anol (6 ml.) added to dissolve the aniline. The yield of amine was 1.35 g. (91%). Benzamide had m.p. 62–65°, lit.[13] 63–65°.

N-Benzylaniline.—The method was similar to the previous with aniline and benzaldehyde (5 ml.), and ethanol (20 ml.). The yield was 1.67 g., (83%), m.p. 36–37.2°, lit.[14] 37–38°.

N-Ethylpiperidine.—The method was similar to the previous with piperidine, 1.0 ml. (10.1 mmoles), and acetaldehyde (10 ml.). The borohydride was added over 30 min.; half of the acetaldehyde was added at the beginning, and the remainder after 15 min. The product was crystallized as the hydrochloride. The yield was 0.81 g. (53%) m.p. (evacuated capillary, uncor.) 225–227°, lit.[15] 225°. The picrate was also prepared, m.p. 165–167.5°, lit.[16] 167–168°. Corresponding synthetic attempts with acetone and cyclohexanone in place of acetaldehyde gave no detectable tertiary amine.

---

[13] W. S. Emerson and C. A. Uraneck, *J. Am. Chem. Soc.*, **63**, 749 (1941).

[14] K. Brand, *Ber.*, **42**, 3460 (1909).

[15] R. Lukes and J. Pliml, *Chem. Listy*, **50**, 557 (1956).

[16] R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

The Reduction of Esters with Sodium Borohydride[1]

MELANCTHON S. BROWN[2] AND HENRY RAPOPORT

Department of Chemistry, University of California, Berkeley, California

Received July 17, 1963

It is generally accepted that sodium borohydride, a powerful reducing agent for aldehydes and ketones, will not reduce carboxylic esters. However, cases are reported in the literature in which reduction of esters to primary alcohols has been observed, and Schenker[3] has included many of these in his excellent review on the uses of complex borohydrides in organic chemistry. Also, instances of reduction of lactones and carbon–carbon double bonds, generally resistant to sodium borohydride, are given. Many of the compounds which undergo such "abnormal" reduction contain neighboring functional groups,[4] and Schenker implies that these groups may, in some way, take part in the reductions, although no suggestion is made as to the mechanism of this effect. We have now found that esters of simple heterocyclic, aromatic, and aliphatic acids are reduced to varying degrees by a large excess of sodium borohydride in methanol. Thus, it is evident that esters are not resistant to reduction by sodium borohydride, although the rate of reduction is much slower than for aldehydes and ketones.

For synthetic purposes, we were interested in preparing 3-(4′-pyrimidyl)-1-propanol.[5] Lithium aluminum hydride reduction of methyl 3-(4′-pyrimidyl)-propenoate or the corresponding saturated ester was complicated by simultaneous reduction of the pyrimidine ring. Therefore, in view of the suggestive reports cited, reduction of the unsaturated ester by sodium borohydride was attempted. A 77% yield of the desired propanol was obtained from the reduction carried out in methanol with a tenfold excess of sodium borohydride.

The reductions of several other unsaturated esters were then investigated, and the results are presented in Table I. The 3-(4′-pyridyl)propenoate, reduced with a tenfold excess of borohydride, behaved similarly to the pyrimidyl compound, giving mostly the saturated alcohol along with small amounts of the saturated ester and the unsaturated alcohol. With lesser amounts of reducing agent, larger amounts of saturated ester, unsaturated alcohol, and recovered starting material were obtained. The 3-(2′-quinolyl)propenoate, with a 16-fold excess of borohydride, surprisingly gave a mixture of products, although it might have been expected to be analogous to the pyridyl and pyrimidyl compounds. Methyl cinnamate and methyl 2-nonenoate also gave mixtures of reduction products and unaffected ester on treatment with a tenfold excess of reducing agent.

