(57%); mp 141–142°; nmr τ 4.00 (s, 1, benzylic), 2.2–3.3 (m, 15, aromatic and vinyl), 2.0–2.2 (m, 1, aromatic peri to Cl).

Anal. Calcd for $C_{25}H_{17}Cl$: C, 85.0; H, 4.9; Cl, 10.1. Found: C, 84.7; H, 4.9; Cl, 10.4.

5,5-Dichloro-5*H*-benzocycloheptene (3).—A solution of 4.5 g (0.029 mol) of 5*H*-benzocyclohepten-5-one[6] in 25 ml of dry methylene chloride was cooled in an ice bath while phosgene was passed in until 10 g (excess) had dissolved. The solution was left at room temperature under nitrogen overnight and the product was distilled: 5.6 g (92%); bp 105° (0.10 mm); nmr τ 4.9–5.0 (m, 1, vinyl), 3.9–4.1 (m, 2, vinyl), 3.1–3.2 (m, 1, vinyl), 2.4–2.8 (m, 3, aromatic), 2.0–2.2 (m, 1, aromatic). The dichloride should be kept in a freezer or under nitrogen because it decomposes when left at room temperature in air.

Anal. Calcd for $C_{11}H_8Cl_2$: C, 62.6; H, 3.8; Cl, 33.6. Found: C, 62.5; H, 3.6; Cl, 33.3.

The dichloride (1.0 g) was dissolved in 10 ml of 10% water in tetrahydrofuran, heated at reflux for 30 min, concentrated, and distilled (0.70 g, 95%). The nmr spectrum of the product was identical with that of 5*H*-benzocyclohepten-5-one.

Thermal Decomposition of Chlorides 1b,[7] 3, and 4.[8]—When each of these chlorides was heated at 180–200° for 10–30 min, black tars resulted. Chloroform extracts afforded poor nmr spectra with no benzylic proton absorption. Column chromatography of the extracts gave no identifiable materials. Similar results were obtained when the chlorides were heated at reflux in *o*-dichlorobenzene until decomposition occurred.

Registry No.—1c, 33482-70-1; 1d, 33482-71-2; 2c, 33482-72-3; 2d, 33482-73-4; 3, 33482-74-5.

(6) G. L. Buchanan and D. R. Lockhart, *J. Chem. Soc.*, 3586 (1969).
(7) G. Berti, *J. Org. Chem.*, **22**, 230 (1957).
(8) B. Föhlisch, P. Brügle, and D. Krockenberger, *Chem. Ber.*, **101**, 2717 (1968).

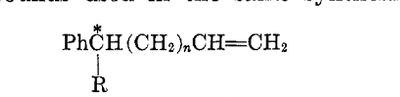
Enantiomeric Purity of 3-Phenyl-4,4-dimethyl-1-pentene. A Chemical Interrelation between the Maximum Rotations of α-*tert*-Butylphenylacetic Acid and β-*tert*-Butyl-β-phenylpropionic Acid

L. LARDICCI* AND R. MENICAGLI

Istituto di Chimica Organica Facoltà di Scienze Mat., Fis. e Nat., Università di Pisa, Pisa, Italy

Received June 23, 1971

In the course of CD investigations of α olefins I,[1] we found it necessary to obtain optically active 3-phenyl-4,4-dimethyl-1-pentene (**5**) for which the relationship between optical purity and $[\alpha]_D$ could be determined with a reasonable reliability by starting from optically active compounds used in the same synthesis. The

