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Reduction of Mixed Carboxylic-Diphenylphosphoric Anhydrides with Sodium Borohydride[1]

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Mixed carboxylic-diphenylphosphoric anhydrides, prepared from carboxylic acid and diphenyl phosphorochloridate in the presence of triethylamine, were reduced with excess sodium borohydride to yield the corresponding primary alcohols in fair yield. It was possible to reduce carboxyl group selectively without affecting nitro, ester, amide, and conjugated double bond. It was observed that the considerable racemization occurred in the present reaction with N-benzoyl-phenylalanine.

Sodium borohydride is one of the most useful agent for the reduction of carbonyl compounds and because of its selectivity the application to the organic synthesis has been a subject of wide investigations. The ease of the reduction seems to depend on the electrophilicity of the carbonyl carbon at which sodium borohydride attacks. In other words, the ease of the reduction is roughly parallel to the nucleophilic reactivity of the carbonyl compounds.

Based on this consideration, Yamada, *et al.*[3] noticed on the acylating activity of mixed carboxylic-carbonic anhydrides and investigated their sodium borohydride reductions to establish the general procedure for reduction of carboxylic acid to primary alcohol *via* carboxylic-carbonic anhydride in the presence of nitro, cyano, ester, and double bond.

As a part of our study on the reaction of mixed carboxylic-phosphoric anhydrides, we have noted on the similarity of these mixed anhydrides to carboxylic-carbonic anhydrides and intended to apply the sodium borohydride reduction to these carboxylic-phosphoric anhydrides.

Although there are two electrophilic sites in the carboxylic-phosphoric anhydrides, *viz.* carbonyl carbon and phosphoryl phosphorus, it seems from the literatures those compounds generally act as an acylating agent instead of phosphorylating agent.[4] Especially in the case of mixed carboxylic-diphenylphosphoric anhydrides, the exclusive formation of the acylation product has been reported. For example, Zervas, *et al.*[5] have successfully synthesized various dipeptides by using the carboxylic(N-protected amino acid)-diphenylphosphoric anhydrides. Therefore we have decided to utilize the carboxylic-diphenylphosphoric anhydrides for the present purpose.

The preparation of the mixed anhydrides is usually carried out by the reaction of a silver phosphate with the corresponding acid chlorides. This procedure has a weak point from the synthetic point of view because acid chlorides should be used. There has been a better preparation method of the mixed anhydrides by the reaction of carboxylic acids with phosphorochloridates in the presence of triethylamine. Although Zervas has utilized the latter method in their peptides synthesis, the formation of the mixed anhydrides from simple carboxylic acids by this method has not been generally established.

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[1] A part of this study was presented at the 91st Annual Meetings of the pharmaceutical Society of Japan, Fukuoka, April, 1971.

[2] Location: *Gofuku, Toyama.*

[3] S. Yamada, K. Ishizumi, and K. Koga, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

[4] F. Cramer and K.G. Gartner, *Chem. Ber.*, **91**, 404 (1958). It is also noteworthy that this type of the mixed anhydrides has been known to play an important role in the protein biosynthesis.

[5] A. Cosmatos, I. Photaki, and L. Zervas, *Chem. Ber.*, **94**, 2644 (1961).

Therefore at the beginning of this research the formation of the mixed carboxylic-diphenylphosphoric anhydrides by the latter method has been examined using benzoic acid and cinnamic acid. When benzoic acid was treated with an equivalent amount of diphenylphosphorochloridate in the presence of one molar equivalent of triethylamine in anhydrous tetrahydrofuran for two hours at room temperature, triethylammonium chloride was deposited. After the deposit was filtered off, the solvent was evaporated to give colorless oil whose infrared (IR) spectrum was identical with an authentic sample prepared by the reaction of silver diphenylphosphate and benzoyl chloride. The experiment with cinnamic acid gave similar result. Since this kind of mixed anhydrides are rather labile to heat,(6) purification by distillation has not been carried out.

