Tetrahedron, 1960, Vol. 11, pp. 22 to 29. Pergamon Press Ltd. Printed in Northern Ireland

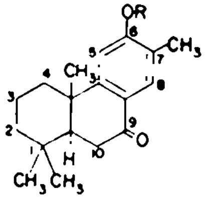
THE CONVERSION OF PODOCARPIC ACID TO NIMBIOL[1]

R. H. Bible, Jr.
Division of Chemical Research, G. D. Searle and Company, Chicago 80, Illinois

(*Received* 13 *April* 1960; *in revised form* 9 *May* 1960)

Abstract Podocarpic acid has been unambiguously converted to nimbiol[2] and nimbiol methyl ether[3] thus confirming the complete structures assigned[3,4] to these substances. In the course of this work, a group of C-7 methyl derivatives of podocarpic acid has been prepared. The physical constants of these methyl derivatives are compared with the constants of the parent substances.

Nimbiol, a compound isolated[2] from the trunk bark of *Melia azadirachta* Linn. has been assigned[3,4] the structure Ia.



Ia R=H

b R=CH3

The pioneering work of Campbell and Todd[5] together with our own previous experience with the introduction of various substituents on the phenolic ring of podocarpic acid (C-7)[6] and with the introduction of a keto group at the carbon adjacent to the phenolic ring (C-9)[7] placed us in a favorable position to confirm the complete structure assigned[4] to nimbiol by Choudhuri *et al.*

Methyl O-methyl-7-carboxypodocarpate (II),[8] a compound readily available by the oxidation of methyl O-methyl-7-acetylpodocarpate,[5a] was reduced with lithium aluminum hydride in tetrahydrofuran to the diol III. The hydroxymethylene on the aromatic ring in III was smoothly converted to the desired methyl group by hydrogenolysis over palladium charcoal in the presence of hydrochloric acid. It was anticipated that the conversion of the alcohol (IV) to the aldehyde (V) would be complicated by oxidation of the aldehyde to the acid and by the conversion of the C-9 methylene group to a keto group. From model experiments using O-methylpodocarpinol it was found that the C-1 hydroxymethylene group could be converted to the aldehyde most

---

[1] A preliminary report of this work has been published: R. H. Bible, Jr., *Tetrahedron Letters* No. 9, 20 (1960); E. Wenkert and V. I. Stenberg have recently reported on the partial synthesis of nimbiol: 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April (1960); and M. Fetizon and J. Delobelle have reported on the synthesis of d,l-nimbiol methyl ether: *Tetrahedron Letters* No. 9, 16 (1960).

[2] P. Sengupta, S. N. Choudhuri and H. N. Khastgir, *Chem. & Ind.* 861 (1958).

[3] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 634 (1959).

[4] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 1284 (1959).

[5] [a] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.* **62**, 1287 (1940); [b] W. P. Campbell and D. Todd, *Ibid.* **64**, 928 (1942).

[6] [a] R. H. Bible, Jr., *J. Amer. Chem. Soc.* **79**, 3924 (1957); [b] U.S. Pat. 2,750,373 (1956).

[7] U.S. Pat. 2,705,725 (1955); U.S. Pat. 2,759,014 (1956); U.S. Pat. 2,854,474 (1958).

[8] U.S. Pat. 2,767,162 (1956).

conveniently by oxidation with chromic acid–sulfuric acid in acetone.[*] The alcohol (IV) was smoothly converted to the aldehyde (V) using these conditions. The work of Campbell and Todd[5b] indicated that the Wolff–Kishner reduction of this aldehyde through the semicarbazone (VI) would be accompanied by partial demethylation of the ether. In view of this anticipated demethylation, the crude reduction product (VII) was remethylated. In order to ascertain if a C-7 alkyl group would undergo oxidation