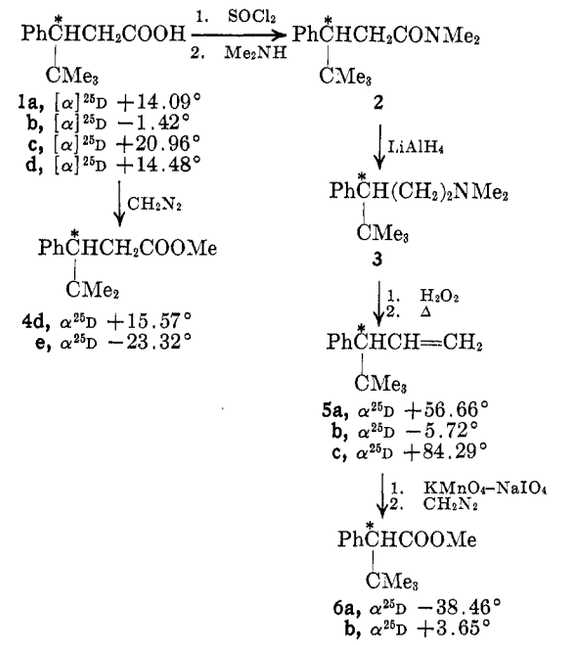


I, R = Me, Et, *i*-Pr, *tert*-Bu; n = 0, 1, 2

absolute configuration of α-*tert*-butylphenylacetic acid (**7**) and β-*tert*-butyl-β-phenylpropionic acid (**1**) has been recently determined[2-4] and the maximum rotations of **1** and **7** have been established from optical resolution criteria.[5,6]

In the present paper we report the synthesis of optically active **5** (Scheme I), the relationship between its optical purity and optical rotation (Scheme I), and some evidences of the reliability of the maximum rotations of **1** and **7** previously reported[5,6] and now interrelated by a chemical method (Schemes I and II).

SCHEME I[a]



[a] All specific rotations are in $CHCl_3$ and all observed rotations are l = 1 dm, neat.

(*S*)- and (*R*)-*N*,*N*-dimethyl-3-phenyl-4,4-dimethylpentylamine (**3**) were prepared[1] (80–90% yield), *via* **2**, from the corresponding optically active β-phenyl-β-*tert*-butylpropionic acid (**1**) (Scheme I), in its turn obtained by resolution of the racemic acid[7] with brucine and cinchonidine.[5]

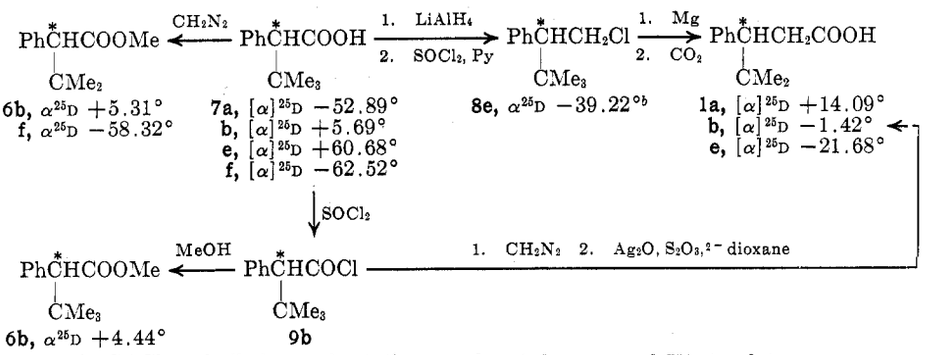
By pyrolysis of the amine **3** oxide at 120° (1.5 mm),[1,8] isomer-free (*S*)- and (*R*)-**5** were recovered in high yield (86–88%) and high chemical purity (99%) (Scheme I). The olefin **5**, $\alpha^{25}D$ +56.66°, was oxidized by permanganate–periodate reagent in 60% aqueous *tert*-butyl alcohol[9] to yield optically active α-*tert*-butylphenylacetic acid (**7**), converted by diazomethane into the methyl ester **6a**, $\alpha^{25}D$ −38.46°.[10]

According to our experimental data the optical purity of **6a** is 65.5% [based on $[\alpha]^{25}D$ max 62.9° ($CHCl_3$) for the optically pure acid **7**][6] and that of **1a**, used in the synthesis of **5** (Scheme I), is 63.4% [based on $[\alpha]^{25}D$ max 22.2° ($CHCl_3$) for optically pure acid **1**].[5]

By assuming that the oxidative degradation of **5**

(1) L. Lardicci, R. Menicagli, and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 738 (1968).
(2) D. R. Clark and H. S. Mosher, *J. Org. Chem.*, **35**, 1114 (1970).
(3) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967).
(4) The configuration assigned to (+)-β-*tert*-butyl-β-phenylpropionic acid by Cram, *et al.*,[3] was confirmed and correctly designated *R* by Clark and Mosher.[2] In a subsequent paper by Almy and Cram [*ibid.*, **91**, 4460 (1969)] the correct configurational formulas were used but the wrong configurational rotation was assigned to this acid and several derivatives.
(5) J. Almy and D. J. Cram, *ibid.*, **91**, 4467 (1969).
(6) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2801 (1967).
(7) C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 1640 (1943).
(8) L. Lardicci, R. Menicagli, and P. Salvadori, *Chim. Ind.* (*Milan*), **52**, 83 (1970).
(9) E. Gil-Av and J. Shabtai, *J. Org. Chem.*, **29**, 261 (1964).
(10) Since the recovered crude acid **7** could be further resolved during the purification, we preferred to check its minimum optical purity by converting it into the methyl ester **6a**, for which the relationship between optical purity and α_D has been established in the present investigation.

