Reduction of Some Grignard Reagent–Carbon Dioxide Adducts to Primary Alcohols by Lithium Aluminum Hydride

By Alex P. Mathers and Maynard J. Pro

Received October 12, 1953

Reduction of carboxylic acids to alcohols by lithium aluminum hydride[1,2] has been studied extensively owing to the fact that most of these acids are quite resistant to other reducing agents. No references were found where lithium aluminum hydride was used to reduce a halomagnesium alkanoate directly to an alcohol.

Tuot[3] describes the conditions necessary for obtaining high yields of acids from the reaction of carbon dioxide and Grignard reagents. Since the same conditions were found to apply in the production of alcohol from the halomagnesium alkanoate, precautions were taken to prevent secondary reactions. Approximately 1 *N* Grignard reagent was prepared and held at −20 to −30° during the admission of carbon dioxide, which was added in excess as rapidly as possible.

Side reactions in the case of the lower molecular weight alkyl groups are suppressed by the insolubility of the halomagnesium alkanoate which precipitates in the ether solution. With the higher molecular weight alkyl groups, the reaction mixture remains homogeneous, but the addition of a second or third alkyl group to the carbon dioxide is apparently slow.

Ketones, secondary and tertiary alcohols are three possible impurities of the Grignard reaction between alkylmagnesium halide and carbon dioxide followed by reduction with hydride. Some of these have boiling points near those of the primary alcohols, thus necessitating various isolation procedures.

Experimental

Syntheses of ethanol, *n*-propyl alcohol, 3-methylbutanol-1 and 7-methyloctanol-1 from methyl iodide, ethyl bromide, 1-chloro-2-methylpropane and 2-bromo-*n*-octane, respectively, entailed identical procedures in the preparation of the Grignard reagent, halomagnesium alkanoate, lithium aluminum hydride reagent, reduction of the Grignard complex and the hydrolysis of the reduced compounds to the alcohols.

Magnesium turnings (0.55 mole) were placed in a three-necked one-liter flask and covered with 100 ml. of anhydrous ether. The alkyl halide (0.5 mole) in 300 ml. of ether was added slowly with stirring and the mixture was refluxed for one hour after the final addition of alkyl halide.

The reaction flask was placed in a Dry Ice–acetone-bath at −20 to −30° and the dropping funnel used for addition of the alkyl halide was exchanged for an inlet tube extending beneath the surface of the ether. A flask containing approximately 75 g. of Dry Ice was attached to the inlet tube and by slight warming about half the carbon dioxide was admitted rapidly to the reaction vessel. The remaining carbon dioxide was admitted slowly while the flask and contents were allowed to come to room temperature. Vigorous stirring was maintained throughout the addition of carbon dioxide.

A slurry of lithium aluminum hydride 0.5 mole was prepared in 200 ml. of absolute ether. The lithium aluminum hydride was carefully powdered under an atmosphere of nitrogen, ether added and the mixture refluxed for three hours. This unfiltered slurry was slowly added to the halomagnesium alkanoate with continuous stirring, at such a rate that ether reflux was maintained. Refluxing was continued for three hours after addition of the slurry.

The reaction mixture was cooled to 0° in an ice-bath and water very cautiously added to destroy the excess hydride. Stirring was vigorous during the addition of water to prevent the possibility of a sudden excess of water causing the reaction to become violent. Following this addition, solid material in the flask was dissolved in 15 to 20% sulfuric acid. The alcohols were recovered by extraction and fractional distillation.

Both aqueous and ethereal portions of the ethanolic solution were fractionated through a packed column with high reflux ratio. When the ether was almost completely removed the still was placed under total reflux and a slow stream of air was admitted through the still head to sweep out the last traces of low boiling components. The air line was disconnected and the distillate between 78 and 79° was collected.

For recovering the *n*-propyl alcohol, the ether layer was separated and the aqueous portion fractionated. The distillate below 95° was added to the ethereal solution. This solution was washed with 10 ml. of water, then dried for two hours with anhydrous potassium carbonate. Most of the ether was removed at atmospheric pressure through a packed column by a procedure similar to that used for the ethanol. The distillate recovered between 90 and 100° was fractionated at 50 mm. and again at 20 mm. pressure. The receiver was immersed in an ice–salt-bath.