The reduction of several other esters with excess borohydride then was investigated, giving the results shown in Table I. The pyridine esters, methyl 4-pyridinepropanoate, ethyl 4-pyridineacetate, and methyl nicotinate, were reduced in high yields to the corresponding alcohols by a 20-fold excess of sodium borohydride in methanol. When less borohydride was used for the reduction of methyl nicotinate, some ester was recovered. Analogous phenyl esters, methyl hydrocinnamate, methyl phenylacetate, and methyl benzoate, also were substantially reduced by a 20-fold excess of borohydride, but not as cleanly as the pyridine esters, 10 to 15% of the ester being recovered. With lesser amounts of borohydride, methyl benzoate followed the same trend as methyl nicotinate, but in each corresponding case, less reduction was observed with the benzoate. One aliphatic ester, methyl nonanoate, was examined, and it was reduced to a lesser extent than the pyridine or phenyl esters, 57% of the ester being recovered.

From these results, it is obvious that no special structural features are necessary for reduction of esters by sodium borohydride to occur at least to some extent. However, such features may, indeed, enhance the reactivity in some manner, as is evident in going from aliphatic to phenyl to pyridine esters, and by the fact that many of the esters previously reported as being reduced contain proximate keto and hydroxyl groups.[3,4] Clearly, the solvent has an influence on the rate of reduction, as Chaikin and Brown[6] found that ethyl butyrate or ethyl phenylacetate, when heated with a suspension of sodium borohydride in dioxane or diethyl carbitol for one hour, showed no evidence of reduction. It was observed[7] that a mixture of ethyl benzoate and sodium borohydride in isopropyl alcohol lost but 12% of the available active hydrogen in six hours at 75°, and a similar mixture in diglyme lost less than 10% of the available hydrogen in twenty-four hours at 75°. In agreement with this behavior of esters is the fact that aldehydes and ketones are also reduced more slowly in these solvents than in

---

[1] Supported in part by the U. S. Army Research Office, Durham, N. C.

[2] Miller Research Fellow.

[3] E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

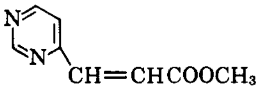
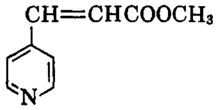
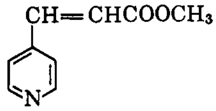
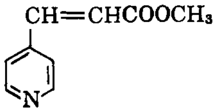
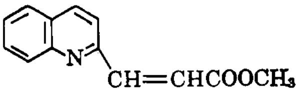
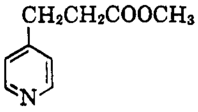
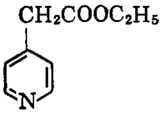
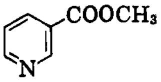
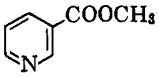
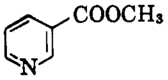
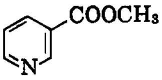
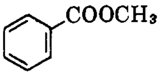
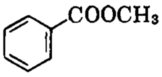
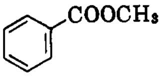
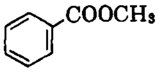
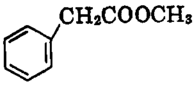
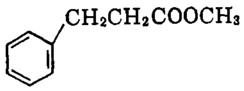
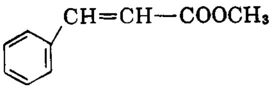
[4] *E.g.*, V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959), and J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963), for the borohydride reduction of some keto and hydroxy esters to diols.

[5] This has been successfully converted to 6-azapyrrocoline [$\lambda_{\max}^{CH_3OH}$ 229 mμ (ε 30,100), 272 (7000), 283 (7800), 345 (900)]. Details will be reported in a forthcoming publication.

[6] S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

[7] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *ibid.*, **75**, 6209 (1955).

