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RANEY NICKEL AS HYDROGENATION CATALYST IN ACID SOLUTIONS. PREPARATION OF AMINO ALCOHOLS FROM MANNICH BASES

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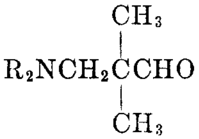
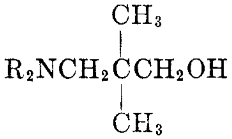
The selection of a suitable catalyst for catalytic hydrogenations is determined by several factors, one of the most important being the *p*H of the solutions to be hydrogenated. Adkins (1) states: "Acids may not be used with base metal catalysts". Therefore, noble metals exclusively are used as catalysts in acid solutions. This paper reports the use of Raney nickel for catalytic hydrogenations in distinctly acid solutions of *p*H 3–6. In the case of the reduction in acid solutions of Mannich bases of formula I (3) to the corresponding alcohols of formula II Raney nickel not only was found to be an efficient hydrogenation catalyst, but it proved even to be superior to noble metal catalysts.



$R_2NCH_2\overset{CH_3}{\underset{CH_3}{C}}CHO$

I



$R_2NCH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2OH$

II

Mannich (3) reduced the free bases of formula I with sodium amalgam in poor yields. He found activated aluminum (2) and catalytic hydrogenation methods (2, 4) unsatisfactory for these compounds. Large amounts of palladium were required, the hydrogenations proceeded very slowly, and for unknown reasons did not always stop at the desired alcohol stage. Tuda, *et al.* (5) likewise report difficulties in the hydrogenation of similarly constituted amines.

When the hydrochlorides of amines of type I were hydrogenated with noble metal catalysts, only poor yields of the alcohols resulted. In all cases the amine portion was partly split out of the molecule. Hydrogenation of the *free* amines was even less satisfactory, no matter whether palladium charcoal, any other noble metal catalyst, or nickel were used.

However, the hydrogenations proceed smoothly and with high yields when the hydrochlorides of the amines of type I are hydrogenated *with Raney nickel* in aqueous solution. The *p*H of the hydrochlorides in aqueous solutions varies from about 3.5 to 5.5. Strongly acid solutions containing a considerable amount of free mineral acid can, of course, not be used. However, down to a *p*H of approximately 3 the hydrogenations take place readily even at temperatures as low as 40–50°, and practically no side reactions occur.

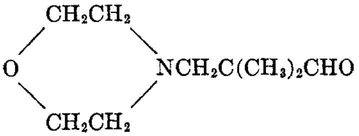
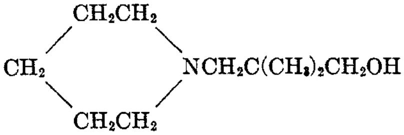
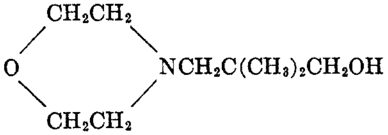
The amino alcohols prepared in this manner are listed in Table I. Since they are liquid and do not differ greatly in physical constants from the starting carbonyl compounds, they were characterized by their *p*-nitrobenzoates, a type of derivative which the carbonyl compounds cannot form.

Some of the amino alcohols have been prepared previously by Mannich (3). The present method makes them readily accessible.

The importance of the results consists in the fact that they prove that Raney nickel may be used as an efficient hydrogenation catalyst in distinctly acid solutions. The method may prove useful for similar reductions.

TABLE I

MANNICH BASES AND THEIR REDUCTION PRODUCTS

FORMULA	STRUCTURAL FORMULA	B.P., °C./MM.	M.P., °C. Hydrochloride	M.P., °C. Hydrochloride of *p*-Nitrobenzoate	LIT. REFERENCE
III	$(n\text{-}C_4H_9)_2NCH_2C(CH_3)_2CHO$	105–110/10	—	—	-
IV		92– 95/10	166	—	—
V	$(CH_3)_2NCH_2C(CH_3)_2CH_2OH$	34– 36/10	118–120	181–183	3
VI	$(C_2H_5)_2NCH_2C(CH_3)_2CH_2OH$	84– 88/10–11	—	157–159	3
VII	$(n\text{-}C_4H_9)_2NCH_2C(CH_3)_2CH_2OH$	113–117/10	—	136–139	—
VIII		93– 94/10	200–203	138–140	3
IX		—	146–148	192–194	—

EXPERIMENTAL

The melting points are uncorrected.