From the above experiments it was concluded that the carboxylic-diphenylphosphoric anhydrides could be prepared by simply reacting carboxylic acids with diphenylphosphorochloridate in the presence of triethylamine in tetrahydrofuran.(7) The tetrahydrofuran solution of the benzoic-diphenylphosphoric anhydride thus prepared was treated with various molar ratio of sodium borohydride and the neutral fraction was distilled and analyzed by VPC. When excess sodium borohydride (molar ratio of $NaBH_4$ to mixed anhydride >0.5) was employed, benzyl alcohol was obtained as a sole product. When less than half a molar equivalent of sodium borohydride was employed, only a trace of benzyl alcohol and benzaldehyde were detected by VPC.

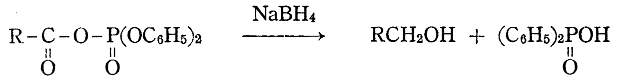
TABLE I. Reduction of Benzoic-Diphenylphosphoric Anhydride with Various Molar Ratio of Sodium Borohydride

Amounts of $NaBH_4$ (molar ratio)	0.25	0.5	0.75	1	1.3	1.5	2
Yield of benzyl alcohol (%)	trace[a]	trace[a]	27.8	50.7	60.4	57.4	58.5

[a] A trace of benzyl alcohol accompanied with benzaldehyde was detected by VPC.

As shown in Table I, more than one molar equivalent of sodium borohydride was required for optimum yield of benzyl alcohol. Therefore all reduction experiments in this paper were carried out with 1.5 to 2.5 molar equivalents of the reagent.

When cinnamic-diphenylphosphoric anhydride was reduced with sodium borohydride, cinnamyl alcohol was obtained in 64% yield and diphenyl phosphate was isolated in 78% yield from the acidic fraction. Accordingly, the reaction of the mixed anhydrides with sodium borohydride may be generally expressed as equation 1.



$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{P}(OC_6H_5)_2 \xrightarrow{NaBH_4} RCH_2OH + (C_6H_5)_2\underset{\underset{O}{\|}}{P}OH \qquad (1)$$

In order to check the general applicability of this method to ordinary carboxylic acids, various kinds of carboxylic acids were converted to mixed anhydrides *in situ* and were treated with sodium borohydride by the general precedure described in the experimental section. In all cases the corresponding alcohols were isolated in fair yields. The results were shown in Table II.

Clearly it was possible to reduce carboxyl group selectively to hydroxymethyl group in carboxylic acid having nitro, amide, ester and conjugated double bond. When optically active N-benzoyl-phenylalanine was reduced by the present method, the product alcohol lost its optical activity almost completely. This result indicates that a racemization of the

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6) J.C. Sheehan and V.S. Frank, *J. Am. Chem. Soc.*, 72, 1312 (1950).

7) All carboxylic acids employed in this paper gave by the same procedure the oily material whose IR spectra strongly indicated the formation of mixed anhydrides.

Table II. Reduction of Mixed Carboxylic-Diphenylphosphoric Anhydrides with Sodium Borohydride

Carboxylic acid	Yieled of alcohol (% from carboxylic acid)
Benzoic acid	60
Cinnamic acid	64
Phenylacetic acid	57
Phenylpropionic acid	64
p-Anisic acid	62
p-Nitrozoic acid	65
n-Capric acid	68
Lauric acid	76
Palmitic acid	77
Monomethyl phthalate	56
N-Acetyltryptophan	58
N-Benzoylphenylalanine	41

α-carbon of amino acid has occurred during the formation of the mixed anhydride or the reduction of the mixed anhydride. The similar racemization was observed in the reduction of carboxylic-carbonic anhydrides[4] and also in the amidation of phosphoric-carboxylic anhyhydrides.[8]

Experimental[9]

Materials——Diphenylphosphorochloridate ($bp_{1.5}$ 160—165°) was prepared by the method reported by Müller[10] using phosphorus oxychloride and phenol. Commercial sodium borohydride (Nakarai Chemical Co. Ltd., purity>95%) was dried and used without further purification. Authentic samples of reduction products were obtained commercially and used after purification unless otherwise stated.

