The reactivity of 2 was investigated by the reactions to carbon–carbon double bonds and carbonyl compounds, and the results are shown in Table I. The

TABLE I
REACTIVITY OF *p*-METHOXYCARBONYLPERBENZOIC ACID

Olefin or ketone	Yield of oxidation product, %	Yield with perbenzoic acid, %
Cyclohexene	90	100[c]
1-Methylcyclohexene	77	50–75[c]
1,5,9-*cis,trans,trans*-Cyclododecatriene	76[a]	64–90[d]
4-Vinylcyclohexene	72[b]	82[e]
Styrene	60	69–75[c]
Cyclopentanone	74	70–80[f]
Cyclohexanone	64	71[f]
Acetophenone	85	50–80[g]

[a] Reacted with only one of trans double bonds. [b] 4-Vinylcyclohexene oxide. [c] D. Swern, "Organic Reactions," Vol. VII, R. Adams, Ed., Wiley, New York, N. Y., 1953, p 378. [d] Peracetic acid was used: G. Wilke, *Angew. Chem.*, **69**, 397 (1957). [e] F. C. Frostick, Jr., B. Phillips, and P. S. Starcher, *J. Amer. Chem. Soc.*, **81**, 3350 (1959). [f] S. L. Friess, *ibid.*, **71**, 2571 (1949). [g] S. L. Friess and A. H. Soloway, *ibid.*, **73**, 3968 (1951).

yields of the epoxidation and Baeyer–Villiger reaction ranged from 60 to 90% and 64 to 85%, respectively, generally corresponding to the reactivity of perbenzoic acid and monoperoxyphthalic acid. The peracid 2 is fairly soluble in dioxane, ethanol, acetone, acetonitrile, and *N*,*N*-dimethylformamide, and less soluble in chloroform, benzene, and ether.

The by-product of the reaction is *p*-methoxycarbonylbenzoic acid, which is far less soluble than 2, and may be separated easily since it precipitates out from the reaction system when a suitable solvent is employed.

Although a more extensive application of the peracid 2 to other organic compounds is necessary, the fact that 2 may be simply prepared and is relatively stable is sufficient to commend it as a new convenient reagent for epoxidation and Baeyer–Villiger oxidation.

Experimental Section

All melting points are uncorrected. The ir spectra were obtained on a Hitachi EPI-S2 spectrophotometer and the nmr spectra on a Varian A-60 spectrometer.

A 2-kW mercury quartz lamp made by Toray Engineering Laboratories was used without any filter.

Preparation of Methyl *p*-Formylbenzoate (1).—The method of Lieberman and Connor was applied to the oxidation of methyl *p*-methylbenzoate.[8]

The crude aldehyde, 52 g (43.8%), was recrystallized from ether or subjected to column chromatography with Woelm neutral alumina (activity I) using ether as an eluent, showing mp 62–63°.[9]

Preparation of *p*-Methoxycarbonylperbenzoic Acid (2).—Methyl *p*-formylbenzoate (1) (2 g) and 50 ml of carbon tetrachloride were placed in a cylindrical glass reactor (50 mm diameter × 250 mm length) equipped with a gas inlet tube connected to a gas buret. The reaction mixture, which was a suspension, was vigorously shaken under an atmosphere of oxygen and irradiated with the 2-kW high-pressure mercury lamp.

Oxygen (290 ml) was absorbed in 0.5 hr at room temperature (theoretical volume was 298 ml at 25°). The material which separated as white crystalline powder was collected and dried. The product was confirmed to be mainly *p*-methoxycarbonylperbenzoic acid (2) (2.0 g, 84% yield). An iodometric titration showed that the purity of the crude product was about 90%. No explosion occurred by heating in a capillary tube and no decomposition point was observed. The peracid thus obtained was pure enough for general oxidation reactions, but, if a purer product is desired, it may be recrystallized from methanol: ir (KBr) 3268 (OH), 1730 cm^{-1} (COOOH); nmr (dioxane) δ 3.91 (s, 3, OCH_3), 8.09 (s, 4, aromatic), and 12.36 (s, 1, OH).