The 3-methylbutanol-1 was separated from the aqueous portion by ether extraction, the ether solution washed with 10 ml. of water and dried with anhydrous potassium carbonate. The ether was removed as above and the alcohol fractionated at 15 mm. pressure.

The 7-methyloctanol-1 was recovered by the same procedure as the 3-methylbutanol-1 except fractionation was at 10 mm.

Alcohol	Yield, %	Refractive index $n^{25}\text{D}$	3,5-Dinitrobenzoate M.p., °C.	B.p. (760 mm.)
Ethanol	74	1.36181	91.5–93	78.0
n-Propyl alcohol	78	1.38375	74	97.0
3-Methylbutanol-1	75	1.40460	60–61	130–132
7-Methyloctanol-1	73	1.43160	47–48	209–210

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[1] A. E. Finholt, G. J. Nystrom, H. C. Brown and H. I. Schlesinger, "Symposium on Hydrides," Amer. Chem. Society, Sept. 10, 1946.

[2] W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 469–509.

[3] M. Tuot, *Compt. rend.*, **208**, 1026 (1939).

Components of Podophyllin. XV. Pyrolysis of Podophyllotoxin Halides[1]

By Anthony W. Schrecker, Gertrude Y. Greenberg and Jonathan L. Hartwell

Received October 16, 1953

Thermal decomposition of picropodophyllin (PP) benzoate (I, R = $OCOC_6H_5$) yields α-apoPP,[2] which on further heating undergoes double bond shift to β-apoPP (II, R = CH_3).[2-4] Analogously, podophyllotoxin (PT) benzoate should yield β-apoPP *via* α-apoPT, the unknown C_3-epimer[1] of α-apoPP. However, either because of the instability of the postulated intermediate[1] or because of a higher temperature needed in this case for the decomposition,[2] only the stable end-product was obtained.[3] Therefore, pyrolytic dehydrohalogenation of the PT halides (I, R = Cl or Br)[5] was carried out since their decomposition temperatures[5] are much lower than those of the carboxylic

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[1] Paper XIV: A. W. Schrecker and J. L. Hartwell, This Journal, **76**, 752 (1954).

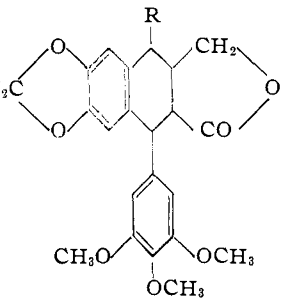
[2] A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5916 (1953).

[3] N. L. Drake and E. H. Price, *ibid.*, **73**, 201 (1951).

[4] A. W. Schrecker and J. L. Hartwell, *ibid.*, **74**, 5676 (1952).

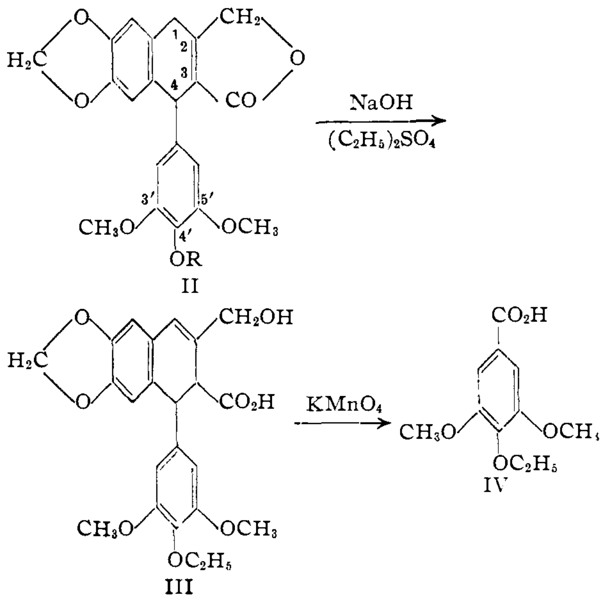
[5] J. L. Hartwell and A. W. Schrecker, *ibid.*, **73**, 2909 (1951).

esters.[2] No α-apoPT could be isolated in these experiments, although there is spectroscopic indication that it was formed. β-ApoPP was again obtained, together with other products. These reactions form the subject of the present communication.