SCHEME II[a]



[a] All specific rotations are in $CHCl_3$ and all observed rotations are l = 1 dm, neat. [b] *Via* tosylate.

occurs without appreciable racemization,[1,8,11] the maximum specific rotation of optically pure 3-phenyl-4,4-dimethyl-1-pentene lies therefore within the range 98–101° (at 25°) and earlier maximum rotations reported for the α-*tert*-butylphenylacetic acid[6] and for the β-*tert*-butyl-β-phenylpropionic acid[5] are substantially in a good agreement as indicated by the results of the Scheme I.[12]

The synthesis of optically active **5** had also been carried out by starting from (*S*)- and (*R*)-α-*tert*-butylphenylacetic acid (**7**) (Scheme II).[6]

The homologation of **7** to **1** was performed both by carbonation of the Grignard reagent prepared from the chloride **8**[1,2] and by Arndt–Eistert reaction[13] on the optically active acid **7b** (Scheme II).

Following the sequence recently reported by Clark and Mosher[2] and starting from **7a** (optical purity 84%),[6] a sample of **1a** (optical purity 63.4%)[5] was recovered (Scheme II).

Reaction of the acid chloride **9b** (from **7b**, optical purity 9%)[6] with diazomethane gave the corresponding crude diazo ketone; its rearrangement was effected in the usual fashion using silver thiosulfate in aqueous dioxane.[13] A sample of (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1b**), having $[\alpha]^{25}D$ −1.42° ($CHCl_3$) (optical purity 6.4%),[5] was recovered.

Using the rotations of methyl ester **6** obtained from (*S*)-(+)-α-*tert*-butylphenylacetic acid (**7b**) by treatment with diazomethane and by conversion to the acid chloride **9b** followed by treatment with methanol, it was possible to evaluate the maximum racemization in the formation and purification of **9b** (Scheme II). On this basis the acid chloride **9b**, used in the Arndt–Eistert reaction, is 7.5% optically pure.

While in the sequence **9b** → **1b** the observed 15% racemization is in agreement with that reported in the literature,[13] the reason for a 24.5% racemization in the sequence **7a** → **8a** → **1a** is not apparent since the homologation reaction *via* alcohol, chloride, Grignard, and carbonation of this reagent has been widely employed in similar cases[1,8,14] as a chemical process not affecting bonds to the asymmetric carbon atom.

However, a parallel investigation on the chemical and optical purity of several samples of optically active 3,3-dimethyl-2-phenyl-1-chlorobutane **8** (from the corresponding alcohol by treatment with thionyl chloride in dry pyridine)[2] showed that the optical rotation of the product from different experiments varied significantly.[15]

Indeed, a sample of (*S*)-(−)-3,3-dimethyl-2-phenyl-1-chlorobutane (**8e**) obtained from **7e**, optical purity 96.5%[6] (*via* alcohol, tosylate, and its treatment with lithium chloride in dimethylformamide),[16] was converted into the Grignard reagent which was carbonated to give (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1e**), the optical purity of which, evaluated through the methyl ester **4e** (Schemes I and II), is 97.5%.

The close agreement between the optical purity of (*S*)-(+)-α-*tert*-butylphenylacetic acid (**7e**) and of (*S*)-(−)-β-*tert*-butyl-β-phenylpropionic acid (**1e**) (Scheme II) confirms that (1) the sequence of homologation *via* Grignard reagent proceeds even in this case with a very high degree of retention of configuration but (2) the conversion of optically active 3,3-dimethyl-2-phenyl-1-butanol into the corresponding chloride **8**, upon treatment of the alcohol with thionyl chloride and pyridine,[2] occurs, at least in the conditions we have adopted, with a 25% racemization. Therefore the sequence **7a** → **8a** → **1a** is not suitable to establish the relationships between optical purities and optical rotations of the acids **1** and **7**.