Anal. Calcd for $C_9H_8O_5$: C, 55.10; H, 4.11; mol wt, 196. Found: C, 55.21; H, 4.11; mol wt, 179 (Rast).

One should be careful in using the peracid, since it irritates the nasal membranes and causes sneezing. The yield of the peracid is greatly influenced by the purity of methyl *p*-formylbenzoate and the presence of heavy metal ions.

Reaction with Cyclohexene.—In a 300-ml three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel were placed 6.112 g of 2 and 200 ml of chloroform. Cyclohexene (2.544 g) dissolved in 20 ml of chloroform was added dropwise to the suspension, keeping the temperature below 20°. After addition, it was allowed to stand overnight with stirring at this temperature.

Precipitates of *p*-methoxycarbonylbenzoic acid (4.650 g) were removed by filtration and the filtrate was washed two times with 100 ml of 10% aqueous sodium carbonate solution, with 2 g of sodium hydrogen sulfite in 100 ml of water, and with a saturated aqueous solution of sodium chloride. After drying, the solvent was removed at atmospheric pressure, and an oily residue was distilled under reduced pressure to obtain 2.763 g of 7-oxabicyclo[4.1.0]heptane as a colorless oil. The yield was 90%.

Reaction with Cyclopentanone.—In a 300-ml erlenmeyer flask equipped with a dropping funnel, 7.632 g of 2 and 150 ml of chloroform were placed and the flask was cooled in an ice bath. Then cyclopentanone (1.628 g) dissolved in 30 ml of chloroform was added to the solution. After addition, the mixture was magnetically stirred under cooling for 4 hr and allowed to stand for 4 days at room temperature. Precipitates of *p*-methoxycarbonylbenzoic acid (6.63 g) were removed by filtration and the filtrate was washed two times with 100 ml of 10% aqueous sodium carbonate solution and washed with a saturated aqueous solution of sodium chloride. After drying, the solvent was removed at atmospheric pressure, and an oily residue was distilled under reduced pressure to obtain 1.437 g of 5-pentanolide as a colorless oil. The yield was 75%. The same procedure was applied to other olefins and carbonyl compounds.

Registry No.—2, 28276-78-0.

(8) S. L. Lieberman and R. Connor, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1955, p 441.

(9) H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949).

The Conversion of Podocarpic Acid to an 18-Nor Steroid

DESMOND M. S. WHEELER* AND PETER R. WITT

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received June 1, 1972

The use of podocarpic acid[1] (**1a**) and other resin acids as starting materials for the synthesis of steroids has been investigated by several groups.[2–5] We now report the synthesis of an 18-nor steroid (**5b**) from **1a**.

(1) J. L. Simonsen and D. H. R. Barton, "The Terpenes," University Press, Cambridge, 1961, Vol. III, p 472.

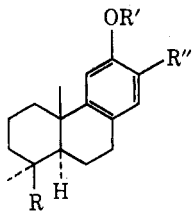
(2) Cambie and his coworkers[3] devised a route for removing the geminal methylcarboxyl group in podocarpic acid and producing a Δ^4-3-one system in ring A; their final product was 12-methoxy-18,19-bisnorpodocarpa-4,8,11,13-tetraen-3-one. Davis and Watkins[4] converted the methyl ether of methyl podocarpate to 4β-methoxycarbonyl-4α-methyl-12-methoxy-18-norandrosta-8,11,13-trien-15-one, a steroid with ring C aromatic, and also the corresponding D-homo steroid.

(3) C. R. Bennett and R. C. Cambie, *Tetrahedron*, **23**, 927 (1967); R. C. Cambie and W. A. Denny, *Aust. J. Chem.*, **22**, 1699 (1969); C. R. Bennett, R. C. Cambie, R. A. Franith, and T. J. Fullerton, *ibid.*, p 1711.