I

PT chloride (I, R = Cl) gave β-apoPP in 65% yield when heated above its melting point, and in 99% yield when refluxed in *sec*-amylbenzene. A somewhat more complex reaction was encountered in the pyrolysis of PT bromide (I, R = Br). When this compound was refluxed in pinene, which was employed to bind the hydrogen bromide liberated in the reaction,[6] β-apoPP and dehydroanhydroPP,[4] which may have resulted from subsequent dehydrogenation or from simultaneous dehydrohalogenation and dehydrogenation,[7] were isolated. A two-component analysis of the reaction product by means of ultraviolet absorbances[8] did not yield satisfactory results. However, fair agreement with the observed values could be obtained by adding the absorbances of a small amount of a third component, namely, α-apoPP. The ultraviolet spectra of the stereoisomeric α-apoPT and α-apoPP would be expected to be identical. This would, therefore, indicate that some α-apoPT was indeed formed, unless epimerization at C_3 had occurred during or prior to elimination. When, on the other hand, PT bromide was decomposed by heating it above its melting point, there was obtained, in one experiment, β-apoPP in low yield, while the only reaction product that could be isolated in repeated runs (yield 22 to 30%) was 4′-demethyl-β-apoPP (II, R = H), m.p. 272–282°, resulting from the cleavage of one of the methoxyl groups by the hydrogen bromide liberated in the pyrolysis. That it was a derivative of β-apoPP was demonstrated by the similarity of their optical rotations and ultraviolet absorption spectra[4] and by the failure of its chloroform solution to decolorize bromine rapidly.[4] The point of attachment of the free hydroxyl group was proven by ethylation with ethyl sulfate and permanganate oxidation of the 4′-ethyldemethyl-α-apopodophyllic acid (III)[9] thus obtained to syringic acid ethyl ether (IV). The formation of 4′-demethyl-β-apoPP is interesting when related to the occurrence in nature of the analogous demethylpodophyllotoxin[10] and α-peltatin.[11]



II
III
IV

Experimental[12]

Pyrolysis of Podophyllotoxin Chloride (I, R = Cl). (a) In the Absence of Solvent.—When 1.0 g. of PT chloride[5] was heated in a quartz vessel at 200° for three minutes, it melted with evolution of hydrogen chloride. The yellow melt was triturated with boiling ethanol (distilled from tartaric acid), and the solid collected after cooling; yield 0.60 g. (65%), m.p. 210–216°. Crystallization in quartz from chloroform–ethanol gave β-apoPP (II, R = CH_3) as colorless needles, m.p. 218–219°, which failed to absorb bromine when dissolved in chloroform. Another crystallization from ethyl acetate provided material, m.p. and mixed m.p. 220–221°.

(b) In *sec*-Amylbenzene.—A solution of 2.0 g. of PT chloride in 10 ml. of *sec*-amylbenzene (b.p. 188–191°) was refluxed for one hour, at which time no further hydrogen chloride was evolved. A yellow solid separated on cooling; precipitation was completed by adding hexane. The crude β-apoPP (1.81 g., 99%) melted at 208–215°. Two recrystallizations from chloroform–ethanol yielded colorless needles, m.p. and mixed m.p. 219.5–220.5°, $[\alpha]^{20}_D$ +98° (*c* 0.50, chloroform).

Pyrolysis of Podophyllotoxin Bromide (I, R = Br) in Pinene.—PT bromide[5] (1.0 g.) was refluxed with 5 ml. of freshly distilled pinene (b.p. 158–161°) for one hour. The mixture was diluted with 20 ml. of hexane, kept in the refrigerator overnight, and the *crude solid* collected and washed with hexane. When the material was boiled with 15 ml. of ethanol, it dissolved, then pale yellow prismatic needles separated, which were collected after several days at room temperature; m.p. 263–266° (darkening). The yields in two such experiments were 453 mg. (55%) and 375 mg. (45%). Recrystallization from chloroform–ethanol provided colorless needles of dehydroanhydroPP,[4] m.p. and mixed m.p. 268–269°, further identified by its characteristic ultraviolet spectrum.[13]

In another experiment, a solution of the "crude solid" in chloroform was chromatographed on alumina and eluted with chloroform. Concentrating with addition of ethanol yielded 0.63 g. (75%) of colorless needles, m.p. 210–215°. Recrystallization from dilute acetic acid, then from ethyl

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[6] H. S. Mason, THIS JOURNAL, **66**, 1156 (1944).