Experimental Section[17]

(*R*)-(+)-*N*,*N*-**Dimethyl-3-phenyl-4,4-dimethylpentanamide** (**2**).—To an ether solution of 16.0 g (0.080 mol) of **1c**, mp 94–95° (lit.[5] mp 94.5–95.0°), $[\alpha]^{25}D$ +20.96° (*c* 2.636, $CHCl_3$), was added 22.14 g (0.186 mol) of thionyl chloride and the mixture was left aside for 24 hr and then refluxed for 4 hr. The crude chloride, in ether, was cooled at −15° and an ether solution of 2 equiv of dimethylamine was added.[18] The reaction mixture was worked up as previously described[18] and the ether was removed to leave 17.0 g (91%) of crude amide **2c**: mp 96–97°;

(11) D. D. Davis and G. G. Ansari, *J. Org. Chem.*, **35**, 4285 (1970).

(12) The little discrepancy (2–3%) between the minimum optical purity values of olefin **5** could fall within the range of the experimental errors either in the evaluation of minimum optical purity of the starting products (Scheme I) or in the assumed values for the maximum rotations of the acids **1** and **7**.

(13) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

(14) L. Lardicci and R. Menicagli, *Chim. Ind. (Milan)*, **51**, 1387 (1969).

(15) The crude **8** recovered showed several glpc peaks and, in order to obtain isomers and impurities-free product, a difficult and tedious purification is to be carried out. Nevertheless, the optical rotations of chlorides **8**, of comparable chemical purity (≥97%), did not agree with those of the corresponding optically active acids **7**. At present the authors think, in agreement with the suggestions of referees, that some rearrangement takes place during the thionyl chloride reaction in the presence of pyridine. This may be responsible of the observed presence of isomers and impurities in the crude **8** and of the observed racemization, too (see sequence **7a** → **8a** → **1a**).

(16) A. Herdenberger, private communication.

(17) All boiling and melting points are uncorrected. Glpc analyses were performed on a C. Erba Fractovap Mod. GT instrument equipped with 2-m columns filled with 10% 1,4-butanediol succinate (BDS) on Chromosorb W 60–80 and N_2 as carrier gas. All rotations were taken on a Schmidt–Haensch polarimeter with sensitivity of ±0.005° in 1-dm tubes.

(18) N. L. Drake, C. M. Eaker, and W. Shenk, *J. Amer. Chem. Soc.*, **70**, 677 (1948).

$[\alpha]^{25}D$ +43.75° (*c* 3.440, benzene). A sample was crystallized once from *n*-heptane: mp 98–99°; $[\alpha]^{25}D$ +47.29° (*c* 3.478, benzene). In a similar manner from **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$), and **1b**, $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$), was obtained **2a**, $[\alpha]^{25}D$ +29.41° (*c* 3.478, benzene), and **2b**, mp 107–108°, $[\alpha]^{25}D$ −2.93° (*c* 3.478, benzene), respectively. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.68; H, 9.80; N, 6.13.

(*R*)-(+)-*N*,*N*-Dimethyl-3-phenyl-4,4-dimethylpentylamine (3).—A solution of 15.5 g (0.066 mol) of crude **2c** in 230 ml of anhydrous ether was slowly added to a stirred suspension of 5.87 g (0.154 mol) of $LiAlH_4$ in 130 ml of ether. The resulting mixture was stirred at the reflux temperature for 26 hr and then it was worked up by a standard procedure[1] to give 13.0 g (90%) of **3c**: bp 84° (1.4 mm); $n^{25}D$ 1.4934–1.4936; $\alpha^{25}D$ +19.08° (neat); $[\alpha]^{25}D$ +18.65° (*c* 2.198, benzene). Runs **a** and **b** were carried out under identical conditions to give amines **3a** [bp 95° (2.3 mm), $\alpha^{25}D$ +12.84° (neat)] and **3b** [bp 79° (1 mm); $n^{25}D$ 1.4930–1.4931; $\alpha^{25}D$ +1.28° (neat)]. *Anal.* Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.89; H, 11.45; N, 6.45.