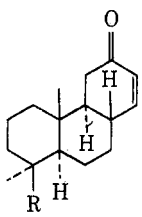
(4) B. R. Davis and W. B. Watkins, *Tetrahedron*, **24**, 2165 (1968); *Aust. J. Chem.*, **21**, 1611 (1968).

(5) J. W. Huffman, *J. Org. Chem.*, **35**, 478 (1970).

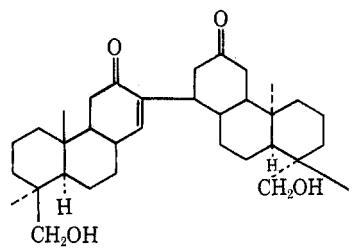
Podocarpic acid (**1a**) was converted into the unsaturated ketones **2a**[6-9] (which is best prepared by Bell



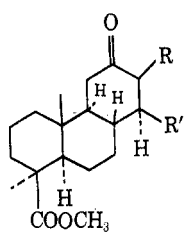
1a, R = COOH; R′ = R″ = H
b, R = $COOCH_3$; R′ = CH_3; R″ = Ac
c, R = COOH; R′ = CH_3; R″ = Ac
d, R = COOH; R′ = CH_3; R″ = $CHOHCH_3$
e, R = $COOCH_3$; R′ = CH_3; R″ = $CHOHCH_3$



2a, R = $COOCH_3$
b, R = CH_2OAc
c, R = CH_2OH



3



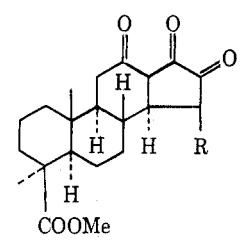
4a, R = H; R′ = $CH(COOC_2H_5)_2$
b, R = H; R′ = $CH(COOH)_2$
c, R = H; R′ = CH_2COOH
d, R = H; R′ = CH_2COOCH_3
e, R = $COCOOCH_3$; R′ = CH_2COOCH_3
f, R = H; R′ = $CH(COOCH_3)_2$

and Gravestock's route[6,7,9]) and **2b**.[7,9,10] In the course of unsuccessful attempts[9] to improve the route to **2a** and **2b** *via* the Birch reduction of derivatives of **1a**,[7,9] we prepared the compounds **1c**, **1d**, and **1e**.

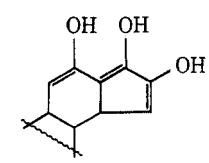
Attempts to use the keto acetate **2b** as an acceptor in Michael additions were complicated by **2b** undergoing a self-condensation to give **3**, the structure of which follows from its analytical and spectral data and its preparation by keeping **2b** in ethanol in the presence of sodium ethoxide. Clearly the mechanism involves a Michael addition of the anion from **2b** or **2c** with another molecule of **2b** or **2c**. Similar dimerizations have been reported for other compounds.[11]

In contrast to **2b**, **2a** showed no tendency to undergo the self-condensation; there is no obvious reason for this difference in behavior. Addition of diethyl malonate to **2a** took place smoothly to give **4a**, whose nmr spectrum showed signals for the two ethyl groups in slightly different positions. The triester was hydrolyzed to the diacid **4b**, which on decarboxylation gave the monoacid **4c**. Methylation with diazomethane gave the diester **4d**. The nmr spectrum of **4d** showed two sharp singlets corresponding to the methoxy groups, thus indicating that **4d** is a single isomer; the stereochemistry of the C_{14} side chain is suggested on the basis that Michael additions of malonate in protonated solvents give the equatorial epimer.[12]

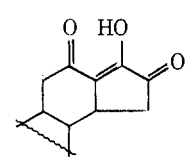
After attempts to convert **4c** to its homolog *via* the Arndt–Eistert synthesis failed,[9] we tried to complete ring D by condensing **4d** with dimethyl oxalate.[13] As the products of these condensations hydrolyzed easily, the reactions were only successful when done under rigorously defined conditions. Condensation of **4d** with dimethyl oxalate in the presence of sodium methoxide gave **4e** as a mixture of tautomers. When the condensation was done in the presence of sodium hydride in dimethylformamide, a product soluble in sodium hydroxide was isolated. The spectral data indicated that the product was mainly **5a**. As we were not able to purify this product, we converted it to crystalline **5b** by hydrolysis and decarboxylation