A. AMINO ALDEHYDES

In addition to the bases reported by Mannich, Lesser, and Silten (3) the following new members of this class of compounds were made:

1. *α-(Di-n-butylaminomethyl)isobutyraldehyde* (III). Di-*n*-butylamine (129 g.) is added to a cold mixture of concentrated sulfuric acid (60 g.) and alcohol (75 cc.). To the solution freshly distilled isobutyraldehyde (76 g.) and paraformaldehyde (73 g.) are added. The mixture is stirred and refluxed for four hours. After cooling, sodium sulfite (100 g.), water (500 cc.), and an excess of sodium hydroxide are added. The crude amino aldehyde separates as an oil and is fractionated *in vacuo*. Pure α-(di-*n*-butylaminomethyl)isobutyraldehyde (120 g.) is obtained as a colorless oil, b.p.$_{10}$ 105–110°. The hydrochloride does not crystallize.

2. *α-(4-Morpholinylmethyl)isobutyraldehyde* (IV). In a cold mixture of concentrated sulfuric acid (60 g.) and alcohol (60 g.), morpholine (85 g.) is dissolved. Isobutyraldehyde (76 g.) and paraformaldehyde (73 g.) are added, and the mixture is refluxed and stirred for about three hours. After cooling, a solution of sodium sulfite (100 g.) in water (800 cc.) is added. The free base is then precipitated by an excess of sodium hydroxide solution. The

crude oil is fractionated *in vacuo*, yielding 120 g. of pure α-(4-morpholinylmethyl)isobutyraldehyde, b.p.$_{10}$ 92–95°. The hydrochloride melts at 166°.

B. AMINO ALCOHOLS

1. *γ-Dimethylaminomethyl-β,β-dimethylpropanol* (V). α-Dimethylaminomethylisobutyraldehyde (3) (20 g.) is dissolved in 60 cc. of 3 *N* hydrochloric acid. The acidity of the solution is adjusted to *p*H 3.5–4. Three grams of Raney nickel are added, and the mixture is hydrogenated at 40–50° and 600 lbs. pressure for about three hours. The catalyst is filtered, and the solution is distilled to dryness *in vacuo*. The hydrochloride of γ-dimethylaminomethyl-β,β-dimethylpropanol crystallizes. It is stirred up with acetone and filtered. Yield, 20 g.; m.p. 118–120° [Mannich (3) had m.p. 136°]. Since the free base is soluble to about 15% in water at room temperature, the base has to be made in concentrated aqueous solution with strong alkalies and must be salted out by saturation with potassium carbonate; it distills at 34–36°/10 mm.

The *methiodide* melted at 225° [Mannich (3) gives m.p. 222°]. It crystallizes from alcohol with one-half mole of alcohol.

Anal. Calc'd for $C_8H_{20}INO \cdot 1/2\ C_2H_6O$: C, 36.50; H, 7.82; N, 4.73.
Found: C, 36.47; H, 7.47; N, 5.00.

p-Nitrobenzoate. The free amino alcohol prepared from 3.4 g. of the hydrochloride is reacted with 4 g. of *p*-nitrobenzoylchloride in 60 cc. of benzene. The crude compound is crystallized from alcohol, yielding 6 g. of the pure hydrochloride of the nitrobenzoate; m.p. 181–183° [Mannich (3) gives m.p. 160°].

Anal. Calc'd for $C_{14}H_{20}N_2O_4 \cdot HCl$: C, 53.07; H, 6.68; N, 8.84.
Found: C, 52.82; H, 6.46; N, 9.04.

2. *γ-Diethylamino-β,β-dimethylpropanol* (VI). Distilled α-diethylaminomethylisobutyraldehyde (3) (100 g.) is slowly added to a cooled and stirred solution of 230 cc. of 10% hydrochloric acid. The resulting solution is acid to Congo paper. α-Diethylaminomethylisobutyraldehyde is added in small amounts until it is no longer dissolved. The solution then shows *p*H 4–4.5. The undissolved oil is removed by gravity filtration. The clear filtrate is hydrogenated at 150 lbs. pressure and about 79–80° with 5 g. of Raney nickel. At 50° the uptake of hydrogen becomes rapid. After two hours the solution is filtered. Generally it is pale green indicating the presence of dissolved nickel. Ammonia or sodium hydroxide is added in excess whereupon about 65 g. of crude amino alcohol separates. The aqueous layer is extracted twice with about 100 cc. of benzene. The combined benzene extracts are evaporated leaving about 30 g. of additional crude amino alcohol. Fractionation of the combined crude products *in vacuo* yields 80–90 g. of pure γ-diethylamino-β,β-dimethylpropanol b.p.$_{10}$ 84–88° [Mannich (3) had b.p.$_{12}$ 90–91°].

p-Nitrobenzoate. The distilled amino alcohol (5 g.) is dissolved in 50 cc. of benzene. A filtered solution of 6.5 g. of *p*-nitrobenzoylchloride in 50 cc. of benzene is added slowly with shaking. The mixture warms up, and an oil precipitates which soon solidifies. It is filtered after several hours, washed with benzene and ether, and dried; m.p. 146° or higher. Recrystallization from alcohol gives the pure *hydrochloride* of the *p-nitrobenzoate*, m.p. 157–159° [Mannich (3) gives m.p. 160°].