Preparation of Mixed Anhydrides——i) Reaction of Acid Chloride and Silver Diphenylphosphate: Silver diphenylphosphate (2 mmoles, 714 mg) was suspended in 20 ml of anhydrous THF and 280 mg of benzoylchloride (2 mmoles) in 15 ml of anhydrous THF was added dropwise under vigorous stirring. The suspension was stirred for 2 hr and the precipitate was filtered off and the filtrate was evaporated to dryness to give 700 mg of an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1760 (s), 1720 (sh), 1595 (m), 1315 (m), 1180 (s), 1010 (s), 970 (s), 940 (s). By the same procedure, cinnamoyl chloride gave an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1750 (s), 1710 (sh), 1630 (m), 1315 (m), 1190 (s), 970 (s), 943 (s).

ii) Reaction of Carboxylic Acid with Diphenylphosphorochloridate: Two millimoles of benzoic acid and 2 mmole of triethylamine was dissolved in 15 ml of anhydrous THF and to the solution was added dropwise 2 mmole of diphenylphosphorochloridate in 15 ml of anhydrous THF under stirring. The mixture was kept stirring for 2 hr and the deposited triethylammonium chloride was filtered off. The filtrate was evaporated to give 730 mg of an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1760 (s), 1720 (sh), 1595 (m), 1315 (m), 1190 (s), 1010 (s), 973 (s), 940 (s). When cinnamic acid was treated similarly to give an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1750 (s), 1710 (sh), 1630 (m), 1315 (m), 1190 (s), 973 (s), 943 (s).

Reduction of Mixed Anhydrides——All reductions were carried out in a similar manner to that described in general procedure unless otherwise stated.

Reduction of Mixed Benzoic-diphenylphosphoric Anhydride with Various Amounts of Sodium Borohydride——Benzoic-diphenylphosphoric anhydride solution (10 mmole) was prepared from 10 mmole of benzoic acid and 10 mmole of diphenylphosphorochloridate by the procedure ii). To the solution was added a certain amount of $NaBH_4$ (2.5—20 mmole) and the heterogeneous solution was stirred for 2 hr at room temperature. After the reduction, dil. HCl was added until no hydrogen evolution and the solution was extracted with ether several times. The ether solution was washed with K_2CO_3 solution and was dried with Na_2SO_4. The solvent was evaporated and the residue was distilled at atmospheric pressure. When less than half a molar equivalent of $NaBH_4$ was used, only a trace of distillate was obtained below 220° (bath temperature). The distillate was analyzed by VPC (5% SE 30 on chromosorb W at 100°) and a trace of benzaldehyde and benzylacohol were detected. Benzyl alcohol was obtained as a sole product with the experiment more than half a molar equivalent of $NaBH_4$ was employed and the yields were given in Table I.

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8) T. Shioiri, K. Ninomiya, and S. Yamada, Abstracts of the Symposium on the Chemistry of Organophosphorus Compounds, Tokyo, 1972, p. 17.

9) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected.

10) H. Müller, *Chem. Ber.*, **72**, 2121 (1939).

Identification of Diphenylphosphate——Two millimoles of cinnamic-diphenylphosphoric anhydride solution was prepared from 2 mmole of cinnamic acid by the procedure ii) and the solution was reduced with 200 mg of $NaBH_4$ and worked up as described in the general procedure. The ether solution was washed with K_2CO_3 solution and H_2O. From the neutral fraction 169 mg of cinnamyl alcohol (mp 30°) was obtained after silica gel column chromatography. IR ν_{max}^{KBr} cm^{-1}: 3320, 1490, 970, 750, 690. The alkaline solution was acidified with dil. HCl and extracted with ether to give 387 mg of the residue, which was recrystallized from $CHCl_3$–hexane to give needles, mp 67—68°, which was identified as diphenylphosphate by comparing the IR spectrum and mixed melting point with standard diphenylphosphate.