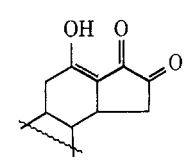
5a, R = COOMe
b, R = H



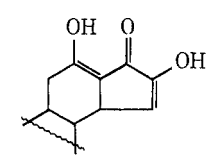
6



7



8



9

under acid conditions. The structure **5b** is supported by the spectral data recorded in the Experimental Section. The properties of **5b** indicate that it exists to a large extent as one or more of seven possible tautomeric enols. Consideration of the observed ultraviolet maxima in conjunction with maxima calculated[14] for each of the possible enols suggests that the tautomer **6** (λ_{max}^{calcd} 307 nm) and one or more of the forms **7** (λ_{max}^{calcd} 266 nm), **8** (λ_{max}^{calcd} 272 nm), and **9** (λ_{max}^{calcd} 272 nm) are the main enolic forms.

(6) R. A. Bell and M. B. Gravestock, *Can. J. Chem.*, **47**, 3661 (1969).
(7) R. H. Bible and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).
(8) T. A. Spencer, R. A. J. Smith, D. L. Storm, and R. M. Villarica, *J. Amer. Chem. Soc.*, **93**, 4856 (1971).
(9) For details see P. R. Witt, Ph.D. Thesis, University of Nebraska, 1970.
(10) R. C. Cambie, W. A. Denny, T. R. Klose, and L. N. Mander, *Aust. J. Chem.*, **24**, 99 (1971).
(11) N. J. Leonard and W. J. Musliner, *J. Org. Chem.*, **31**, 639 (1966); J. E. Engelhart and J. R. McDivitt, *ibid.*, **36**, 367 (1971).
(12) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(13) *Cf.* J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Amer. Chem. Soc.*, **90**, 439 (1968).
(14) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, pp 50, 60–71, 257, and 264–269.

Experimental Section[15]

The Base-Catalyzed Self-Condensation of 19-Acetoxypodocarp-13-en-12-one (2b).—A solution of sodium (120 mg, 5 mg-atoms) in absolute ethanol (5 ml) was added to 19-acetoxypodocarp-13-en-12-one (**2b**),[9,10] (150 mg, 0.5 mmol) in ethanol (4 ml) in a nitrogen atmosphere. After stirring for 1.25 hr the solution was diluted with water (75 ml) containing concentrated hydrochloric acid (1 ml). The precipitate (100 mg, 78%), 19-hydroxypodocarp-13-en-12-one-13-(14-(19-hydroxypodocarp-12-one)) (**3**), crystallized from ethyl acetate–acetonitrile to give product with mp 231–250°, which showed as a single spot on tlc: ν_{max} 3640, 1705, and 1670 cm^{-1}; nmr δ 0.60–2.63 (45 H, m with strong s at 0.87, 0.90, and 0.93), 3.52 (4 H, m, $-CH_2OH$), and 6.37 (1 H, d, J = 1 Hz, =CH); λ_{max} 241 nm (ϵ 5500).

Attempted Michael reactions of diethyl malonate with **2b** were complicated by the formation of the dimer, **3**.

Anal. Calcd for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.44; H, 9.76.

