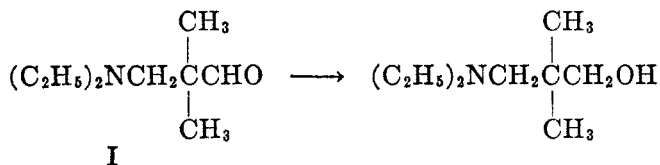


THE REDUCTION OF SOME ALIPHATIC *beta*-AMINO ALDEHYDES

KENYON HAYES AND GORDON DRAKE

Received March 13, 1950

We have sought methods of reducing 2,2-dimethyl-3-diethylaminopropionaldehyde (I) to the corresponding amino alcohol which would be less cumbersome than the acid and sodium amalgam used by Mannich, *et al.* (1, 1a, 1b).



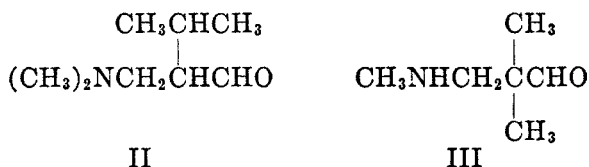
The mild conditions of the Meerwein-Ponndorf-Verley reduction, employing an aluminum alkoxide in alcohol, were thought to be attractive. The use of lithium aluminum hydride was also investigated following the report of Nystrom and Brown (2) that *p*-dimethylaminobenzaldehyde could be smoothly reduced to the amino alcohol with this reagent. After this work was completed a patent was issued to Wenner (3) which disclosed the reduction of *beta*-tertiary-amino-alkyl aldehydes by catalytic (Raney nickel) hydrogenation of the hydrochlorides. This method of Wenner, described in more detail in a later paper (3a), would appear to be more economical of time and chemicals. However, it requires the use of heated pressure-hydrogenation equipment (10–40 atmospheres), which is not always convenient, particularly on a small scale. Further, it has not been applied to *beta*-amino aldehydes bearing an α -hydrogen.

No report of an aluminum alkoxide reduction of an amino aldehyde could be found in the literature. Bersin (4), in his excellent review of this reaction, notes that the number of successful aluminum alkoxide reductions of compounds containing basic nitrogen atoms is not great and that the known cases are amino ketones. Harradence, *et al.* (5, 6) have reduced some saturated alicyclic *beta*-amino ketones, such as 2-morpholinomethylcyclohexanone, by this method. However, these authors encountered complete deamination with 2-morpholinomethylcyclopentanone under the customary conditions of the Meerwein-Ponndorf-Verley reduction. Work (7) reported failure in the case of 1,12-*bis*-diethylamino- and 1,12-*bis*-piperidino-dodeca-2,11-dione. He concluded that for ready reduction of *alpha*-amino ketones with aluminum alkoxide the carbonyl group must be conjugated with an aromatic system.

We subjected 2,2-dimethyl-3-diethylaminopropionaldehyde (I), as the free base, to the standard reduction with aluminum isopropoxide in isopropanol. The detection of acetone in the distillate indicated reduction occurred, and an 81–91% yield of 2,2-dimethyl-3-diethylamino-1-propanol was isolated. This alcohol was identified by its boiling point and the melting points of the *p*-nitro-

benzoate hydrochloride and *p*-aminobenzoate hydrochloride, which were in agreement with the constants reported by Mannich, *et al.* (1, 1b).

It was thought that success with this particular aldehyde might be due to the absence of hydrogen on the *alpha*-carbon atom with the resultant freedom from losses by aldol condensation. To determine this point a *beta*-amino aldehyde bearing an *alpha*-hydrogen, 2-isopropyl-3-dimethylaminopropionaldehyde (II) (1, 1a) was treated with aluminum isopropoxide. The corresponding alcohol was obtained in 66% yield. Thus the *alpha*-hydrogen seems to have little influence on the course of the reduction.



It was of interest to explore the influence of a *secondary*-amino group on the aluminum isopropoxide reduction of an aliphatic *beta*-amino aldehyde. Burger and Deinet (8) had observed that in the case of some 2-benzofuryl aminomethyl ketones the monobenzylaminomethyl ketone was reduced almost as satisfactorily as the dibenzylaminomethyl compound. They also reduced 2-benzofuryl methylaminomethyl ketone, but reported no yield. We observed that 2,2-dimethyl-3-methylaminopropionaldehyde (III) (9), when reduced (as the free base) with aluminum isopropoxide, gave an 8-27% yield of the corresponding alcohol.