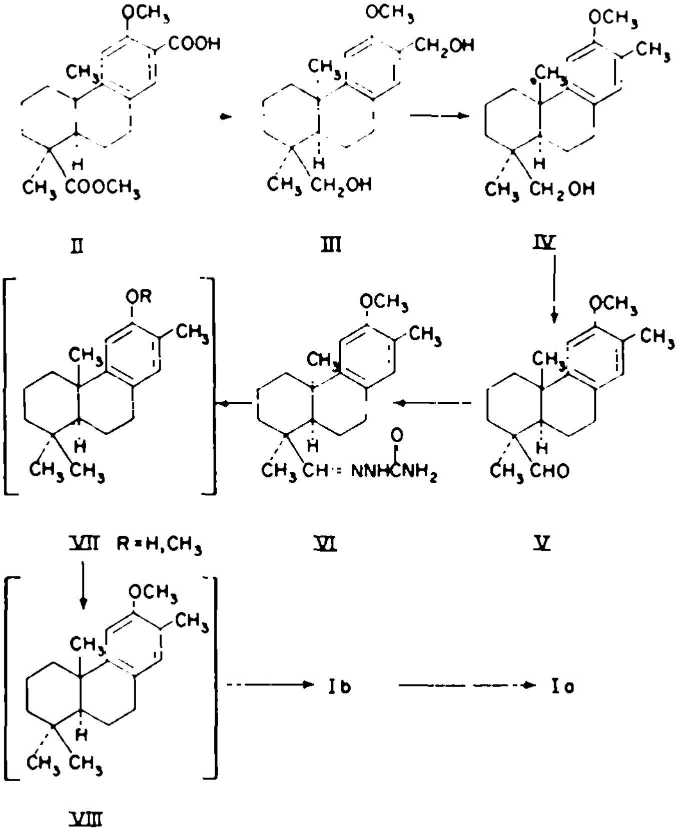


FIG. 1.

under conditions similar to those which we had previously employed[7] for the introduction of a C-9 keto group, methyl O-methyl-7-propylpodocarpate was subjected to these conditions. Methyl O-methyl-7-propyl-9-oxopodocarpate was obtained in good yield. Application of these oxidizing conditions to the crude remethylated Wolff–Kishner reduction product (VIII) gave an easily isolable crystalline solid having the structure Ib. This material was shown to be identical with nimbiol methyl ether by a comparison of physical constants (Table 1) and by a direct comparison of the substances (no depression of the melting point on admixture; identical infrared absorption spectra; identical ultraviolet spectra). Demethylation of the ether Ib with pyridine hydrochloride gave the corresponding free phenol Ia. The physical properties

---

[*] The use of this method was suggested by an observation made by Dr. Robert R. Burtner. The reagent was prepared by dissolving chromic acid (136.2 g) and conc sulfuric acid (110 ml) in water (total volume = 500 ml). See K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

of this phenol (Table 2) were in good agreement with those reported for nimbiol; direct comparison (no depression of the melting point on admixture; identical infrared absorption spectra in KBr) proved that these two substances were identical. Remethylation of the phenol (Ia) gave the starting methyl ether (Ib).

This conversion of podocarpic acid to nimbiol thus confirms the complete structure assigned[4] to nimbiol by Choudhuri *et al.*

Our first approach to the synthesis of VI was by the Rosenmund reduction of the

TABLE 1. COMPARISON OF Ib PREPARED FROM PODOCARPIC ACID WITH NIMBIOL METHYL ETHER

Compound	m.p.	$[\alpha]_D^{CHCl_3}$	λ_{max}^{EtOH} mμ (ϵ)
Ib	142–144°	+43°	229·5 (15,000) 278·5 (13,900) 300 (shoulder)
Nimbiol methyl ether[3]	142–143°	+43·7°	229·5 (15,000)* 278·5 (14,000) 300 (shoulder)

* Our values obtained using a sample from Dr. P. Sengupta.

TABLE 2. COMPARISON OF Ia PREPARED FROM PODOCARPIC ACID WITH NIMBIOL

Compound	m.p.	$[\alpha]_D^{CHCl_3}$	λ_{max} mμ (log ϵ)	
			EtOH	0·1 N NaOH/95% EtOH
Ia	248–252°	+33°	234 (4·13), 283 (4·10), 300 (shoulder)	253 (3·84), 345 (4·38)
Nimbiol[3]	244°	+32·2°	231 (4·07), 286 (4·06)	251 (3·89), 344 (4·33)

