authors wish to express their gratitude to the Chemical Research Laboratories, The Takeda Pharmaceutical Co., Ltd., for measuring the mass spectra.

Synthesis of the Eight Stereoisomers of a Tetrahydrocannabinol Congener

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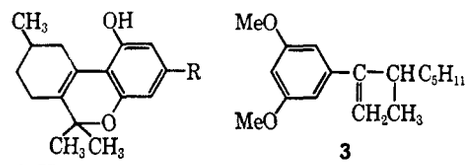
The eight stereoisomers of a tetrahydrocannabinol congener (**2**) have been synthesized from the eight pyrones (**9**) obtained by the condensation of (+)- and of (−)-2-carbethoxy-5-methylcyclohexanone (**8**) with each of the four optical stereoisomers of (demethylated) 2-(3,5-dimethoxyphenyl)-3-methyloctane (**6**). The four *threo* isomers of **6** were obtained optically pure; the four *erythro* isomers of **6** were obtained only as partially resolved materials. The relative configurations of the *erythro* and *threo* isomers of **6** have been assigned by two independent methods. The final products (**2**) were isolated as their acetate esters. Glpc analysis of the latter revealed the presence of two minor unidentified impurities.

The structures and stereochemistry of the physiologically active tetrahydrocannabinol principles of marijuana (hashish) have been recently elucidated.[1] Earlier, in an extensive series of investigations, Adams,[2] Todd,[3] and co-workers independently synthesized a material (**1**) that differed from the natural products by the position of the alicyclic double bond. A series of homologous congeners also were prepared, and structure–activity studies revealed the most active compound to be the 1,2-dimethylheptyl analog (**2**).[4a]



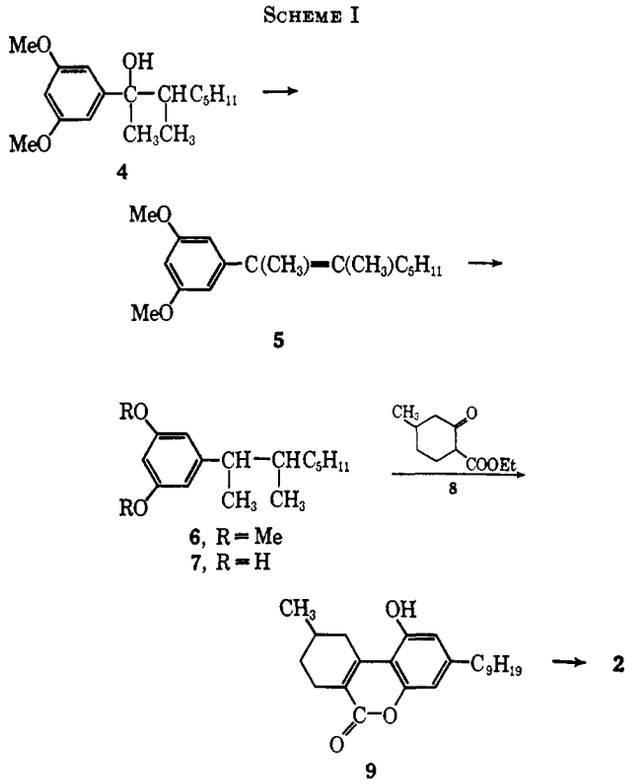
3

1, R = C_5H_{11}
2, R = $CH(CH_3)CH(CH_3)C_5H_{11}$

Because it possesses three asymmetric carbon atoms, **2** can exist as four diastereoisomeric racemates, each consisting, in turn, of a (+) and (−) enantiomorph. Since the stereochemical composition of the Adams product (**2**) was not known, we decided to synthesize the isomers of this interesting material.

The synthesis of **2** by the Adams procedure[4] is summarized, in part, in Scheme I. By this route, the carbinol **4**, obtained in two steps from 3,5-dimethoxybenzamide, was dehydrated to the olefin **5**, and then reduced to the alkane **6**. Reinvestigation of this reaction sequence revealed that the dehydration tends to give, initially, the vinyl olefin **3** ($\nu^{neat}_{H_2C=}$ 3080; $\delta_{H_2C=}$ 898 cm^{-1}) which then rearranges into a *cis–trans* mixture of **5** under the acidic conditions. However,

SCHEME I



all attempts to separate any of these intermediates into characterizable stereoisomers proved unsuccessful in our hands.[5] A new synthetic procedure had to be devised, therefore, which would give, unambiguously, the stereoisomers of the final product. Since **6** represents the key intermediate in the process, its synthesis was investigated from this point of view. Eventually, two independent routes were achieved.

(1) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964); E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966); R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

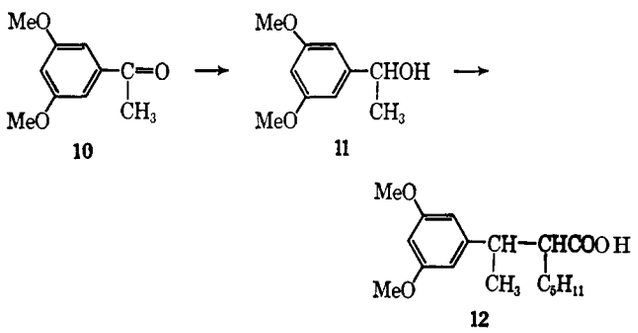
(2) R. Adams and B. R. Baker, *ibid.*, **62**, 2405 (1940).