3. *γ-Di-n-butylamino-β,β-dimethylpropanol* (VII). α-(Di-n-butylaminomethyl)isobutyraldehyde (18.5 g.) (Exp. A2) is dissolved in 3 *N* hydrochloric acid. By the addition of ammonia the *p*H is adjusted to 4–5.5. Hydrogenation with 3 g. of Raney nickel at 60–70° and 400 lbs. pressure is complete after about two hours. The filtered solution is made alkaline with sodium hydroxide. The liberated crude amino alcohol is fractionated *in vacuo* yielding 12–13 g. of pure γ-di-*n*-butylamino-β,β-dimethylpropanol, b.p.$_{10}$ 113–117°.

Anal. Calc'd for $C_{13}H_{29}NO$: C, 72.50; H, 13.37; N, 6.50.
Found: C, 72.79, 72.74; H, 13.16, 13.22; N, 6.76.

p-Nitrobenzoate. The base (3.1 g.) is reacted with 3 g. of *p*-nitrobenzoyl chloride in 60 cc. of benzene. The ester hydrochloride separates slowly. After standing overnight it is filtered and washed with benzene. Yield 5 g., m.p. 135–139°.

Anal. Calc'd for $C_{20}H_{32}N_2O_4 \cdot HCl$: C, 59.91; H, 8.30; N, 6.99.
Found: C, 59.73; H, 7.71; N, 6.71.

4. *γ-(1-Piperidyl)-β,β-dimethylpropanol* (VIII). α-(1-Piperidylmethyl)isobutyraldehyde (3) (34 g.) is dissolved in dilute hydrochloric acid. The *p*H is adjusted to 4–5 by means of sodium carbonate. After addition of 2 g. of Raney nickel, the solution is hydrogenated at 60° and 300 lbs. pressure for about two hours. The filtered solution is evaporated, yielding the crystallized hydrochloride. It is washed with acetone and dried, m.p. 200–203°. The free base liberated from the hydrochloride with sodium hydroxide is distilled *in vacuo.* The pure compound boils at 93–94°/10 mm. [Mannich (3) gives b.p.$_{39}$ 140°]. Yield 22 g.

Anal. Calc'd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36.
Found: C, 69.92; H, 12.10.

p-Nitrobenzoate. The base (3 g.) is reacted with 3.5 g. of *p*-nitrobenzoylchloride in 80 cc. of benzene, yielding 6 g. of the hydrochloride of the nitrobenzoate, m.p. 138–140° [Mannich (3) gives m.p. 162–163°].

Anal. Calc'd for $C_{17}H_{24}N_2O_4 \cdot HCl$: C, 57.21; H, 7.06; N, 7.85.
Found: C, 57.16; H, 6.86; N, 7.82.

5. *γ-(4-morpholinyl)-β,β-dimethylpropanol* (IX). α-(4-Morpholinylmethyl)isobutyraldehyde (Exp. A3) (21 g.) is dissolved in an equivalent amount of 10% hydrochloric acid. Water is added to bring the volume to 100 cc. The *p*H is adjusted to 4–5 by means of ammonia. After the addition of 2 g. of Raney nickel, the mixture is hydrogenated for about 3–4 hours at 50–60° and 600 lbs. pressure. The solution is filtered and evaporated. The crystallized crude hydrochloride is recrystallized from alcohol, yielding 15 g. of the pure hydrochloride, m.p. 146–148°. It contains one-half mole of alcohol.

Anal. Calc'd for $C_9H_{19}NO_2 \cdot HCl \cdot 1/2\ C_2H_6O$: C, 51.60; H, 9.96; N, 6.02.
Found: C, 51.37; H, 9.42; N, 5.88, 5.86.

p-Nitrobenzoate. The hydrochloride (4 g.) is converted into the free base with sodium hydroxide. The free amino alcohol is extracted with 30 cc. of benzene, the solution dried and 3.6 g. of *p*-nitrobenzoylchloride dissolved in 50 cc. benzene added. The *p*-nitrobenzoate separates soon. Recrystallization from alcohol gives 4 g. of the pure hydrochloride of the nitrobenzoate, m.p. 192–194°.

Anal. Calc'd for $C_{16}H_{22}N_2O_4 \cdot HCl$: C, 53.25; H, 6.98; N, 7.77.
Found: C, 53.48; H, 6.43; N, 7.73.

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SUMMARY

Hydrogenations of Mannich bases of the type $R_2NCH_2C(CH_3)_2CHO$ proceed with high yields when their hydrochlorides are hydrogenated with Raney nickel in acid solution of *p*H 3–6.

NUTLEY 10, N. J.

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