(*R*)-(+)-3-Phenyl-4,4-dimethyl-1-pentene (5).—The amine **3c** (12.5 g, 0.057 mol) was converted to its oxide[19] which was heated under 1.5 mm of pressure at a temperature of 120° until the decomposition was complete, 25 min. The distillate was worked up by the usual manner[19] and the crude alkene was distilled to give 8.5 g (86%) of **5c** [99% pure by glpc analysis (on 2-m Apiezon L column at 160°)]: bp 94° (15 mm); $n^{25}D$ 1.5032; $\alpha^{25}D$ +84.29° (neat). In run **a** the olefin was purified by preparative glpc (on 5-m 10% BDS column at 140°) to give pure **5a** (>99%): bp 97° (16 mm); $n^{25}D$ 1.5028; d_4^{25} 0.8808; $\alpha^{25}D$ +56.66° (neat); $[\alpha]^{25}D$ +64.33° (neat). Its ir spectrum showed no bands at 1625 and 980–960 cm^{-1}.[1] On a later run from **3b** was obtained **5b**: $n^{25}D$ 1.5029–1.5030; $[\alpha]^{25}D$ −6.49° (neat). *Anal.* Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.87; H, 10.16.

(*R*)-(+)-2-Phenyl-3,3-dimethyl-1-butanol.—To 25.2 g (0.664 mol) of $LiAlH_4$ in 326 ml of ether was added dropwise 70.0 g (0.364 mol) of **7a**, $[\alpha]^{25}D$ −52.89° (*c* 5.294, $CHCl_3$),[6] in 270 ml of dry ether. The mixture was refluxed 20 hr and then worked up by a standard procedure[1,2] to give 63.5 g (98%) of crude (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol which was extracted continuously with pentane; from the resultant solution the carbinol (62.0 g), mp 96° [lit. mp of partially active material,[2] 75–90°], $[\alpha]^{25}D$ +2.00° (*c* 5.212, $CHCl_3$), was recovered. On a later run from **7e**, $[\alpha]^{25}D$ +60.68° (*c* 4.958, $CHCl_3$), was obtained (−)-carbinol: mp 97°; $[\alpha]^{25}D$ −2.31° (*c* 6.060, $CHCl_3$). In run **f** the acid **7**, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), was reduced to give a product with mp 97°, $[\alpha]^{25}D$ +2.38° (*c* 5.988, $CHCl_3$).

(*R*)-(+)-3-Phenyl-4,4-dimethylpentanoic Acid (1).—(*R*)-(+)-2-Phenyl-3,3-dimethyl-1-butanol, $[\alpha]^{25}D$ +2.00 ($CHCl_3$), was converted into **8a**, 88% pure (glpc).[2] The Grignard reagent from the above chloride was carbonated with Dry Ice. The reaction mixture was processed in the usual way[1] to give 9.5 g (57%) of crude **1a**, mp 108–110° (lit.[7] 114–116°). The acid was extracted continuously with pentane to yield 9.0 g of **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$); its methyl ester was shown to be 99% pure (glpc). On a later run from **8e** (98% pure), bp 79° (1.5 mm) [lit.[2] 79–82° (1 mm)], $n^{25}D$ 1.5153, $\alpha^{25}D$ −39.22° (neat) [obtained by reacting the tosylate of the carbinol, $[\alpha]^{25}D$ −2.31 ($CHCl_3$), with LiCl in dimethylformamide (62% yield)],[15] was prepared **1e**, mp 94–95°. This acid was converted, by diazomethane, to its methyl ester **4e**: bp 133° (13 mm); $n^{25}D$ 1.4953; $\alpha^{25}D$ −23.32° (neat).

(*S*)-(+)-2-Phenyl-3,3-dimethylbutanoic Acid Methyl Ester (6).—To a solution of 2.13 g (0.011 mol) of **7f**, mp 142°, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), in 15 ml of ether at 0° was added slowly and with shaking an ether solution of diazomethane. The excess of diazomethane and ether was removed under reduced pressure and distillation gave 2.0 g (88%) of **6f**: bp 122° (15 mm); $n^{25}D$ 1.4938; $\alpha^{25}D$ −58.32° (neat). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.02; H, 8.67.

(*R*)-(+)-3-Phenyl-4,4-dimethylpentanoic Acid Methyl Ester (4).—By the method above described 2.04 g (0.0098 mol) of **1d**, mp 93–94°, $[\alpha]^{25}D$ +14.48° (*c* 2.624, $CHCl_3$), was converted to **4d** (82%): bp 139–140° (15 mm); $n^{25}D$ 1.4946; $\alpha^{25}D$ +15.57° (neat). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.12.