(3) R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1121 (1940).

(4) (a) R. Adams, S. MacKenzie, and S. Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948); (b) R. Adams, K. H. Chen, and S. Loewe, *ibid.*, **67**, 1534 (1945).

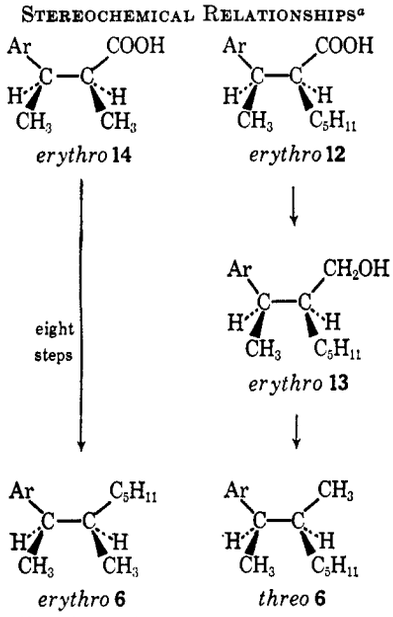
(5) It was subsequently found, after this approach had been abandoned, that the isomers of **5** and **6** (and to some extent, **4**) could be separated by gas–liquid partition chromatography, a technique not available to us at that time.

In the more direct route, 3,5-dimethoxyacetophenone (**10**) was reduced to the carbinol **11**, which was converted into its corresponding bromo analog, then into **12** by a malonic ester synthesis (with diethyl amylmalonate), without isolating either of the intermediate products. Compound **12** was obtained as an isomeric mixture that was readily separated into a dicyclohexylamine salt of the *erythro* isomer and a benzylamine salt of the *threo* isomer. These stereochemical assignments are discussed in a separate section, below.



The *erythro* and *threo* **12** isomers were each liberated from their respective amine salts and reduced (see Chart I) with lithium aluminum hydride to the

CHART I
STEREOCHEMICAL RELATIONSHIPS[a]



[a] Ar = 3,5-dimethoxyphenyl.

corresponding carbinols **13**, which were converted *via* a hydride reduction of their tosylates (not isolated) into *threo* and *erythro* **6**, respectively. The two pure **6** isomers may be distinguished by small differences in their infrared spectra, and by their relative glpc retention times. Mixtures of the two isomers, however, are best determined by glpc analysis.

Using the Adams' procedure outlined above, the alkanes **6** were each converted into a new isomeric mixture of their respective pyrones **9**, which, though solids, could not be fractionally crystallized into two distinct racemates. Therefore, it became necessary to prepare, stereospecifically, each of the eight pyrone isomers. Accordingly, the isomers of **12** had to be resolved.

erythro **12** was readily resolved using (+) and (−)-α-methylbenzylamine. A similar resolution of *threo* **12** proved to be much more difficult, however, and in this case only a partial resolution was achieved. The physical properties of the resolved isomers thus obtained are summarized in Table I. These isomers were each converted into the corresponding isomers of **13** and of **6**, the physical properties of which are also summarized in Table I.

TABLE I
PHYSICAL PROPERTIES OF OPTICAL ISOMERS OF **12**, **13**, AND **6**

First series[a]			Second series[a,b]		
Compd	[α]D, deg[c]	Mp, °C, or n^{25}D	Compd	[α]D, deg[c]	Mp, °C, or n^{25}D
erythro **12**	+35.6	49–52	*threo* **12**	+7.1	47–53
	−35.2	49.5–53		−6.7	49–52
erythro **13**	+35.2	1.5126	*threo* **13**	+2.4[d]	1.5130
	−34.4	1.5113			1.5128
threo **6**	+36.9	1.4980	*erythro* **6**	+3.0[d]	1.4967
	−36.2	1.4974		−3.2[d]	1.4986

[a] Within each series, each member is derived (**12** → **13** → **6**) from the preceding compound of like sign (see Chart I). [b] Not optically pure. [c] Methanol solutions at ambient temperature. [d] Neat, 1 dm.

The four alkane isomers of type **6** were each demethylated, then treated with the (+) and (−) forms, respectively, of 2-carbethoxy-5-methylcyclohexanone (**8**) to give eight pyrone isomers of type **9**, the physical properties of which are summarized in Table II. The

TABLE II
PHYSICAL PROPERTIES OF THE EIGHT PYRONE (**9**) ISOMERS AND THEIR DERIVED PYRAN (**2**) ACETATES[a]

Isomer no.	Synthesis intermediates **6** and **8**		Pyrone **9** Mp, °C	Pyrone **9** [α]D, deg (MeOH)	Pyran (**2**) acetate [α]D, deg (MeOH)
1	(−) *threo*	(+)	142–143	+71	+65
2	(−) *threo*	(−)	131–133	−146	−130
3	(+) *threo*	(+)	133–135	+152	+133
4	(+) *threo*	(−)	141–143	−67	−70
5[b]	(−) *erythro*	(+)	138–140	+106	+94
6[b]	(−) *erythro*	(−)	135–137	−108	−110
7[b]	(+) *erythro*	(+)	135.5–137.5	+118	+105
8[b]	(+) *erythro*	(−)	135–138	−95	−93

[a] Isomers 1 and 4, 2 and 3, 5 and 8, and 6 and 7 are enantiomorphic pairs. [b] Prepared from **6** (Table I), not optically pure.

pyrones were converted into their corresponding pyran isomers **2**, which were not isolated as such, but were converted into their more stable acetate esters (Table II). The acetates were isolated as viscous, pale yellow oils which were shown (glpc) to be about 85% chemically pure.