TABLE I PRODUCTS FROM THE REDUCTION OF ESTERS WITH SODIUM BOROHYDRIDE

Ester	Moles $NaBH_4$/Mole ester	Product composition, %				Satd. alcohol, yield, %
		Satd. ester	Unsatd. ester	Satd. alcohol	Unsatd. alcohol	
	10			100		77
	10	1		91	8	74
	5	10		54	36	
	2	34	36	8	22	
	16	22	7	34	37	
	10			100		90
	10			100		93
	10	2		98		81
	5	19		81		
	2.5	52		48		
	1	85		15		
	10	15		85		75
	5	68		32		
	2.5	87		13		
	1	97		3		
	10	15		85		73
	10	10		90		72
	10	13	55	15	17	
$CH_3(CH_2)_5CH{=}CH{-}COOCH_3$	10	35	30	15	20	
$CH_3(CH_2)_7COOCH_3$	10	57		43		

water, methanol, or ethanol.[7] Reduction of the double bond in the unsaturated esters is also noteworthy.

Thus, in some cases where it is desirable not to use a stronger reducing agent, a large excess of sodium borohydride in methanol may serve quite effectively to reduce saturated or unsaturated esters to saturated alcohols. When a ketone or an aldehyde is to be reduced in the presence of an ester function, care should be taken to avoid a large excess of borohydride and elevated temperatures if partial reduction of the ester is to be avoided.

Experimental

Sodium Borohydride.—The sodium borohydride used was obtained from Metal Hydrides, Inc., Beverly, Mass., Lot. No. 191-1, rated purity, 98 plus %. Spectrographic analysis indicated the following: Li, not detectable; K, 0.01%; Ca and Si, traces.

Esters.—The heterocyclic unsaturated esters were prepared by esterification of the appropriate acids with methanol and hydrochloric acid, the acids having been prepared[8] by condensation of the appropriate methyl heterocycle with chloral and hydrolysis of the product with alkali. Methyl 3-(4′-pyridyl)propanoate was prepared from the saturated acid obtained by hydrogenation of the unsaturated acid. The other esters were obtained from stock or prepared by esterification of the appropriate acid. All the esters [except methyl 3-(4′-pyrimidyl)propenoate, which see] are known compounds, and structures and purity were confirmed by n.m.r. spectroscopy.

Reductions.—All the reductions were done in a similar manner. A weighed amount of the ester was dissolved in methanol and added to a weighed amount of sodium borohydride. When the initial vigorous reaction had subsided, the mixture was heated under reflux for 1–2 hr. The solution was cooled, an equal volume of water was added, and some of the methanol was removed on a rotary evaporator. The aqueous solution was extracted with five 50-ml. portions of chloroform, the combined extracts were dried over sodium sulfate, and the chloroform was removed on the rotary evaporator at 30 to 40°. A portion of the product was dissolved in carbon tetrachloride or deuteriochloroform, and its n.m.r. spectrum was determined with a Varian A-60 spectrometer. Peak assignments were made by comparison with the spectra of the expected products where available or by analogy with similar compounds. The per cent of each product in the mixture was calculated from the integral of the spectrum. The reduction products from methyl cinnamate and methyl 2-nonenoate gave n.m.r. spectra which were too complex to allow calculation of the composition, but vapor phase chromatography (carried out on a 0.25-in. Ucon polar column at 210° for the methyl cinnamate reduction product and at 185° for the methyl 2-nonenoate reduction product), in conjunction with the n.m.r. data, allowed calculation of the per cents. The values given in Table I are probably accurate to within a few per cent.

3-(4′-Pyrimidyl)-1-propanol.—3-(4′-Pyrimidyl)propenoic acid[8] was esterified by treatment at room temperature with methanolic hydrochloric acid for 3 days. Concentration of the reaction mixture, addition of aqueous sodium bicarbonate, extraction into chloroform, evaporation of the chloroform, and crystallization of the residue from cyclohexane gave **methyl 3-(4′-pyrimidyl)-propenoate** in 71% yield, m.p. 86–88°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.8; H, 5.1; N, 16.8.