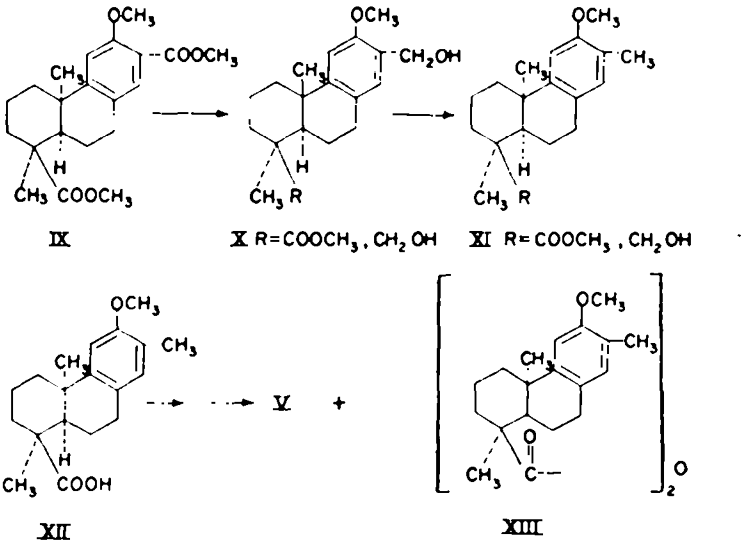
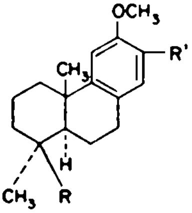


FIG. 2.

TABLE 3. COMPARISON OF C-7 METHYL DERIVATIVES OF PODOCARPIC ACID WITH THE CORRESPONDING PARENT COMPOUNDS



Compound	R	R′	m.p.	$[\alpha]_D^{CHCl_3}$*	λ_{max}^{MeOH} mμ (ε)*
O-Methylpodocarpinol[1b]	CH_2OH	H	90–91·5°	+67°	279 (2330) 286·5 (2080)
IV	CH_2OH	CH_3	83–85°	+68°	280 (2970) 287 (2830)
O-Methylpodocarpinal[1b]	CHO	H	133–135°	+87°	279 (2490) 286·7 (2250)
V	CHO	CH_3	110–111·5°	+87°	281 (3090) 286 (2990)
O-Methylpodocarpinal semicarbazone[1b]	$\mathrm{CH{-}NNH\overset{O}{C}NH_2}$	H	205° (d)		278·5 (2570) 286·6 (2305)
VI	$\mathrm{CH{-}NNH\overset{O}{C}NH_2}$	CH_3	210 212°		280 (3290) 286 (3060)
O-Methylpodocarpic acid[11]	COOH	H	158°	+132°	278·5 (2320) 286·5 (2106)
XII	COOH	CH_3	196·5 199·5°	+131°	280 (3020) 286·5 (2900)
Anhydride of O-methylpodocarpic acid	$(CO)_2O$	H	212·5 215°	+116°	278·5 (4650) 286·5 (4200)
XIII	$(CO)_2O$	CH_3	199·5–203°	+112°	

* The values given here for the known substances were obtained by us using samples prepared by the published procedures.

corresponding acid chloride. For this purpose the diester (IX) was allowed to react with lithium aluminum hydride in tetrahydrofuran at room temperature for a short time. It was anticipated that the highly hindered C-1 ester would not be reduced under these conditions.[10] Quite unexpectedly the hindered ester was reduced to a large extent. The resulting product (X) was hydrogenated to give the corresponding mixture (XI) of C-7 methyl derivatives. Hydrolysis of this mixture followed by purification of the acidic portion gave O-methyl-7-methylpodocarpic acid. The reduction of the acid chloride of XII gave the anhydride (XIII) along with the aldehyde

---

[10] H. H. Zeiss, C. E. Slimowicz and V. Z. Pasternak, *J. Amer. Chem. Soc.* **70**, 1981 (1948), found that podocarpic acid was reduced only very slowly (4·6% in 2 hr) by lithium aluminum hydride. Since these authors had used a 4 day reaction time for the reduction of methyl O-methylpodocarpate, we had assumed that the ester group was also reduced very slowly.

[11] I. R. Sherwood and W. F. Short, *J. Chem. Soc.* 1006 (1938).

(V) which was isolated as the semicarbazone (VI). This route was not as convenient as that shown in Fig. 1 for the preparation of a reasonable amount of VI.