The greater success of Burger, *et al.* (8) with an *alpha*-*secondary*-amino ketone may be due in part to their use of the amine hydrochloride. Drake and Goldman (10) have proposed that salt formation suppresses the basic character of the amine and allows the successful reduction of some amino ketones. However, the closely related *tertiary*-amino aldehyde (I) would be expected to have a basic strength at least as great as the *secondary*-amino aldehyde (III), yet I is reduced quite smoothly in the form of the free base, in contrast to III. Thus the acidic nature of the catalyst causing the formation of a complex with the amine of the type $\text{R}_3\text{N}:\text{AlR}'_3$, with the resultant removal of the catalyst and amine from the sphere of action, as proposed by Woodward, Wendler, and Brutschy (11), would not seem to be the cause of the low yield in the reduction of III. Supporting this was the absence of any precipitate in the reduction mixtures.

It is probable that the reduced yield with the *secondary*-amine is due to its lesser stability. With the three amino aldehydes investigated some deamination occurred in each case, as observed by the presence of volatile amines in the distillate. This was especially prominent with the *secondary*-amino aldehyde, III. Harradence, *et al.* (5) had observed deamination in the case of one *beta*-amino ketone.

These three saturated aliphatic *beta*-amino aldehydes were also reduced with lithium aluminum hydride by the method of Nystrom and Brown (2). The

tertiary-amino aldehydes, I and II, reacted smoothly and gave good yields of the alcohols. The *secondary*-amino aldehyde, III, gave almost as good a yield, but required a large excess of reducing agent. The alcohols prepared with lithium aluminum hydride were identical with those produced by the aluminum isopropoxide reduction.

EXPERIMENTAL

2,2-Dimethyl-3-diethylamino-1-propanol (1, 1b). *I A.* 2,2-Dimethyl-3-diethylamino-propionaldehyde (I) (prepared by the method of Mannich, *et al.* (1, 1a)), of b.p. 118–123° (103–104 mm.), 11.6 g. (0.074 mole), and 15.1 g. (3 equivalents) of freshly prepared, crude aluminum isopropoxide in 118 ml. of anhydrous isopropanol were slowly distilled to remove the acetone formed. An electrically-heated, 45-cm. column packed with glass helices was used to effect the separation. After 145 minutes the acetone test was negative. The brown reaction mixture was reduced to $\frac{1}{3}$ the original volume by distillation at 100 mm., and the residue was shaken with five volumes of cold 10% sodium hydroxide solution. The crude amino alcohol, which appeared as an oily layer, was separated and the aqueous portion was extracted with ether. The ether extract and the crude oil were combined, dried with potassium hydroxide pellets, and fractionally distilled (Vigreux column) *in vacuo*. The 2,2-dimethyl-3-diethylamino-1-propanol was obtained as a colorless liquid of b.p. 90.0–90.5° (12 mm.) 10.0 g. (84.7%). Numerous reductions gave yields ranging from 81 to 91%. This material yielded a *p*-nitrobenzoate hydrochloride of m.p. 159–160°, and a *p*-aminobenzoate hydrochloride of m.p. 196–197°; Mannich (1b) reported melting points for these derivatives of 160° and 195–196°, respectively, and a boiling range of 90–91° (12 mm.) for this amino alcohol.

I B. Twenty grams (0.127 mole) of 2,2-dimethyl-3-diethylaminopropionaldehyde (I) in 190 ml. of absolute ether were added during 30 minutes to a solution of 1.5 g. of 90+ % lithium aluminum hydride dissolved in 70 ml. of absolute ether. The mixture refluxed spontaneously and was stirred one-half hour after the addition was completed. It was then poured over 100 g. of ice, the aluminum salts were dissolved by adding 60 ml. of 10% sodium hydroxide, and the ether layer was separated. The aqueous portion was re-extracted with ether, and after drying the combined extracts with sodium hydroxide pellets, the ether was removed by distillation. The residue was distilled at reduced pressure to yield 17.5 g. (86.4%) of amino alcohol, b.p. 82–88° (8–12 mm.). This material gave a *p*-nitrobenzoate hydrochloride of m.p. 159–160°.