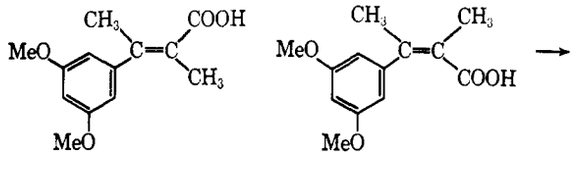
In the alternate route (first, chronologically), the *erythro* and *threo* isomers of α,β-dimethyl-3,5-dimethoxyhydrocinnamic acid (**14**) were prepared and separated; then each was converted in eight steps into the isomers of **6**: $-COOH$, $-CH_2OH$, $-CH_2OTos$, $-CH_2CN$, $-CH_2COOH$, $-CH_2C(=O)C_3H_7$, $-CH(OH)-$, $-CH(OTos)-$.

Products obtained *via* **14** were subsequently found (glpc) to be contaminated with various unidentified impurities, in comparison to the clean products obtained by the more direct route (*via* **12**), which was

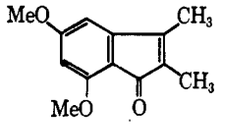
developed out of desire for a simpler synthesis. Therefore, the preparation of **6** *via* **14** is not of synthetic utility, although the route was used to establish the stereochemistry of the **6** isomers, as discussed below.

Stereochemical Assignments

The *erythro* and *threo* configurations of the **6** isomers have been assigned on the basis of the agreement obtained between two independent methods. According to the first method, (Chart I) the alkanes (**6**) must possess the same configuration as the acid (**14**) from which each was stereospecifically derived. The configurations of **14**, in turn, were related to the isomers of α,β-dimethyl-3,5-dimethoxycinnamic acid. These were synthesized by dehydration and hydrolysis of the Reformatsky product of 3,5-dimethoxyacetophenone (**10**) with ethyl α-bromopropionate, and separated into a *cis* (**15**) and a *trans* (**16**) isomer by fractional crystallization of their dicyclohexylamine salts. The *cis* configuration was assigned from the fact that **15** was converted by sulfuric acid into a cyclic ketone (**17**) under conditions from which the *trans* isomer was recovered largely unchanged. The *cis* (**15**) and *trans* (**16**) acid dicyclohexylamine salts were each stereospecifically hydrogenated over palladium on charcoal to the dicyclohexylamine salts of the pure **14** isomers, assigned as *erythro* and *threo*, respectively, from the presumed *cis* mode of the hydrogenation reaction.[6] Although the above represents an alternate synthesis of **14**, this route is not preparatively attractive, due to the tendency (previously noted[7]) for reverse aldolization to occur in the Reformatsky product in this system.



16 **15**



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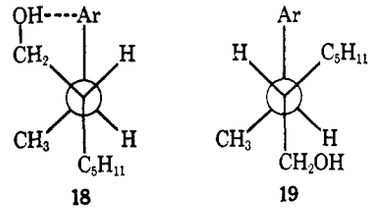
As indicated in Chart I, the basis for the stereochemical designation of **14** is self-evident. For the isomers of **12**, the designation is based upon the recognition that the two alkyl groups are the more closely related of the nonidentical substituents. The designation of the carbinols (**13**) is based upon their relationship to the corresponding isomer (**12**) from which each was derived with retention of configuration. The conversion of the hydroxymethyl group in **13** to a methyl group (**6**) by reduction of the corresponding tosylate also occurs with retention of configuration. However, upon the introduction of this second methyl group, the stereochemical structure of the resulting product (**6**) must be redesignated from a new frame of reference. The stereochemistry of the isomers of **12** was established from the fact that the identical (*erythro*) alkane (**6**) was obtained from both *erythro* **14** and *threo* **12**, as shown by glpc and infrared analyses. Actually, the stereochemical relationship between the **12** and **14** isomers was anticipated on the basis of the relative solubilities of their dicyclohexylamine and benzylamine salts. Although not examined in this study, it is expected that the ethyl, propyl, butyl, and perhaps other *n*-alkyl homologs in this hydrocinnamic acid series could also be separated and stereochemically related in this way.