Methyl 14-(Diethylmalonyl)-12-ketopodocarp-19-oate (4a).—A solution of the unsaturated keto ester **2a**[6,8,9] (290 mg, 1 mmol) in ethanol (4 ml) was added dropwise to a stirred solution of sodium (12 mg, 0.5 mg-atom) and diethyl malonate (320 mg, 2 mmol) in ethanol (6 ml) at room temperature in a nitrogen atmosphere. The mixture was stirred for 4 hr and diluted with water (125 ml) containing concentrated hydrochloric acid (7 drops). The product was recovered by extraction with ether and the ethereal extract was washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether *in vacuo* gave an oil which was refluxed (30 min) with glacial acetic acid (0.5 ml), ethanol (5 ml), and Girard's "T" reagent (0.52 g). The cooled mixture was diluted with water (25 ml) and saturated aqueous sodium chloride (5 ml), and the nonketonic material was removed by extraction with ether. The aqueous layer was acidified to pH 2, kept for 2 hr, and then extracted with ether. The ethereal extract was washed three times with water and once with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether *in vacuo* yielded the adduct **4a** (225 mg, 50%) as a yellow oil: ν_{max} 1740 (shoulder) and 1720 cm^{-1}; nmr δ 0.65–2.9 (30 H, m with strong s at 0.69 and 1.19 and triplets at 1.27 and 1.30), 3.48 [1 H, d, J = 7 Hz, $C(COOC_2H_5)_2H$], 3.67 (3 H, s, $-OCH_3$), and 4.21 and 4.26 (2 H each, q, J = 7 Hz, $-OCH_2CH_3$).

In a similar way dimethyl malonate was added to keto ester **2a**. The product (**4f**), which was obtained in 56% yield, had ν_{max} at 1715 (shoulders at 1730 and 1750) cm^{-1} and nmr δ 0.6–3.00 (22 H, m with sharp s at 0.70 and 1.20), 3.48 (1 H, d, J = 7 Hz), 3.82 (3 H, s, OCH_3), and 3.93 (6 H, 2s, OCH_3).

Dimethyl 12-Keto-14-(acetic acid)podocarp-19-oate (4d).—A solution of the unsaturated keto ester **2a** (363 mg, 1.25 mmol), diethyl malonate (588 mg, 3.68 mmol), and sodium (9 mg, 0.375 mg-atom) in absolute ethanol (7.5 ml) was stirred under nitrogen for 3.5 hr. A solution of sodium hydroxide (0.68 g, 17 mmol) in water (6.6 ml) was added and the mixture was stirred (15 min) and then refluxed (45 min). The cooled solution was diluted with water (20 ml) and saturated aqueous sodium chloride (20 ml) and was extracted with ether, and the extracts were discarded. The aqueous layer was acidified with hydrochloric acid (6 *N*) at 0° and extracted with ether. The combined ethereal extracts were washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether under reduced pressure gave the diacid **4b** (384 mg, 78%) as a white foam. The diacid was heated (150–170°) in a nitrogen atmosphere for 1 hr, producing a glass which crystallized from ether–light petroleum to give the acid **4c**, mp 157–163° (293 mg, 67%). Recrystallization gave mp 161–165°; ν_{max} 3490 and 1720 cm^{-1}; nmr δ 0.55–2.85 (26 H, m with strong s at 0.72 and 1.20) and 3.67 (3 H, s, OCH_3).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.57; H, 8.77.

The methyl ester **4d** was prepared by treating the acid **4c** (2.22 g, 6.35 mmol) in ether with excess ethereal diazomethane. Removal of the ether *in vacuo* afforded a yellow oil which on crystallization from ether–hexane gave the ester **4d**: mp 72.5–75.5° (1.97 g, 85%), ν_{max} 1720 cm^{-1}; nmr δ 0.6–2.75 (26 H, m with sharp s at 0.70 and 1.18) and 3.65 (6 H, 2 s, OCH_3).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.80; H, 8.99.