2-Dimethylaminomethyl-3-methyl-1-butanol (1, 1a). *II A.* This was prepared by the same procedure as in *I A* starting with 2-isopropyl-3-dimethylaminopropionaldehyde (II) of b.p. 57–58° (11 mm.). This amino aldehyde was prepared by the method of Mannich, *et al.* (1, 1a), who reported the boiling point variously as 63–66° (13 mm.) (1) and 66–68° (12 mm.) (1a). Fifteen grams of II (0.105 mole), 22.4 g. of distilled aluminum isopropoxide, and 115 g. of isopropanol were fractionally distilled during 80 minutes to remove acetone; working up as above gave 10.1 g. (66.3%) of amino alcohol of b.p. 82.0–83.5° (14–15 mm.). Mannich, *et al.* in reference (1) reported b.p. 80° (13 mm.). This gave a *p*-nitrobenzoate hydrochloride of m.p. 175–176°; Mannich, *et al.* reported variously, 176° (1) and 174° (1b).

II B. This amino aldehyde (II) was reduced with lithium aluminum hydride in the same manner as *I B* above. Yield 86.4%, b.p. 83–85° (14–16 mm.); *p*-nitrobenzoate hydrochloride, m.p. 175.0–175.5°.

2,2-Dimethyl-3-methylamino-1-propanol (9). *III A.* Twenty grams (0.174 mole) of 2,2-dimethyl-3-methylaminopropionaldehyde (III) of b.p. 48.0–50.5° (12–13 mm.) [prepared by the method of Mannich and Wieder (9), who reported b.p. 48° (12 mm.)] were reduced with three equivalents of distilled aluminum isopropoxide as described in *I A* above. Acetone was produced continuously but considerable quantities of some volatile amine were evolved. When the reduction was arbitrarily stopped after 190 minutes a 12% yield of crude

amino alcohol of b.p. 68–90° (9–11 mm.) was obtained. Mannich, *et al.* (9) reported a b.p. of 75–77° (12 mm.). Increasing the time of reduction to 335 minutes decreased the yield to 8%; whereas decreasing the reaction time to 125 minutes increased the yield to 27%. Shorter reduction times were not investigated. This crude alcohol gave a *p*-nitrobenzoate hydrochloride in good yield; m.p. 206–208°. Mannich (9) reported m.p. 207° for this ester.

III B. This *secondary*-amino aldehyde (III) was reduced quite smoothly to the corresponding alcohol as in *I B* above except that a large excess (5 equivalents) of lithium aluminum hydride was employed; yield, 72%; b.p. 70–82° (11–12 mm.).

SUMMARY

1. Three saturated aliphatic *beta*-amino aldehydes, 2,2-dimethyl-3-diethylaminopropionaldehyde, 2-isopropyl-3-dimethylaminopropionaldehyde, and 2,2-dimethyl-3-methylaminopropionaldehyde, have been successfully reduced to the corresponding alcohols by the action of aluminum isopropoxide and isopropanol on the free bases.

2. The presence of a hydrogen atom on the carbon atom *alpha* to the carbonyl group does not appear to affect the reduction.

3. *Tertiary*-amino groups cause little interference, but *secondary*-amino groups markedly reduce the yield, in the Meerwein-Ponndorf-Verley reduction of *beta*-amino aldehydes.

4. Lithium aluminum hydride reduced these three aliphatic *beta*-amino aldehydes in good yield.

NORWICH, NEW YORK

REFERENCES

- (1) MANNICH, LESSER, AND SILTEN, *Ber.*, **65**, 378 (1932).
- (1a) MANNICH, U. S. Patent, 1,824,676 (1931).
- (1b) MANNICH, U. S. Patent, 1,889,678 (1932).
- (2) NYSTROM AND BROWN, *J. Am. Chem. Soc.*, **70**, 3738 (1948).
- (3) WENNER, U. S. Patent, 2,477,842 (1949).
- (3a) WENNER, *J. Org. Chem.*, **15**, 301 (1950).
- (4) BESSIN, *Newer Methods of Preparative Organic Chemistry*, translated by Webster and Crawford; Interscience Publishers, Inc., New York, 1948, p. 130.
- (5) HARRADENCE AND LIONS, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939).
- (6) HARRADENCE, HUGHES, AND LIONS, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 280 (1939).
- (7) WORK, *J. Chem. Soc.*, 1315 (1940).
- (8) BURGER AND DEINET, *J. Am. Chem. Soc.*, **67**, 566 (1945).
- (9) MANNICH AND WIEDER, *Ber.*, **65**, 385 (1932).
- (10) DRAKE AND GOLDMAN, *J. Org. Chem.*, **11**, 100 (1946).
- (11) WOODWARD, WENDLER, AND BRUTSCHY, *J. Am. Chem. Soc.*, **67**, 1425 (1945).