During the course of this work a number of C-7 methyl derivatives of substances related to podocarpic acid became available. The physical properties of these homologs are summarized in Table 3. The introduction of the C-7 methyl group causes an increase in the molecular extinction coefficient of the ultraviolet absorption bands. Consistent differences can be detected in the infrared absorption spectra (Table 4). A number of these differences can be assigned to various effects on the aromatic ring[11] [decrease in intensity of the in-plane skeletal vibration bands in the 6 μ region; disappearance of the out-of-plane hydrogen bending band (two adjacent hydrogens) at about 12·4 μ; increase in intensity of the 11·72 μ band (isolated hydrogens)] while others (doublet near 8 μ becomes a single band; decrease in intensity of the 9·58 μ band) can probably be attributed to the change in the environment of the methoxy group.[12]

TABLE 4. CONSISTENT CHANGES IN THE INFRARED ABSORPTION SPECTRA BROUGHT ABOUT BY THE INTRODUCTION OF A C-7 METHYL GROUP IN PODOCARPIC ACID DERIVATIVES (SOLUTIONS IN CHLOROFORM)*

These bands disappear:	7·77, 8·51 μ, and 12·38 ± 0·07 μ (KBr)
These bands appear:	8·76 and 9·96 μ†
The ratios of intensities of these bands decrease:	6·18, 6·34 (pair)‡/6·64 μ, 9·58/9·37 μ
This doublet becomes a single band:	7·89, 7·96 → 7·94 μ
The intensity of this band is increased:	11·72 μ

* Wave lengths of these bands have varied ± 0·03 μ.
† The anhydride of O-methylpodocarpic acid also has a strong band in this region.
‡ The semicarbazones have a complicating band at 6·37 μ.

EXPERIMENTAL[13]

Except where noted, rotations were determined using 0·5–1·20% chloroform solutions; infrared adsorption spectra were obtained using chloroform solutions; and ultraviolet adsorption spectra were run on methanol solutions. All melting points were taken on a Fisher–Johns block and were corrected using standard compounds.

Methyl O-methyl-7-carboxypodocarpate[6,14] (II). A solution of sodium hydroxide (72 g) in water (600 ml) was cooled to 3°. Bromine (36 ml) was added dropwise with stirring while the reaction mixture was maintained at 3–5° over a period of 45 min. The resulting mixture was stirred for an additional 15 min. A solution of methyl O-methyl-7-acetylpodocarpate[6] (68·8 g) in t-butanol (1300 ml) was added to the reaction mixture at 4–6° over a period of 50 min. The reaction mixture was stirred at 3–5° for an additional 30 min followed by stirring at room temp overnight. A solution of sodium sulfite (83·4 g) in water (800 ml) was added to the reaction mixture. The solution was acidified with conc HCl and was then diluted with water to a total volume of 12 l. The solid was collected, washed with water, and then recrystallized twice from aqueous acetone (charcoal); 59·7 g; m.p. 169·5–170·5°; $[\alpha]_D$ +134°; λ_{max} 242 (ϵ 9410) and 302 mμ (ϵ 3420); 5·85 (broad) and 3·06μ

---

[11] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.) p. 65. John Wiley, New York (1958).

[12] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.) p. 115. John Wiley, New York (1958).

[13] All U.V. and I.R. spectra and rotations were performed by the Analytical Department of G. D. Searle and Company under the direction of Dr. R. T. Dillon. Elementary analyses were determined by the Analytical Department and by Micro-Tech, Skokie, Illinois.

[14] This oxidation was patterned after the method described [U.S. Pat. 2,769,822 (1956)] for progesterone.

(KBr). (Found: C, 69·51; H, 7·52. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%). (Reported:[8] m.p. 164°.)

O-*Methyl-7-hydroxymethylpodocarpinol* (III). A solution of II (25·4 g) in tetrahydrofuran (150 ml) was added with stirring over a period of 27 min to a solution of lithium aluminum hydride (10 g) in tetrahydrofuran (200 ml). Within 30 min a large amount of white solid separated from the reaction mixture. An additional 100 ml of tetrahydrofuran was added. The reaction mixture was stirred and refluxed for 1·5 hr and was then allowed to stand at room temp for 16 hr. The reaction mixture was decomposed by the sucessive addition of a solution of water (11 ml) in tetrahydrofuran (100 ml), 20% (w/v–8 ml) aqueous sodium hydroxide, and water (37 ml). The white solid was filtered off and washed with tetrahydrofuran. The combined filtrates were diluted to a total volume of 6 l., with water. The resulting crystalline solid (19·3 g; m.p. 119·5–123°) was recrystallized from aqueous methanol (charcoal); $[\alpha]_D$ +69°; λ_{max} 280 (ϵ 2860); and 285 mμ (ϵ 2,850) 2·73 and 2·85 μ. (Found: C, 74·94; H, 9·19. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%).