4α-Methyl-4β-carbomethoxy-18-norandrostane-12,16,17-trione (5b).—Sodium hydride (520 mg of 50% dispersion in mineral oil, 10.9 mmol) was added to a mixture of the methyl ester **4d** (944 mg, 2.75 mmol) and dimethyl oxalate (650 mg, 5.48 mmol) in dimethylformamide (7 ml). The addition of methanol (7 drops), *ca.* 2.75 mmol) to this mixture led to a vigorous evolution of hydrogen. The mixture was stirred at room temperature for 65 min and then was heated for 30 min at 50–80°. The cooled (ice) mixture was acidified with glacial acetic acid (1 ml) and poured into water (75 ml). The aqueous mixture was extracted with ether and the ethereal extract was washed four times with water and once with saturated aqueous sodium chloride and dried (Na_2SO_4). The ethereal solution was treated with charcoal and the ether was removed *in vacuo* to yield an orange-brown foam (1.08 g). A solution of the foam in ether was extracted with 0.5 *N* sodium hydroxide solution and the aqueous extract was acidified with 2 *N* hydrochloric acid and extracted with ether. The ethereal extract was washed with water and saturated aqueous sodium chloride and filtered through anhydrous sodium sulfate, and the ether was removed *in vacuo* to yield a yellow foam (520 mg, 50%). The product gave a strong color with ethanolic ferric chloride: ν_{max} 3550–3000, 1740 (sh), 1725, 1660, and 1625–1600 cm^{-1}; nmr (broad singlets) δ 0.66, 1.20, 3.66, and 8.16; λ_{max} 218 nm (ϵ 3600) and 295 (5900) shifted to 240 (inflection) (ϵ 5000), 330 (7200), and 370 (6700) in ethanol–0.01 *N* sodium hydroxide solution. Structure **5a** is assigned to this material.

A solution of crude **5a** (92 mg, 0.22 mmol) in glacial acetic acid (1.75 ml), concentrated hydrochloric acid (1.25 ml), and water (5 drops) was heated at 90–100° for 1 hr in a nitrogen atmosphere. The cooled mixture was diluted with water (8 ml) and extracted with ether. The ethereal extract was washed twice with water and then with 1% aqueous sodium hydrogen carbonate until the final washing was basic to litmus. (Vigorous agitation during these basic washings was avoided.) The ethereal solution was filtered through anhydrous sodium sulfate and evaporated *in vacuo* to yield a tan foam (54 mg, 69%), which crystallized from ether–hexane. Recrystallization from ether gave **5b** as fine tan crystals: mp 174–178° (16 mg, 20%) (red-brown color with methanolic ferric chloride); ν_{max} 3550–3025, 1752 (sh), 1725, 1660, and 1600 cm^{-1}; nmr δ 0.50–3.00 (24 H, m with strong s at 0.69 and 1.21), 3.64 (3 H, s, OCH_3), and 7.50 (1 H, broad s, disappears on addition of D_2O, C=COH); λ_{max} 223 nm (ϵ 4500), 267 (3500), and 295 (4200) shifted to 240 (4200), 271 (2200), and 367 (5300) in ethanol–0.01 *N* sodium hydroxide; *m/e* (rel intensity) 356 (56), M^+ 332 (100), M − 28, 304 (11), M − 28 − 28, 301 (11), M − 59, 273 (9), M − 59 − 28, 272 (7), M − 60 − 28, 244 (7), M − 28 − 28 − 60, 221 (35), possibly rings A and B with C_{11}, 189 (9), 221 − 32, 161 (52), 221 − 60, 136 (32), 135 (22), 134 (20), 123 (31), 121 (35), 109 (17), 107 (16), 82 (15), and 81 (16).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.46; H, 7.90.[16]

Methyl 12-Methoxy-13-(1-hydroxyethyl)podocarpa-8,11,13-trien-19-oate (1e).—A solution of sodium borohydride (0.125 g, 3.4 mmol) in water (5 ml) was added dropwise to methyl 12-methoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (**1b**)[10,17] (0.516 g, 1.5 mmol) in ethanol (15 ml) at 0°. The mixture was kept at 0° for 1 hr, stirred at room temperature for 23 hr, and then acidified to congo red with dilute hydrochloric acid. The ethanol was removed under reduced pressure, and water (30 ml) was added. The product, which was isolated through extraction of the acidified mixture with chloroform, crystallized from aqueous ethanol to yield **1e** (0.381 g, 76%) as fine crystals: mp 113–116°; ν_{max} 3575, 1720, and 1607 cm^{-1}; nmr δ 0.95–3.0 (20 H, m with s at 1.03 and 1.27 and a d at 1.65, J = 7 Hz), 3.68 (3 H, s, $-OCH_3$), 3.82 (3 H, s, OCH_3), 5.03 (1 H, q, J = 7 Hz, $CHOHCH_3$), 6.77 (1 H, s, C_{arom} H), and 7.03 (1 H, s, C_{arom} H).