The second method used for relative stereochemical assignments was based upon a conformational analysis of the **13** isomers, as related to their dilute solution infrared spectra.[8a]

Thus, for each **13** isomer in dilute (0.0064 *M*) carbon tetrachloride solution, the hydroxyl stretching absorption appears as a doublet that is concentration independent, with bands at 3638 (free OH) and 3583 cm^{-1}.[9] The latter is due to the intramolecularly bonded OH–phenyl system.[10] At this dilution, no intermolecular bonding was observed. The extinction coefficients (ϵ) of the free and bonded hydroxyl bands and the ratio of $\epsilon_{free}/\epsilon_{bonded}$ were: *threo*, 59, 23, 2.6; *erythro*, 63, 15, 4.2. Examination of models of the three noneclipsed conformations of each **13** isomer (which arise as a result of free rotation about the bond linking the two asymmetric carbon atoms) reveals that, in each system, intramolecular OH–phenyl hydrogen bond formation is possible in two of the conformations (Ar and CH_2OH *gauche*, *e.g.*, **18**)[8b] and impossible in the third (Ar and CH_2OH *anti*, *e.g.*, **19**). A summation of the total unfavorable nonbonded Ar, C_5H_{11}, CH_3, and CH_2OH *gauche* interactions in each system further reveals that the *threo* alcohol has one more *gauche* CH_3/C_5H_{11} interaction in the free OH conformation, and correspondingly one less in the sum of the two so-called bonded forms, than its *erythro* isomer. Therefore, the population of conformations which permit intramolecular hydrogen bonding should be favored in the *threo* isomer, which may be assigned on the basis of the smaller $\epsilon_{free}/\epsilon_{bonded}$ ratio of the two isomers.

Though not examined in this study, a third method based upon a recent empirical nmr correlation[11] may also be useful for configurational assignments in this series (**14**).



18 **19**

(6) K. N. Campbell and B. K. Campbell, *Chem. Rev.*, **31**, 77 (1942).

(7) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

(8) (a) See M. Tichý, *Advan. Org. Chem.*, **5**, 125 ff (1965), for a similar analysis. (b) Due to the rotational entropy of the $-CH_2OH$ group, not all of the molecules present in these two so-called bonded conformations will be intramolecularly bonded. However, the percentage of the total population of each of these two conformations that are so bonded should be identical, in effect, in both series.

(9) Recorded on a Perkin-Elmer 421 grating spectrophotometer in matched 5-mm sodium chloride cells.

(10) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, No. 14, 1 (1959).

(11) M. Barbieux and R. H. Martin, *ibid.*, 2919 (1965).

Experimental Section[12]

α-(3,5-Dimethoxyphenyl)ethanol (11).—3,5-Dimethoxyacetophenone[7,13] (**10**), 83 g (0.46 mole) in 50 ml of methanol, was added dropwise with stirring to a solution of 18 g of sodium borohydride in 300 ml of methanol containing 1 g of sodium hydroxide. The mixture was refluxed for 30 min, then concentrated by distillation. About 100 ml of water was added during the distillation. After the methanol had been removed, the mixture was cooled and extracted with several portions of ether, which were combined, dried, filtered, concentrated, and distilled to give 80 g (95%) of **11** as a colorless viscous oil, bp 123–126° (0.65 mm), $n^{25}D$ 1.5340.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 66.0; H, 7.75. Found: C, 65.9; H, 7.4.

In some cases, a small amount of crystalline 3,5-dimethoxybenzonitrile, which was present as an impurity in the **10** starting material, sublimed into the condenser and was carried over with the **11** forerun. The nitrile, which was not soluble in the cold carbinol, was filtered off. It melted at 85–87° (lit.[14] mp 86–87°) upon recrystallization from ether–petroleum ether; $\nu_{C\equiv N}^{KBr}$ 2240 cm^{-1}.

α-Amyl-β-methyl-3,5-dimethoxyhydrocinnamic Acid (12).—Phosphorus tribromide (18 ml in 70 ml of ether) was added dropwise with stirring during 1 hr to **11** (28.5 g, 0.16 mole) in 70 ml of ether in an ice bath. The mixture was warmed to room temperature, refluxed for 2 hr on the steam bath, cooled, and poured over 200 g of crushed ice. The mixture was shaken in a separatory funnel, then extracted three times with ether. The ether layers were combined, washed with 10% bicarbonate solution, then water, and dried. The solution of α-(3,5-dimethoxyphenyl)ethyl bromide thus obtained was filtered, concentrated by distillation on the steam bath and then added with stirring under anhydrous conditions to 42 g (0.18 mole) of diethyl *n*-amylmalonate (Matheson Coleman and Bell) in about 300 ml of ethanol containing 4.6 g (0.20 g-atom) of freshly dissolved sodium. The ethanol had been previously dried by distillation from magnesium ethoxide. The mixture was allowed to stir at room temperature for 1.5 hr and then heated to distil off the ether and complete the reaction. When the head temperature reached 78°, water was added, and the distillation was continued until the head temperature had reached 99°. The mixture was then cooled and extracted with three 250-ml portions of ether, and the ether layers were combined and concentrated by distillation. The crude malonate ester thus obtained was hydrolyzed in ethylene glycol (180 ml) with sodium hydroxide (35 g) by stirring for 6 hr at 160°. The mixture was then cooled, diluted to 1500 ml with water, and washed with ether. The aqueous phase was acidified and extracted with four 200-ml portions of ether. These were combined and concentrated by distillation on the steam bath. The residue was taken up in 150 ml of xylene, distilled to remove residual ether and water until the head temperature had reached 140°, and refluxed for 6 hr. The solvent was removed by heating to 115° under reduced pressure (0.15 mm) to give crude **12**, 33.5 g of an amber oil, as a mixture of the *erythro* and *threo* isomers. This product had a titrimetric equivalent weight of 296 (theory 294).