(19) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2137 (1952).

Arndt–Eistert Reaction on the (*S*)-2-Phenyl-3,3-dimethylbutanoic Acid (7).—The acid **7b** (73.0 g, 0.379 mol), $[\alpha]^{25}D$ +5.69° (*c* 5.443, $CHCl_3$), was converted to its chloride (**9b**) with the procedure above described for **1c**. A 3.5-g sample of distilled acid chloride was treated with absolute methanol.[13] Distillation gave 2.5 g (75%) of **6b**: $n^{25}D$ 1.4940; $\alpha^{25}D$ +4.44° (neat); $[\alpha]^{25}D$ +4.36° (*c* 5.150, MeOH). The residual chloride (75.0 g, 0.356 mol), bp 89° (2 mm), in 180 ml of ether was reacted with an ice-cold ether solution of diazomethane, prepared from 2.9 mol of *N*-nitrosomethylurea.[13] The crude diazo ketone, in 575 ml of purified dioxane, was subjected to the Wolff rearrangement in a solution of aqueous dioxane containing silver oxide and sodium thiosulfate.[13] The recovered acid was extracted continuously with pentane to give 53.1 g (72%) of **1b**: mp 116°; $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$).

Oxidation of (*R*)-(+)-3-Phenyl-4,4-dimethyl-1-pentene (5).—The alkene **5a** (3.0 g, 0.017 mol), $[\alpha]^{25}D$ +64.33° (neat), was oxidized in 112 hr, by $KMnO_4$–$NaIO_4$ mixture in 60% aqueous *tert*-butyl alcohol, according to the procedure of Gil-Av and Shabtai.[9] The crude acid (83%) was esterified with diazomethane to give **6a**: $n^{25}D$ 1.4935; $\alpha^{25}D$ −38.46° (neat). In another experiment **5b**, $[\alpha]^{25}D$ −6.49° (neat), afforded **6b**: $n^{25}D$ 1.4940; $\alpha^{25}D$ +3.65° (neat).

Registry No.—**1**, 23406-59-9; **2**, 33124-15-1; **3**, 33124-16-2; **4**, 33124-17-3; **5**, 33124-18-4; **6**, 26164-17-0; **7**, 13490-71-6; (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol, 33124-21-9.

Acknowledgment.—This work was partially supported by the Consiglio Nazionale delle Ricerche through the "Istituto di Chimica delle Macromolecole," Milan, Italy.

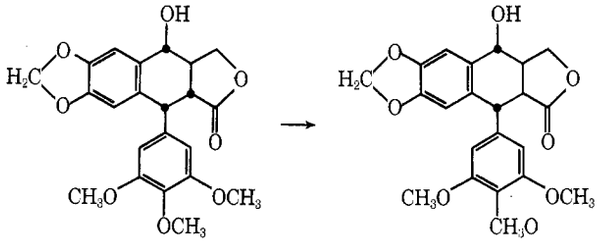
2-Carboxydeoxypicropodophyllin

WALTER J. GENSLER,* JOHN FRANCIS X. JUDGE, AND MERVYN V. LEEDING

Department of Chemistry, Boston University, Boston, Massachusetts 02215

Received August 26, 1971

Podophyllotoxin (**1**) and also derivatives such as deoxypodophyllotoxin (**3**), which have the same con-



podophyllotoxin (**1**) → picropodophyllin (**2**)

figurations at positions 1, 2, and 3,[1] are active cytotoxic agents and have been extensively investigated as cancer chemotherapeutic agents.[2] All of these podophyllo-

(1) J. L. Hartwell and A. N. Schrecker, *Progr. Chem. Org. Natur. Prod.*, **15**, 83 (1958).

(2) *Cf.* M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954); H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim.-Forsch.*, **11**, 327, 459 (1961); E. Schreier, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966, Paper P-34. Two derivatives have actually received considerable clinical application, namely, *O*,*O*-benzylidenepodophyllotoxin-β-D-glucoside and podophyllic acid *N*-ethylhydrazide (*cf.* H. Lettré and S. Witte, "Experimentelle und Klinische Erfahrungen mit Podophyllinderivaten in der Tumortherapie," F. K. Schattauer-Verlag, Stuttgart, 1967).