O-*Methyl-7-methylpodocarpinol*[15] (IV). A solution of the diol III (12 g) in 95% ethanol (100 ml) was shaken with 5% palladium–charcoal (3 g) in an atmosphere of hydrogen (35–60 lb/in²) at room temp for a total of 16·5 hr. The product was crystallized from aqueous methanol and the resulting solvated material was azeotroped dry with benzene. The residue was stirred with a small amount of hexane. This mixture was permitted to evaporate. The resulting crystalline solid amounted to 9·2 g; λ_{max} 2·75 and 2·85 μ (see Table 3). (Found: C, 79·11; H, 9·94. $C_{19}H_{28}O_2$ requires: C, 79·12; H, 9·79.)

O-*Methyl-7-methylpodocarpinal* (V). The alcohol IV (4·00 g) in acetone (25 ml) was oxidized with a standard chromic acid sulfuric acid solution[9] (3·37 ml). The product was purified by the method used below for O-methylpodocarpinal. Two recrystallizations from aqueous acetone gave the desired aldehyde; 2·48 g; λ_{max} 3·62 and 5·79 μ. (See Table 3.) The sample for analysis was sublimed at 0·1 mm (Found: C, 79·44; H, 9·34. $C_{19}H_{26}O_2$ requires: C, 79·68; H, 9·15). A small amount of O-methyl-7-methylpodocarpic acid (XII) was obtained as a by-product in this oxidation.

Semicarbazone of O-*methyl-7-methylpodocarpinal* (VI). The aldehyde V (2·02 g) in pyridine (75 ml) was treated[16] with a solution of semicarbazide acetate (prepared from 4 g of semicarbazide hydrochloride and 4·0 g of sodium acetate) in 95% ethanol (40 ml). This solution was allowed to stand overnight and then was diluted with water. The crude product was washed with water and was then dried at 100° at 0·1 mm for 2 hr; 2·34 g; m.p. 200·5–211·5°. An analytical sample was obtained by two recrystallizations from aqueous methanol; λ_{max} 2·81, 2·86, 2·92, 2·96, 5·88 and 6·36 μ. (See Table 3.) (Found: C, 69·88; H, 8·38. $C_{20}H_{29}N_3O_2$ requires: C, 69·94; H, 8·51%).

6-*Methoxy-7-methyl-9-oxopodocarpane*[15] (Ib). The crude semicarbazone (2·34 g) was heated with a solution of sodium ethoxide in ethanol (prepared by dissolving 5 g of sodium in 50 ml of absolute ethanol) at 200–210° for 15 hr. The reaction mixture was diluted with water and ether. The ether layer was washed with water. The residue resulting from removal of the ether was dissolved in methanol and remethylated by treatment with 10% sodium hydroxide and dimethyl sulfate. The remethylated material was taken up in ether. The ether was washed with water. The residue remaining after removal of the ether was azeotroped dry with benzene, and then dissolved in acetic acid (50 ml). A slurry of chromic acid (0·650 g) in water (0·25 ml) and acetic acid (1·0 ml) was added slowly to the acetic acid solution. This reaction mixture was allowed to stand at room temp overnight. The reaction mixture was diluted with water and ether. The ether solution was washed with water, Claisen's alkali, and then with water. The ether was removed to give a crystalline residue. This material was recrystallized 4 times from aqueous methanol (charcoal); 0·71 g. This product was identical (no depression of the m.p. on admixture; identical infrared absorption spectrum at 5% in chloroform; identical ultraviolet spectra) with nimbiol methyl ether.[2] (See Table 1).

6-*Hydroxy-7-methyl-9-oxopodocarpane* (Ia). The ether Ib (0·30 g) was heated with pyridine hydrochloride (2·0 g) at 210° for 40 min. The reaction mixture was diluted with water. The product was collected, washed with water, recrystallized twice from aqueous methanol, and then sublimed (0·01 mm); 0·13 g; platelets. This product was identical [no depression of the m.p. on admixture; identical infrared absorption spectra (KBr)] with nimbiol.[2] (See Table 2.) Remethylation of the phenol with 10% NaOH and dimethyl sulfate gave the original methyl ether (Ib).