Separation of the Diastereoisomers of 12.—The 33.5 g of crude **12**, above, was dissolved in 125 ml of ether with warming, combined with 22 g of dicyclohexylamine, and placed in the refrigerator overnight to give 19 g of salt, mp 131–135°, which was recrystallized from 250 ml of acetone to give 15 g of dicyclohexylamine salt, mp 138–140°.

Anal. Calcd for $C_{29}H_{49}NO_4$: C, 73.22; H, 10.38; O, 13.45; equiv wt, 475.7. Found: C, 73.6; H, 10.6; O, 13.5; equiv wt (titrimetric), 477.

The original filtrate was concentrated, then shaken with ether and aqueous hydrochloric acid. Some dicyclohexylamine hydrochloride precipitated; it was filtered and washed with ether. The aqueous phase was extracted with several portions of ether, which were combined, dried, and concentrated to about 350 ml. Treatment with benzylamine (7 g) in a little ether gave 19 g of benzylamine salt, mp 113–116°, which was recrystallized from 150 ml of benzene to give 17 g of benzylamine salt, mp 121–122°.

Anal. Calcd for $C_{24}H_{35}NO_4$: C, 71.78; H, 8.79; O, 15.94; N, 3.49. Found: C, 71.7; H, 8.8; O, 16.0; N, 3.4.

The purified dicyclohexylamine salt, 15 g, above, was dissolved in 35 ml of methanol, acidified with 10 ml of 6 *N* hydrochloric acid, and diluted with 800 ml of water. The oil which formed was cooled, seeded, and scratched to give 9 g of *erythro* **12**, mp 55–57°. (The original seed was obtained from another sample of the oil which had crystallized after 3 weeks standing.) Recrystallization from petroleum ether containing a little cyclohexane did not raise the melting point.

The purified benzylamine salt, 17 g, above, was dissolved in 30 ml of methanol, acidified with 10 ml of 6 *N* hydrochloric acid, and diluted with 200 ml of water. The oil which formed solidified on standing in the refrigerator over the weekend to give 11 g of *threo* **12**, mp 54–57°. A sample recrystallized from petroleum ether gave mp 55–57°.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90; O, 21.73; neut equiv, 294.4. Found: C, 68.9; H, 8.5; O, 21.4; neut equiv, 294.

Resolution of *erythro* 12.—The (±)-*erythro* **12** was resolved with (−)- and (+)-α-methylbenzylamine.[15] The initial salt was prepared in ether (2–5 ml/1 g of salt), then recrystallized once or twice from ether (10 ml/g). The tail crop fractions were shaken with aqueous base and then acidified to obtain the free acid, which was resolved as above using the enantiomorphic amine. This process, twice repeated on an initial 35 g of (±)-*erythro* **12**, gave 9 g of the (+)-α-methylbenzylamine salt of (−)-*erythro* **12**, mp 96–98°, $[\alpha]^{28}D$ −21.8° (methanol, *c* 2), and 9 g of the (−)-α-methylbenzylamine salt of (+)-*erythro* **12**, mp 96–98°, $[\alpha]^{26}D$ +22.0° (methanol, *c* 2).

The resolved amine salts were dissolved in 2 *N* aqueous sodium hydroxide (10 ml/g), washed with ether and then petroleum ether, acidified, and cooled to give the free acids in essentially quantitative yield (see Table I).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90; O, 21.73; neut equiv, 294.4. Found, (+)-*erythro* **12**: C, 69.0; H, 9.0; O, 21.5; neut equiv, 295.

Resolution of *threo* 12.—The resolution of this acid with (−)- and (+)-α-methylbenzylamine proved to be difficult and tedious, and only a partial resolution was achieved. Ether was most conveniently used as the initial solvent. After a point, however, ethyl acetate had to be used to obtain further resolution. Thus, the (±)-*threo*-(+)-amine salt, obtained as the head crop in 75% yield, melted at 75° and had a specific rotation of about +3° (methanol). It was recrystallized five times from ether (15 ml/g), and then four times from ethyl acetate (5 ml/g). The melting point showed little or no change during this process, but the specific rotation changed by about 1° with each recrystallization, decreasing at first, then increasing with a negative sign. About a 60% recovery of head crop was obtained on cooling at each step. The filtrates were concentrated, and successive new crops were combined on the basis of their rotations, recrystallized as above, and eventually added to the head crops of the resolution. The final filtrates of the tail crops were converted to *threo* **12** (as in the *erythro* series) and treated with the (−)-amine, and the process was repeated.

By this procedure, from 200 g of (±)-*threo* **12**, there was obtained 12 g of the (+)-*threo* **12** salt of (−)-α-methylbenzylamine, $[\alpha]D$ +5.0° (methanol, *c* 3.5), and 11 g of the (−)-*threo* **12** salt of the (+)-amine, $[\alpha]D$ −5.0° (*c* 4.3). The optical purity of these salts is uncertain, since a known optically pure product was not obtained, even upon several additional recrystallizations of another, comparably resolved, sample.

The partially resolved amine salts were each converted (as in the *erythro* series) in quantitative yield to (−)- and (+)-*threo* **12** (Table I).

2-(Amyl)-3-(3,5-dimethoxyphenyl)butanol (13).—*erythro* **12** (14.5 g, 0.049 mole) was refluxed 7 hr with excess lithium aluminum hydride (5 g) in 250 ml of ether, then cooled and carefully decomposed by successive additions of methanol in

(12) Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer, unless otherwise indicated; glpc data were obtained on an Aerograph A-90-P chromatograph equipped with a thermal conductivity detector and using helium carrier gas. Petroleum ether was bp 30–60°; Drierite was used throughout as the drying agent. Titrations were run on a Beckman H-2 pH meter.