[7] E. R. Alexander and A. Mudrak, *ibid.*, **72**, 3194 (1950), obtained 2-methylnaphthalene rather than 2-methyl-3,4-dihydronaphthalene in the pyrolysis of *cis*-2-methyl-1-tetralyl acetate and showed that elimination and dehydrogenation were simultaneous.

[8] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 29.

[9] The α-structure has been assigned to the acid by analogy with the formation of α-apopodophyllic acid from β-apoPP.[4]

[10] M. V. Nadkarni, J. L. Hartwell, P. B. Maury and J. Leiter, THIS JOURNAL, **75**, 1308 (1953).

[11] J. L. Hartwell and W. E. Detty, *ibid.*, **72**, 246 (1950); *cf.* A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5924 (1953).

[12] Melting points are corrected. We are indebted to Dr. W. C. Alford and co-workers for the microanalyses.

[13] A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **74**, 5672 (1952).

acetate gave β-apoPP (II, R = CH_3), m.p. and mixed m.p. 218.5–219.5°.

The composition of the reaction product was studied further by preparing solutions in chloroform, diluting with ethanol and measuring ultraviolet absorbances at various wave lengths. The proportions of α-apoPT (or α-apoPP), β-apoPP and dehydroanhydroPP were determined by three-component analysis.[8,14] Fair agreement was obtained between the values calculated from the absorbances at 350,[13] 311[4] and 290[4] mμ, and the ones obtained by the method of least squares from absorbances at ten different wave lengths. Thus the "crude solid" in one experiment appeared to contain 14% of α-apoPT (or α-apoPP), 65% of β-apoPP and 7% of dehydroanhydroPP.[15,16] In another run, the reaction mixture was directly diluted with chloroform, then with ethanol, without isolation of the product. About 16% of dehydroanhydroPP and 7 to 10% of α-apoPT (or α-apoPP)[15] were found to be present, correction being made for the absorption of pinene. After chromatography on acid-washed alumina, the following percentage yields of α-apoPT (or α-apoPP), β-apoPP and dehydroanhydroPP, respectively, were calculated: 0.8, 64, 7 (chloroform solution of "crude solid" chromatographed); 2.4, 61, 16 (reaction mixture diluted with chloroform, then chromatographed). Isomerization of α-apoPT to β-apoPP thus seems to have taken place during chromatography.

4'-Demethyl-β-apopicropodophyllin (II, R = H).—PT bromide (33.85 g.) was heated at 165° for 30 minutes. The red-brown plastic mass was triturated with 400 ml. of boiling ethyl acetate; the pink powder (6.68 g.) was collected after cooling and washed with ethyl acetate; m.p. 266–282° (immersed at 260°). The brown mother liquor, when treated with charcoal and concentrated with addition of ethanol, gave another 1.35 g. of tan-colored solid, m.p. 265–279° (immersed at 260°), bringing the total yield to 8.03 g. (30%). Crystallization from chloroform–ethanol provided 6.6 g. of light-colored crystals, m.p. 272–282° (darkening, immersed at 260°). Further recrystallization gave small colorless rectangular plates without any improvement in the melting point, which varied with the temperature of immersion; $[\alpha]^{20}\text{D}$ +106° (*c* 0.31, chloroform), $\lambda_{\text{max}}^{\text{EtOH}}$ 287.5 mμ (log ε 3.74), $\lambda_{\text{min}}^{\text{EtOH}}$ 261.5 mμ (log ε 3.54). The compound gave a red-brown color with concd. sulfuric acid and its chloroform solution did not absorb bromine rapidly.[4] It was soluble in aqueous sodium hydroxide.

Anal. Calcd. for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75; OCH_3, 16.23. Found: C, 65.67; H, 5.04; OCH_3, 16.48.

In a similar run, which yielded 25% of this compound, impure β-apoPP (II, R = CH_3), m.p. 208–214°, was isolated from the mother liquors in 7% yield. Recrystallization from chloroform–ethanol, then from ethyl acetate, gave colorless needles, m.p. and mixed m.p. 217–218°.