O-*Methylpodocarpinal.*[16] A standard chromic acid sulfuric acid solution[9] (2·43 ml) was added

---

[15] We are indebted to M. G. Scaros for technical assistance in the hydrogenations and in the Wolff–Kishner reduction.

[16] This procedure was patterned after that described by Campbell and Todd[17].

with stirring to a solution of O-methylpodocarpinol (2·74 g) in acetone (25 ml). The reaction was maintained at 15–26° during this addition. The reaction mixture was diluted with water and ether. The aqueous layer was separated and re-extracted twice with ether. The combined ether layers were washed successively with water, 10% aqueous sodium hydroxide, and then with water. Distillation of the ether gave a crystalline residue which was recrystallized from aqueous acetone to give the aldehyde; 2·02 g; m.p. 135 139·5°; λ_{max} 3·64 and 5·81 mμ (see Table 3).

A solution of O-methylpodocarpinol (2·74 g) in pyridine (30 ml) was added to a cold solution of chromic acid (1·55 g) in pyridine[17] (30 ml). The resulting mixture was allowed to stand overnight. The mixture was diluted with water and ether. After removal of the solid by filtration, the ether solution was washed with water, 2% sodium hydroxide, and finally with water. Removal of the solvent gave a residue which was recrystallized from aqueous acetone to give the aldehyde; 0·65 g; m.p. 132–136·5°.

A mixture of O-methylpodocarpinol (2·00 g), toluene (100 ml), cyclohexanone (32 ml), and 16·8 ml of a 25% (w/v) solution of aluminum isopropoxide in toluene was refluxed for 30 min. The cooled mixture was treated with a saturated solution of sodium potassium tartrate (100 ml). The organic layer was separated and washed with sodium potassium tartrate solution and then with water. The solvent and excess cyclohexanone were distilled under vacuum. The residue was dissolved in acetone. After removal of a small amount of insoluble material, the acetone solution was diluted at its b.p. with water until the solution was turbid. The crystalline material which precipitated on cooling was recrystallized 3 more times from aqueous acetone; 0·15 g; m.p. 131–136°.

Methyl O-methyl-7-methoxycarbonylpodocarpate (IX). The acid II was methylated by repeated treatment with 10% sodium hydroxide and dimethyl sulfate in methanol. The product was dissolved in ether. The ether solution was washed successively with water, 2% sodium hydroxide, and then with water. The ester was recrystallized from aqueous methanol; m.p. 141 143·5°; $[\alpha]_D$ +132°; λ_{max} 243 (ε 10,000) and 305 mμ (ε 3660); 5·78 μ (broad). (Found: C, 69·73; H, 7·78. $C_{21}H_{28}O_5$ requires: C, 69·97; H, 7·83%).

O-*Methyl-7-methylpodocarpic acid* (XII). The diester IX (20·0 g) was dissolved in ether (750 ml) and benzene (100 ml). This solution was added (45 min) to a mixture of lithium aluminum hydride (4 g) in ether (100 ml). An additional 100 ml of benzene was added to the mixture. The resulting slurry was stirred for 40 min at room temp. The excess lithium aluminum hydride was decomposed by the successive addition of ethyl acetate (100 ml), water (100 ml), and 10% HCl (200 ml). The organic layer was separated and washed with water, 2% HCl, and then with water until the washings were neutral. The solvents were distilled. The residual glass was dissolved in 95% ethanol (total volume, 120 ml).

Part of this ethanol solution (110 ml) was shaken under an atmosphere of hydrogen (35–60 lb/in^2) at room temp overnight with 5% palladium-charcoal (3·0 g) and conc HCl (1 drop). After the catalyst and solvent were removed, the residue was recrystallized 3 times from aqueous ethanol. The product melted over a wide range beginning at 56·5° (11·3 g).

This mixture (9·7 g) was heated for 5 hr at 165° with potassium hydroxide (20 g), water (10 ml), and diethylene glycol (200 ml). The resulting solution was diluted with water. The precipitate, which was shown by infrared to be O-methyl-7-methylpodocarpinol, was removed by filtration. Acidification of the filtrate gave a solid which was recrystallized from aqueous methanol (charcoal); 2·27 g; λ_{max} 2·84, 3·66, 3·72, 5·74, and 5·88 μ (see Table 3). (Found: C, 75·63; H, 8·86. $C_{19}H_{26}O_3$ requires: C, 75·46; H, 8·67%).