(15) Spectra were measured with Perkin-Elmer 237, Cary 14, Hitachi RMU-6D, and Varian A-60 instruments; unless otherwise specified, ir spectra are for dichloromethane solutions, uv spectra for ethanol solutions, nmr spectra for solutions in deuteriochloroform (tetramethylsilane as internal standard), and mass spectra were determined at an ionization potential of 70 eV, with samples being introduced through the direct inlet. Light petroleum had bp 60–69°. The condensations of **4d** were carried out in a dry box under N_2 using carefully dried reagents and solvents (kept over molecular sieves). In the work-up of these reactions cold dilute solutions of acids and bases were used and extractions were done rapidly.

(16) Although the carbon figure is outside the normally acceptable limits, the mass spectral data confirm the structure. Shortage of material precluded reanalysis.

(17) W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 929 (1942).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.71; H, 8.82; O, 18.43.

12-Methoxy-13-acetylpodocarpa-8,11,13-trien-19-oic Acid (1c).[18]—A solution of methyl 12-methoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (**1b**) (0.500 g, 1.51 mmol) in concentrated sulfuric acid (6 ml) was kept at room temperature for 5 min and then poured over ice. A solution of the precipitate in aqueous sodium hydroxide was filtered. Acidification of the filtrate with hydrochloric acid gave a solid which crystallized from aqueous ethanol to give **1c** (0.280 g, 59%) as needles: mp 205–207°; a second crop (0.037 g) brought the yield to 65%; ν_{max} 3490, 1720, 1690, 1670, and 1600 cm^{-1}; nmr δ 1.05–3.05 (20 H, m with s at 1.14, 1.36, and 2.60), 3.87 (3 H, s, OCH_3), 6.82 (1 H, s, C_{arom} H), and 7.48 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.41; H, 8.07.

12-Methoxy-13-(1-hydroxyethyl)podocarpa-8,11,13-trien-19-oic Acid (1d).—A solution of sodium borohydride (90 mg, 2.4 mmol) in water (5 ml) was added to a solution of **1c** (0.237 g, 0.72 mmol) in 0.2 *N* sodium hydroxide (4.5 ml). The mixture was kept in ice water for 30 min and then was stirred at room temperature for 5 min. The solution was acidified with dilute hydrochloric acid and the resulting tan precipitate was crystallized from aqueous ethanol to yield **1d** (0.184 g, 78%) as fine needles: mp 160–168°; $\nu_{max}^{CHCl_3}$ 3600–2350 (broad absorption), 1695, and 1615 cm^{-1}; nmr δ 0.95–3.0 (20 H, m with s at 1.05 and 1.32 and a d at 1.49), 3.65 (3 H, s, OCH_3), 6.77 (1 H, s, C_{arom} H) and 7.00 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 72.27; H, 8.50; O, 19.06.

Registry No.—**1a**, 5947-49-9; **1c**, 30801-46-8; **1d**, 36504-20-8; **1e**, 36504-21-9; **3**, 36504-22-0; **4a**, 36504-23-1; **4c**, 36504-24-2; **4d**, 36504-25-3; **4f**, 36504-26-4; **5a**, 36504-27-5; **5b**, 36504-28-6.

Acknowledgments.—P. R. W. was an NDEA Title IV Fellow, 1966–1969. Financial support was also supplied by NSF Grant GU-2054 and the Research Council of the University of Nebraska. We are grateful for this support and also to the Searle Company for a gift of rimu resin, to Drs. R. H. Bible and D. Goldsmith for details of unpublished work, and Dr. M. M. Wheeler for assistance.