(13) Furnished, in part, by the FMC Corporation, Baltimore, Md., and the University of Delaware, under U. S. Army Research and Development Contracts.

(14) H. Frei and H. Schmid, *Ann.*, **603**, 169 (1957).

(15) W. Theilacker and H. Winkler, *Chem. Ber.*, **87**, 690 (1954); A. Ault, *J. Chem. Educ.*, **42**, 269 (1965).

ether, water, and finally dilute hydrochloric acid. The layers were separated, and the aqueous layer was saturated with sodium chloride and extracted with ether. The ether layers were combined and extracted with aqueous bicarbonate solution, which was then acidified. The lack of any **12** precipitation indicated the reaction had been completed. The ether solution was dried, concentrated, and distilled (bp 134–138° at 1 μ) to give 12.3 g (90%), of *erythro* **13**, $n^{25}D$ 1.5126.

The infrared spectra (neat) of *erythro* and *threo* **13** are very similar. The main difference is found in their 1057-cm^{-1} infrared bands. Here, a shoulder on the high wavelength side of this band results in an inflection point at 1040 cm^{-1} for the *erythro* carbinol, compared to 1025 cm^{-1} for the *threo* isomer. The same distinction is seen in their derived alkanes (**6**). Other distinctions in the infrared spectra ($\nu_{OH}^{CCl_4}$) of the **13** isomers are discussed in the text.

2-(3,5-Dimethoxyphenyl)-3-methyloctane (6).—*erythro* **13** (11.7 g, 0.040 mole) and *p*-toluenesulfonyl chloride (8.5 g, 0.044 mole) were each dissolved in 20 ml of dry pyridine, cooled in an ice bath, combined, and placed in the freezing compartment of the refrigerator for 16 hr. The mixture was then poured over ice and extracted with several portions of ether. The latter were combined and washed with cold dilute hydrochloric acid until the wash water was acidic to pH paper. The combined aqueous solutions were acidified and extracted with ether. The ether solutions were combined, washed with bicarbonate solution, dried, then added dropwise with stirring to 3 g of lithium aluminum hydride in 75 ml of ether. The mixture was refluxed for 4.5 hr, then worked up as for **13**, above. The undistilled product was chromatographed on activated alumina (1 × 4 in.) by elution with 600 ml of petroleum ether, then with 200 ml of methanol. The petroleum ether fraction was concentrated and distilled to give 8.3 g (0.032 mole, 80%) of *threo* **6** with bp 92–95° (1 μ) and $n^{25}D$ 1.4974. The methanol fraction was concentrated to give 2.0 g (0.0071 mole, 18%) of *erythro* **13**, which was recycled, as above, to give an additional 0.6 g of *threo* **6**. The carbinol **13** is formed, apparently, as a result of O–S tosylate bond cleavage in the hydride reduction, and not from unreacted carbinol carried through from the tosylate preparation.

To verify stereoisomeric purity, a 15% 5 ft × 0.25 in. column of Carbowax 20M on 60–80 Gas-Chrom P was used. At 231° and 62 cc/min., *threo* **6** had a retention time of 11.5 min, *erythro* **6**, 13 min. The carbinols (**13**) are not eluted under these conditions, but may be detected, if present, on an SE-30 column.

Although the infrared spectra (neat) of the **6** isomers are very similar, differences exist between the *erythro* and *threo* series. The most characteristic distinction (also found in the isomers of **13**) is found in the shoulders that occur on the high wavelength side of the 1060-cm^{-1} infrared bands. This shoulder results in an inflection point at 1040 cm^{-1} in *threo* **6**, and 1025 cm^{-1} in *erythro* **6**.

1-Hydroxy-3-(1,2-dimethylheptyl)-9-methyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyrone (9).—The four isomers of **6**, about 4.5 g of each, were converted into 2-(3,5-dihydroxyphenyl)-3-methyloctane (**7**) in yields of 90% or better by 5-hr reflux with 48% hydrobromic acid in glacial acetic acid.[2,4] The products, obtained as viscous yellow oils, were not distilled, but were each divided in half and condensed[2,4] using phosphorus oxychloride in benzene with the (+) and (−) isomers of 2-carbethoxy-5-methylcyclohexanone (**8**), $\alpha^{25}D$ +75.7° (neat, 1 dm), $n^{25}D$ 1.4678, and −74.8°, 1.4680, respectively. The latter were obtained from (+)- and (−)-3-methylcyclohexanone[16,17] as described.[18] The eight pyrone products were each purified[19] by chromatography on activated alumina (1 × 4 in.) in benzene. The column was washed with 50-ml portions of 5, 10, and 50% acetone in benzene, then acetone and finally methanol. The first two eluent fractions were evaporated, and the residues were triturated with petroleum ether to give tan solids. These were combined and recrystallized (charcoal treatment) from cyclohexane to give the **9** isomers (see Table II) as off-white to light tan powders in 39–52% yields. Satisfactory analyses (C, H, O) were obtained for each isomer.

(16) H. Rupe and E. Kambli, *Ann.*, **459**, 195 (1927).