Rosenmund reduction of the acid chloride.[18] The acid XII (2·00 g) was refluxed for 40 min with thionyl chloride (2 ml; purified). The excess thionyl chloride was distilled. Benzene was added and distilled yielding a crystalline product.

The crude acid chloride was dissolved in xylene (250 ml) and treated at reflux temp. with a slow stream of hydrogen in the presence of palladium over 5% barium sulfate (0·55 g) for 5 hr. Removal of the catalyst and solvent gave a residual glass which was crystallized from ethanol; 0·51 g; m.p. 194 198·5°. Purification by recrystallization from ethanol followed by sublimation gave the pure *anhydride of* O-*methyl-7-methylpodocarpic acid*; λ_{max} 5·55 and 5·75 μ (see Table 3). (Found: C, 77·45; H, 8·84. $C_{38}H_{50}O_5$ requires: C, 77·78; H, 8·59%).

The mother liquor from the recrystallization of the anhydride was concentrated and then diluted with water. The resulting solid was used for the preparation of the semicarbazone by the method

[17] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* 75, 422 (1953).

used above. The product, when recrystallized 4 times from aqueous ethanol (charcoal) melted at 205·5–212·5° and was undepressed on admixture with the semicarbazone prepared from the pure aldehyde.

Methyl O-*methyl-7-propylpodocarpate.* A solution of methyl O-methyl-7-propionylpodocarpate[6a] (40·0 g) in acetic acid (210 ml) was shaken in an atmosphere of hydrogen (10–30 lb/in²) in the presence of conc HCl (1 drop) and 5% palladium–charcoal (4·0 g) for 24 hr at room temp. The resulting mixture was warmed on a steam-bath. The catalyst was removed and the filtrate was diluted at its b.p. with water until the solution was slightly turbid. The desoxy compound crystallized on cooling; 34·0 g; platelets, m.p. 104–105°; $[\alpha]_D$ +125°; λ_{max} 280 (ε 3240) and 287 mμ (ε 3170). (Found: C, 76·95; H, 9·41. $C_{22}H_{32}O_3$ requires: C, 76·70; H, 9·36%).

Methyl O-*methyl-7-propyl-9-oxopodocarpate.* To a cool (15°) solution of methyl O-methyl-7-propylpodocarpate (10·0 g) in acetic acid (150 ml) was added a slurry of chromic acid (6·31 g) in water (2·5 ml) and acetic acid (10 ml) at such a rate that the temp of the reaction did not exceed 21°. This reaction was allowed to stand at ice-water bath temp for an additional 30 min and was then allowed to stand at room temp overnight. The solution when diluted with water (total volume, 3·5 l.) gave a solid which was collected, washed with water, and then recrystallized twice from aqueous methanol; 7·9 g; m.p. 115·5–118°; $[\alpha]_D$ +86°; λ_{max} 230·5 (ε 17,300) and 277·5 mμ (ε 13,830), (shoulder at 298 mμ);[10] 5·78 and 5·97 μ. (Found: C, 73·46; H, 8·37. $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44%).

Anhydride of O-*methylpodocarpic acid* (XIII). This substance was isolated as a by-product in the preparation of the amide of O-methylpodocarpic acid. O-methylpodocarpic acid (21·2 g) was converted to the crude acid chloride.[6b] This material was stirred into conc ammonium hydroxide (250 ml). The resulting mixture was heated on the steam-bath for 5 min with stirring. The product was taken up in a mixture of benzene and ether. This solution was washed with water, 10% sodium hydroxide, and then with water. The washed solution was stripped to give a residual glass. Treatment of this residue with acetone (400 ml) gave a white granular solid (1·4 g). This solid was recrystallized twice from aqueous acetic acid. The anhydride of O-methylpodocarpic acid crystallized as short needles; λ_{max} 5·59 and 5·76 μ (Table 3). (Found: C, 76·91; H, 8·13. $C_{36}H_{46}O_5$ requires: C, 77·38; H, 8·30%).

Acknowledgement—We are highly indebted to Dr. P. Sengupta of the East India Pharmaceutical Works Ltd., Calcutta-34, India, for the gift of the nimbiol and the nimbiol methyl ether.

---

[10] Compare with the isomeric methyl O-methyl-7-propionylpodocarpate[6a] m.p. 103.5–105°; $[\alpha]_D$ −134°, $\lambda_{max}^{ethanol}$ 255 (ε 10,500) and 315 mμ (ε 4090).