(18) The acid **1c** was first prepared by Picha[19] who reported mp 198–202.5°. Our preparation is based on unpublished work by Bible.[20]

(19) G. M. Picha, U. S. Patent 2,774,784 (Dec 18, 1956); *Chem. Abstr.*, **51**, 9695*e* (1957).

(20) R. H. Bible, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, p 49p.

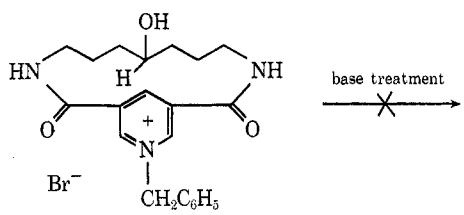
Dehydrogenase Enzyme Models. Approximation of an Alcohol and a Pyridinium Ring

LARRY E. OVERMAN[1a]

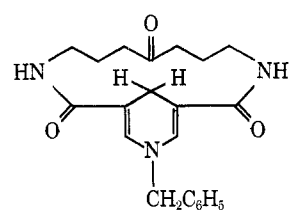
Department of Chemistry, University of California, Irvine, California 92664,[1b] *and Department of Chemistry, Columbia University, New York, New York 10027*

Received June 9, 1972

The pyridine nucleotides (NAD^+, $NADP^+$) with their reduced forms (NADH, NADPH) are coenzymes in many biological oxidation–reduction reactions,[2] *e.g.*, the interconversions of ethanol $\rightleftharpoons$ acetaldehyde and lactate $\rightleftharpoons$ pyruvate, which are catalyzed by the dehydrogenase enzymes liver alcohol dehydrogenase and muscle lactate dehydrogenase, respectively. Although it has been possible to achieve the nonenzymatic reduction of reactive carbonyl compounds *via* direct hydride transfer from several 1,4-dihydropyridine reductants, the reverse reaction, the oxidation of an alcohol by a pyridinium salt (NAD^+ model), has not been reported.[2] Attempts in this direction involving flexible intramolecular model systems[3] were unsuccessful and involved in part addition of the side chain to the 2 position of the pyridinium ring. We wish to report studies of a rigid model system, **1**, in which intramolecular hydride transfer to positions other than the 4 position is precluded, and to report that the mere existence of intramolecular approximation is *not* sufficient to guarantee intramolecular hydride transfer, as depicted in eq 1. Compound **1** appeared to be a likely



1



1a

$$+ H^+ + Br^- \quad (1)$$

candidate for the observation of intramolecular hydride transfer since, even though transannular hydride migrations in 14-membered rings has to our knowledge not been reported, space-filling models (CPK) show that the hydroxyl methine hydrogen and the pyridinium 4 position are held tightly together and that conformations of the 14-membered ring do exist in which hydride addition could occur perpendicular to the plane of the pyridinium ring. Moreover attempts to make analogs of **1** with only five bridging methylenes were unsuccessful, presumably owing to the even tighter fit in this case.[4]

The synthesis of **1** by high-dilution cyclization followed the route used by Stetter[5] for the preparation of macrocyclic bisamides of isopthalic acid, and is outlined in Scheme I. For the cyclization step, the hydroxyl group was blocked as the *tert*-butyl ether. The crucial step in this synthesis, high-dilution cyclization of **4** with dinicotinoyl dichloride, was affected in 6.6% yield as described in the Experimental Section. The 4-deoxy analog, **7**, was prepared by similar cyclization in 6.9% yield.

(1) (a) NIH Postdoctoral Fellow, 1969–1971, Columbia University; (b) Address inquiries to author at this address.

(2) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 9; (b) S. Chaykin in "Annual Review of Biochemistry," Vol. 36, Part 1, P. D. Boyer, Ed., Annual Reviews, Inc., Palto Alto, Calif., 1967, pp 149–170.

(3) E. J. Gabbay, Ph.D. Thesis, Columbia University, New York, N. Y., 1965.

(4) High-dilution cyclization of dinicotinoyl dichloride and 1,5-diaminopentane afforded no macrocyclic bisamide, and only a dimeric tetraamide (*m/e* 466) could be isolated.

(5) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).