General Procedure for the Conversion of Carboxylic Acid to Primary Alcohol——Two to ten millimoles of carboxylic acid was dissolved in anhydrous THF (15 ml or more) and an equimolar amount of triethylamine was added under stirring. To this solution was added dropwise under stirring an equimolar amount of diphenylphosphorochloridate in THF (15 ml or more). After stirring the mixture for 2 hr, the deposited triethylammonium chloride was filtered off. To the THF solution was added 1.5—2.5 molar equivalent of $NaBH_4$ and the suspension was stirred vigorously for two hr. After the reaction the excess $NaBH_4$ was decomposed with dil. HCl and the clear solution obtained was extracted with ether. After washing with K_2CO_3, and H_2O, the ether layer was dried with Na_2SO_4 and the solvent was evaporated to dryness. The residue was fractionated by column chromatography or distillation to give a product alcohol in a yield shown in Table II. The yield was based on the carboxylic acid employed. The properties of the product alcohols are shown below. They were identified by comparison of IR and other physical data with standard specimens.

Product Alcohol——Benzyl Alcohol——was obtained as colorless liquid in 60% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3380, 1500, 1040, 1020, 700.

Phenethyl Alcohol——was obtained from phenylacetic acid as a colorless liquid, in 57% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3340, 1055, 750, 700.

3-Phenylpropanol——was obtained from phenylpropionic acid as a colorless liquid in 64% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 1490, 1450, 1060, 1040, 750, 700.

p-Methoxybenzylalcohol——was obtained from *p*-anisic acid as a colorless liquid in 62% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3360, 1610, 1510, 1245, 1035, 820.

n-Decyl Alcohol——was obtained from *n*-capric acid as a colorless liquid in 68% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3340, 2900, 2840, 1460, 1058.

Lauryl Alcohol——was obtained from lauric acid as a colorless liquid in 76% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3340, 2900, 2840, 1460, 1060.

Cetyl Alcohol——was obtained from palmitic acid as a colorless viscous oil in 77% yield. IR $\nu_{max}^{benzene}$ cm^{-1}: 3560, 3400, 2920, 2840, 1460, 1025.

p-Nitrobenzyl Alcohol——was obtained from *p*-nitrobenzoic acid as pale yellow needles, mp 92—93° (lit[11] 96°), in 65% yield. IR ν_{max}^{KBr} cm^{-1}: 3480, 1603, 1500, 1340, 1060, 860—830, 740.

Phthalide——was obtained from monomethyl phthalate as white crystals, mp 68—69° (lit.[11] mp 75°) in 56% yield. IR ν_{max}^{KBr} cm^{-1}: 1750, 1460, 1435, 1050, 1000, 740.

DL-2-(N-Acetylamino)3-indolyl-propanol——was obtained from DL-N-acetyltryptophan as colorless needles, mp 137—138° (from acetone–hexane) in 58% yield. IR ν_{max}^{KBr} cm^{-1}: 3360, 3200, 1600, 1560, 1040, 750. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.30; H, 6.95; N, 12.08. Found: C, 67.46; H, 7.00; N, 12.27.

N-(2-(Hydroxymethyl)phenethyl)benzamide——was obtained from (+)-N-benzoylphenyl alanine, mp 140—141°, $[\alpha]_D^{25}$ +10.4° (c=4, 1N KOH), as colorless needles, mp 150—151° from acetone–hexane in 41% yield. IR ν_{max}^{KBr} cm^{-1}: 3300, 1635, 1535, 1050, 1030, 700. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.36; H, 6.72; N, 5.49. Found: C, 75.32; H, 6.90; N, 5.48. $[\alpha]_D^{25}$ −6° (c=2.5, EtOH) lit.[12] $[\alpha]_D^{25}$ −77.3° (c=0.356, EtOH). The IR was identical with those of DL- and L-N-(2-(hydroxymethyl)phenethyl)-benzamide which were kindly offered by Prof. S. Yamada, and Dr. K. Achiwa of University of Tokyo.

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[11] Dictionary of Organic Compounds, Maruzen Co. Ltd., 1965.

[12] K. Koga, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 243 (1966).