(17) N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).

(18) R. Adams, C. M. Smith, and S. Loewe, *J. Am. Chem. Soc.*, **64**, 2087 (1942).

(19) Adapted from the unpublished procedure of A. M. Reeves and co-workers of these laboratories.

1-Acetoxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyran (2-acetate).—The eight pyrone isomers (**9**) were converted into eight pyran isomers (**2**) as described.[2,4] The products were obtained as red viscous oils, which were not distilled, but were converted directly into their acetate esters by 3 hr of reflux with acetic anhydride and sodium acetate.[20] Each product was chromatographed on a column (1 × 3.5 in.) of silicic acid in petroleum ether, then eluted with a solution of ether (2%) in petroleum ether. After a fluorescent forerun (first 100 ml), the product was collected in the second 100 ml of eluent. The solvent was removed under reduced pressure, and the products (Table II) were obtained as nearly colorless, clear, viscous oils in yields of 49–82%. These were not distilled, but were characterized by infrared, nmr, and glpc analyses.

Infrared spectra (neat and in carbon tetrachloride solution) were essentially identical for all eight acetate isomers, and also with a total-isomer mixture from which a good elemental analysis had been obtained. No hydroxyl absorption was detected.

Nmr spectra were consistent with the structure. There were no vinylic hydrogens detectable for any isomer, which would represent products containing the alicyclic double bond in other than the indicated (**2**) 6a,10a position. However, up to 12% of such an impurity (see below) cannot be definitely excluded on this basis, since it is possible that this amount of vinylic hydrogen may not have been detectable by nmr. Though not too useful for characterization purposes, the *erythro* series showed a slightly more complex multiplet in the δ 0.7–1.0 ppm region than the *threo* series.

The products were examined by glpc on 10% Apiezon N (5 ft × 0.25 in.) on 60–80 Chromosorb W at a flow rate of 60 cc/min. At 305°, a total mixture of the pyran (**2**) isomers and their acetates was separated (though not completely resolved) into four peaks corresponding to *threo* (9 min) and *erythro* (10 min) acetate, and *threo* (12 min) and *erythro* (13 min) pyran. Of the eight acetates, the four *erythro* isomers had identical retention times, as did the four *threo* isomers. The products each exhibited three peaks:[21] a main (product) peak representing about 85% (by area) of the total mixture, followed by a second (10–12%) and a third peak (3–5%) with retention times of about 1 and 2 min longer, respectively, than the product peak. These impurities have not been identified.

α,β-Dimethyl-3,5-dimethoxyhydrocinnamic acid (14) isomers were synthesized from **11** by the same procedure used to prepare **12** (except diethyl methylmalonate was used instead of the amylmalonate) and the isomers were separated similarly. The dicyclohexylamine salt of *erythro* **14** had mp 158–159° (acetone).

Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.57; H, 9.85; mol wt, 420. Found: C, 71.6; H, 10.0; mol wt, 426 (titrimetric).

The benzylamine salt of *threo* **14** had mp 159–160° (benzene).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.6; H, 7.9. Found: C, 69.6; H, 8.0.

erythro **14**, mp 105–106°, and *threo* **14**, mp 90–92°, were recovered in quantitative yield from the above salts. Compound **14** has been reported[7] (mp 75°) undoubtedly consisting of a mixture of the two diastereoisomers.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6; neut equiv, 238. Found for *erythro:* C, 65.1; H, 7.6; neut equiv, 241. Found for *threo*: C, 65.7; H, 7.7; neut equiv, 243.

In an earlier experiment, a fractional recrystallization of the dicyclohexylamine salts of **14** from ether–petroleum ether resulted in the isolation of the dicyclohexylamine salt of the *threo* **14** isomer, mp 103–104.5°, from the tail crop filtrates.

Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.57; H, 9.85; mol wt, 420. Found: C, 71.8; H, 9.9; mol wt, 418 (titrimetric).

***cis*- and *trans*-α,β-Dimethyl-3,5-dimethoxycinnamic Acids (15 and 16).**—The ether solution (10 ml) of a crude isomeric mixture of **15** and **16** (2.2 g, by titration of an aliquot), obtained by hydrolysis of a mixture of their crude ethyl esters,[7] was combined with 1.8 g of dicyclohexylamine in 5 ml of ether. Petroleum ether (23 ml) was added, and the solution was seeded (with product earlier obtained in this way) and set aside at room temperature, then cooled to give 0.7 g of needles,

(20) Procedure suggested by Dr. R. L. Hively, formerly of these laboratories.

(21) In the corresponding *n*-amyl series **1**, three (crystalline) compounds have been isolated from product prepared by the Adams' procedure: F. Korte and H. Sieper, *J. Chromatog.*, **13**, 90 (1964), and references cited therein.

mp 153–158°. A portion (0.3 g) was recrystallized from ether (10 ml, after concentration) to give 0.25 g of the dicyclohexylamine salt of the *trans* acid (**16**), mp 161–163°. The original filtrates were evaporated down, then taken up in about 10 ml of petroleum ether to give the dicyclohexylamine salt of the *cis* acid, 1.8 g of prisms, mp 92–95° (raised to 93.5–95° on recrystallization from petroleum ether).

Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.9; H, 9.42; mol wt, 418. Found for *trans*: C, 72.1; H, 9.5; mol wt, 423 (titrimetric). Found for *cis*: C, 72.4; H, 9.7; mol wt, 418.

The *trans*-dicyclohexylamine salt, 0.25 g, was taken up in 30 ml of dilute aqueous hydrochloric acid to form a milky solution which rapidly crystallized on stirring. Recovery yielded 0.12 g of **16**, mp 110–112°.

The *cis* salt, 0.6 g, was treated with 50 ml of dilute acid to form an oil which crystallized when scratched and cooled to give 0.3 g of **15**, mp 56–60° (62–63° after recrystallization from petroleum ether).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.1; H, 6.8.

Reaction of 16 and 15 with Sulfuric Acid.—The *trans* acid **16** (0.10 g) was dissolved by shaking with 4 ml of concentrated sulfuric acid. After standing at ambient temperature for 5 hr, the mixture was poured onto 100 ml of ice and water to produce a milky solution, which crystallized on standing in the cold to return the starting material (0.07 g), mp 108–110°. This material was redissolved in aqueous base and reprecipitated with acid to give **16** (0.06 g), mp 111–113°.

The original aqueous filtrate (yellowish) was extracted with ether. Part of the yellow color was extracted into the ether layer; a second ether wash did not remove any additional coloration. The aqueous phase was pale yellow. The ether layers were combined and concentrated to a yellow oil, which when stirred with a little aqueous base, formed a yellow solid, **17** (0.0036 g), mp 130–132°, apparently formed by isomerization of some of **16** to **15** and subsequent ring closure, under the acidic conditions.

When **15** (0.10 g) was treated exactly as above, no starting material was recovered. In this case there was obtained 2,3-dimethyl-5,7-dimethoxyindenone, **17** (0.010 g), mp 132–134° and infrared band at $\nu_{C=O}^{CCl_4}$ 1700 cm^{-1} (Perkin-Elmer 237B).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.6; H, 6.46. Found: C, 71.3; H, 6.1.

The ketone (**17**) gave a phenylhydrazone, mp 160–162°.

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.2; H, 6.54. Found: C, 73.7; H, 6.6.

The major portion of the *cis* acid (**15**) was converted into yellow, water-soluble products, apparently sulfonated derivatives of **17**, which were not investigated.

Hydrogenation of 15 and 16.—The dicyclohexylamine salt of **15**, 0.30 g in 10 ml of methanol, was shaken for 2 hr with 0.1 g of 10% palladium on charcoal in a Parr hydrogenator at 40 psig at ambient temperature. The solution was filtered, concentrated to 2 ml, cooled, and diluted with a little water to give 0.15 g of the dicyclohexylamine salt of *erythro* **14**, mp 157–159°, undepressed when admixed with authentic material. The filtrate was acidified with dilute aqueous hydrochloric acid to give 0.05 g of *erythro* **14**, mp 102–103.5°, undepressed when admixed with authentic material.

The dicyclohexylamine salt of **16** (0.20 g) was reduced as above, filtered, and evaporated to dryness to give 0.17 g of the dicyclohexylamine salt of *threo* **14**, mp 101–105°, undepressed when admixed with authentic material.

Registry No.—**2** acetate, isomer 1, 14950-75-5; **2** acetate, isomer 2, 14950-76-6; **2** acetate, isomer 3, 15077-23-3; **2** acetate, isomer 4, 14950-77-7; **2** acetate, isomer 5, 14950-78-8; **2** acetate, isomer 6, 14950-79-9; **2** acetate, isomer 7, 15206-43-6; **2** acetate, isomer 8, 14950-80-2; **6**, (+) *threo*, 14950-73-3; **6**, (−) *threo*, 14950-74-4; **6**, (+) *erythro*, 14950-84-6; **6**, (−) *erythro*, 14950-83-5; **9**, isomer 1, 15077-24-4; **9**, isomer 2, 14950-50-6; **9**, isomer 3, 14950-51-7; **9**, isomer 4, 14950-52-8; **9**, isomer 5, 14950-53-9; **9**, isomer 6, 15077-25-5; **9**, isomer 7, 14950-54-0; **9**, isomer 8, 14950-71-1; **11**, 14950-55-1; **12**, (+) *threo*, 14950-56-2; **12**, (−) *threo*, 14950-57-3; **12**, (+) *erythro*, 14950-82-4; **12**, (−) *erythro*, 14950-81-3; **12**, *erythro*-dicyclohexylamine salt, 14950-58-4; **12**, *threo*-benzylamine salt, 14950-59-5; **13**, (+) *threo*, 15077-26-6; **13**, (−) *threo*, 14950-72-2; **13**, (+) *erythro*, 14950-60-8; **13**, (−) *erythro*, 14950-61-9; **14**, *threo*, 14950-85-7; **14**, *threo*-dicyclohexylamine salt, 14950-62-0; **14**, *threo*-benzylamine salt, 14950-63-1; **14**, *erythro*, 14950-64-2; **14**, *erythro*-dicyclohexylamine salt, 14950-65-3; **15**, 15077-27-7; **15**, dicyclohexylamine salt, 14950-67-5; **16**, 14950-66-4; **16**, dicyclohexylamine salt, 14950-68-6; **17**, 14950-69-7; **17**, phenylhydrazone, 14950-70-0.

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