4'-Ethyldemethyl-α-apopodophyllic Acid (III).—A refluxing solution of 1.56 g. of II (R = H) in 27 ml. of 80% ethanol and 2.6 ml. of 5 *N* sodium hydroxide was treated at 30-minute intervals with three 1.6-ml. portions of ethyl sulfate. Alkalinity was maintained by the gradual addition of 6.5 ml. of 5 *N* sodium hydroxide. The solution was finally refluxed for 30 minutes, treated with another 6.6 ml. of 5 *N* sodium hydroxide, concentrated to remove ethanol and filtered from a small amount of tar (charcoal). It was then chilled, after adding 25 ml. of chloroform, and acidified gradually with 2 *N* hydrochloric acid. Separation of layers and further extraction with chloroform gave a yellow solution, which was washed twice with water, dried over sodium sulfate and evaporated. The remaining oil was dissolved in 15 ml. of benzene and crystallization induced by scratching. The yellowish solid (0.92 g., 53%) melted at 152° (effervescence). Two further recrystallizations from benzene produced soft, colorless, tiny needles, m.p. 153° (effervescence, immersed at 130°), 155–156° (immersed at 150°); $[\alpha]^{21}\text{D}$ −159° (*c* 1.0, chloroform). The compound was soluble in warm aqueous sodium bicarbonate.

Anal. Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; alkoxyl (as OCH_3), 21.73. Found: C, 64.50; H, 5.88; OCH_3, 21.81.

Oxidation of 4'-Ethyldemethyl-α-apopodophyllic Acid to Syringic Acid Ethyl Ether (IV).—One gram of III was oxidized with potassium permanganate by the method previously described.[11] The yield was 137 mg. (26%), m.p. 114–120.5°. Recrystallization from benzene–hexane, followed by vacuum-sublimation, gave material melting at 123.0–123.6°; no depression with an authentic sample[11] (m.p. 123–124°).

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[14] The ultraviolet spectrum of α-apoPT was assumed to be identical with that[4] of α-apoPP.

[15] Percentages calculated as yields obtained from starting material.

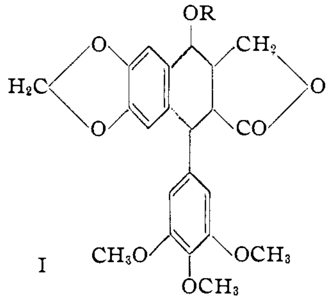
[16] The large amounts of dehydroanhydroPP that were isolated when the "crude solid" was boiled with ethanol were, therefore, not present in the original material. The absorbances at 350 and 342 mμ did not increase when a chloroform–ethanol solution of this material was heated. No further study of this discrepancy was made.

Components of Podophyllin. XVI.[1] Podophyllotoxin Haloacetates and Quaternary Derivatives

BY ANTHONY W. SCHRECKER, GERTRUDE Y. GREENBERG AND JONATHAN L. HARTWELL

RECEIVED OCTOBER 24, 1953

Because of its tumor-damaging property,[2] podophyllotoxin[3] (I, R = H) has been employed in pharmacological[4] and biochemical[5] studies on the mechanisms of its actions. Its low solubility in aqueous vehicles, however, constitutes an obstacle to its use. Therefore, attempts were made to prepare active water-soluble derivatives. The present communication describes results obtained so far in this direction.



I

Reaction of podophyllotoxin with chloroacetic anhydride in pyridine furnished the chloroacetate (I, R = $COCH_2Cl$). The yield of the corresponding bromoacetate (R = $COCH_2Br$), obtained with bromoacetyl bromide, was much lower because of formation of tarry by-products. The iodoacetate (R = $COCH_2I$) was prepared from the chloroacetate by metathetical reaction with sodium iodide in acetone.[6]

The quaternary pyridinium iodide I (R = $COCH_2NC_5H_5^+I^-$) was obtained in good yield from the iodoacetate by treatment with pyridine. This compound did, however, not prove satisfactory since its solubility in cold water was low, while

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[1] Paper XV, A. W. Schrecker, G. Y. Greenberg and J. L. Hartwell, THIS JOURNAL, **76**, 1182 (1954).

[2] J. Leiter, V. Downing, J. L. Hartwell and M. J. Shear, *J. Natl. Cancer Inst.*, **10**, 1273 (1950).

[3] (a) J. L. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951); (b) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5916 (1953).

[4] M. G. Kelly, J. Leiter, O. Ghosh and P. K. Smith, *J. Natl. Cancer Inst.*, **12**, 1177 (1952).

[5] V. S. Waravdekar, A. Domingue and J. Leiter, *ibid.*, **13**, 393 (1952).

[6] The three haloacetates have been submitted to Dr. Ray Pepinsky of Pennsylvania State College for X-ray diffraction analysis.