The ester was reduced and the product was isolated by the standard procedure as described. Short-path distillation at 90° (50 μ) gave **3-(4′-pyrimidyl)-1-propanol** as a clear, slightly viscous oil; ultraviolet absorption, $\lambda_{\mathrm{max}}^{\mathrm{CH_3OH}}$ 245 mμ (ϵ 2950), 270 (330); n.m.r. absorption (in deuteriochloroform), C-2′ H, δ 9.50 (s); C-6′ H, 9.00 (d); C-5′ H, 7.67 (d); C-3 H_2, 4.05 (t); C-1 H_2, 3.28 (t); C-2 H_2, 2.42 (m).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 60.8; H, 7.3; N, 20.3. Found: C, 60.6; H, 7.1; N, 20.1.

---

[8] R. G. Jones, E. C. Kornfield, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950).

Optically Active Benzylamine-*α*-*d*[1]

A. STREITWIESER, JR., AND J. R. WOLFE, JR.[2]

Department of Chemistry, University of California, Berkeley, California

Received January 30, 1963

As part of a study of optically active benzyl-*α*-*d* compounds,[3–5] we prepared the corresponding amine. Since we contemplate no further work with this material in the near future, we report herein the preparation and properties of optically active benzylamine-*α*-*d*. The preparation followed our previous stereospecific preparations of 2-octylamine and 1-aminobutane-1-*d*[6]; namely, conversion of the alcohol to an arenesulfonate, displacement by sodium azide, and reduction of the product azide with lithium aluminum hydride. By this procedure, alcohol having $[\alpha]\mathrm{D}$ $-0.215°$ gave a 54% over-all yield of crude amine which, on purification, had $[\alpha]\mathrm{D}$ $+0.24°$. The reactions involve a single inversion of configuration; hence, amine and alcohol of the same sign of rotation have the same configuration.

The degree of optical purity of the amine relative to the alcohol was checked by the method of Snyder and Brewster.[7] The benzylamine-*α*-*d* was converted to the N,N-dimethylamine with formic acid and formaldehyde and thence to the trimethylammonium acetate by treatment successively with methyl iodide, silver oxide, and acetic acid. Pyrolysis of the quaternary acetate gave benzyl-*α*-*d* acetate which was reduced with lithium aluminum hydride to benzyl-*α*-*d* alcohol having $[\alpha]\mathrm{D}$ $-0.180°$. Snyder and Brewster used a similar sequence to convert *α*-phenethylamine to *α*-phenethyl acetate with essentially complete inversion of configuration. In our over-all conversion of benzyl-*α*-*d* alcohol to amine and back to alcohol, there occurred 18% racemization.

We suspect that most, if not all, of this racemization occurred in the first step, the preparation of benzyl-*α*-*d* tosylate. During the Schotten–Bauman procedure used, any reaction of the aqueous sodium hydroxide with the benzyl-*α*-*d* tosylate formed would generate alcohol of inverted configuration and would result in tosylate having lower optical purity than the starting alcohol; hence, this method is not recommended for stereochemical studies. The benzyl-*α*-*d* tosylates used in our other studies were prepared in dry pyridine in which this problem does not occur.[4,5]

Experimental

(+)-**Benzylamine-*α*-*d*.**—A solution of 50 ml. of 25% sodium hydroxide was added over a period of 1.5 hr. to a stirred mixture of 21 g. of benzyl-*α*-*d* alcohol,[3] $\alpha^{25}\mathrm{D}$ $-0.860 \pm 0.004°$, $\alpha^{25}{}_{5463}$ $-1.044 \pm 0.007°$ (l 4), and 29 g. of *p*-toluene sulfonyl chloride,

---

[1] Stereochemistry of the Primary Carbon. XII. This research was supported in part by a grant from the Petroleum Research Fund.

[2] Monsanto Chemical Company Fellow, 1956–1957.

[3] A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **79**, 903 (1957).

[4] A. Streitwieser, Jr., and J. R. Wolfe, Jr., *ibid.*, **81**, 4912 (1959).

[5] A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

[6] A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **78**, 5597 (1956).

[7] H. Snyder and J. Brewster, *ibid.*, **71**, 291 (1949).