# REACTIONS OF SODIUM BOROHYDRIDE IN ACETIC ACID: REDUCTIVE AMINATION OF CARBONYL COMPOUNDS

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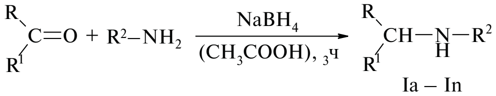
Sodium borohydride is widely used for the reduction of carbonyl-containing compounds to alcohols. Previously [1], we demonstrated that sodium borohydride can be also successfully employed for the reductive amination of carbonyl compounds by inorganic acid salts of ammonia and primary and secondary amines. The purpose of this work was to study the interaction of carbonyl compounds with ammonia, primary amines, and sodium borohydride in acetic acid according to the scheme



$$RR^1C{=}O + R^2{-}NH_2 \xrightarrow[(CH_3COOH),\ 3ч]{NaBH_4} RR^1CH{-}NH{-}R^2$$

Ia – In

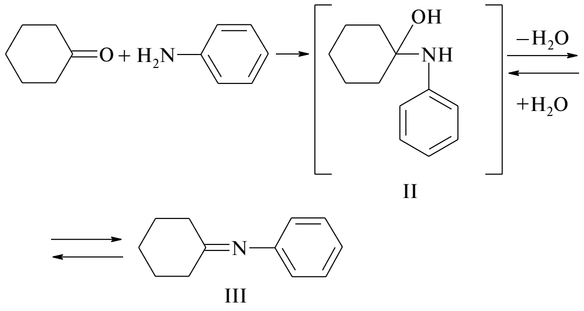
Ia: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=H;
Ib: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=$CH_3$;
1c: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=Ph;
Id: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=$C_6H_{11}$(cyclo);
Ie: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=$C_3H_7$-i;
If: $R + R^1 = C_5H_{10}$(cyclo), $R^2$=$C_2H_5$;
Ig: $R + R^1 = C_4H_8$(cyclo), $R^2$=H;
Ih: R = Ph, $R^1$=$R^2$=H;
Ii: R = Ph, $R^1$=H, $R^2$=$CH_3$;
Ij: R = Ph, $R^1$=H, $R^2$=$C_2H_5$;
Ik: R = Ph, $R^1$=H, $R^2$=$C_3H_7$-*i*;
Il: R = Ph, $R^1$=H, $R^2$=Ph;
Im: R = Ph, $R^1$=$CH_3$, $R^2$=H;
In: R=$R^2$=Ph, $R^1$=$CH_3$.

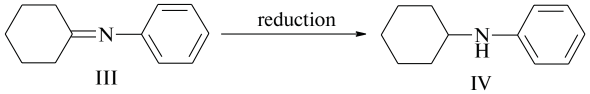
The yields of compounds Ia – In vary from 25 to 80%. In addition, the reaction mass contains the products of the carbonyl group reduction to alcohol, but their yields do not exceed 10 – 15%. The reductive amination process is conducted at a temperature of 15°C, the reaction time not exceeding 3 h. The initial compounds were cyclic ketones, acetophenone, and benzaldehyde.

The proposed method was used to obtain the series of primary and secondary amines presented in Table 1. The maximum yields of substituted amines were observed in the reaction between cyclohexanone (initial carbonyl) and aniline (initial amine). The proposed structures of the synthesized compounds were confirmed by the data of IR spectrometry, mass spectroscopy, elemental analyses, and TLC.

It was experimentally established that the optimum molar ratio of components in the initial carbonyl compound – amine – sodium borohydride mixture is 1 : 1.1 : 1.1, respectively. Acetic acid is used both as the reagent and as the solvent for preparing a 10% solution of the initial carbonyl compound.

The reductive amination reaction using complex hydrides is sufficiently well studied [2] and can be adequately described by the following scheme:





In the first stage, the carbonyl compound interacts with the initial amine to form an intermediate product II which, eliminating water, converts into azomethine III. The second stage consists in the reduction of compound III by various reducing agents.

As is known, one mole of sodium borohydride reacts with 3 moles of acetic acid to form sodium triacetoxyborohydride [3]:

$$NaBH_4 + 3CH_3COOH \rightarrow NaBH(CH_3COO)_3 + 3H_2.$$

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[1] "Belvitaminy" Joint-Stock Company, Belgorod, Russia.

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The experimental data indicate that sodium triacetoxyborohydride participates in reductive amination. Indeed, replacing sodium borohydride by triacetoxyborohydride (synthesized as described in [3]) in the reaction between cyclohexanone and aniline in acetic acid medium did not lead to any significant decrease in the yield of N-cyclohexylaniline (72%). In addition, the experiments showed that the reduction of azomethine III to compound IV with sodium borohydride in acetic acid medium reaches a 20% conversion in 10 h, while the reductive amination of cycloxexanone with aniline and sodium triacetoxyborohydride under the same conditions is completed within 1.5 h.

Thus, the mechanism of the reductive amination reaction studied in this work is somewhat different from the traditional scheme and, probably, azomethine II is not a single intermediate product in this process.

## EXPERIMENTAL PART

The IR absorption spectra of the synthesized compounds were measured on a Perkin-Elmer Model 577 spectrophotometer using samples prepared as thin films. The elemental analyses were conducted in a Perkin-Elmer Model 240 analyzer. The mass spectra were obtained with a

**TABLE 1.** Yields and Physicochemical Characteristics of the Synthesized Compounds

| Compound | Reaction time, h | Yield, % | M.p., °C | $n_D^{20}$ | IR spectrum: ν, δ, cm$^{-1}$ | Mass spectrum: $m/z$ ($I_{rel}$, %) | Empirical formula |
|---|---|---|---|---|---|---|---|
| Ia | 2.0 | 35 | 134 | 1.4585 | ν: 3280, 3350 ($NH_2$); 2850, 2910 ($CH_{aliph}$); δ: 1450 ($CH_2$); 840 ($NH_2$) | 99 (12); 70 (8.4); 56 (100); 43 (30.6); 79 (7.2); 28 (16); 15 (2) | $C_6H_{13}N$ |
| Ib | 2.5 | 33 | 149 – 150 | 1.4559 | ν: 3350 (NH); 2900 ($CH_{aliph}$); δ:1460 ($CH_2$) | 113 (7); 112 (18); 98 (7); 84 (100); 71 (21); 41 (17); 39 (11); 28 (20); 15 (6) | $C_7H_{15}N$ |
| Ic | 1.5 | 80 | 134 (6) | 1.4321 | ν: 3440 (NH); 2850 ($CH_{aliph}$); 1500, 1600 ($C{=}C_{arom}$) | 175 (76); 146 (16); 132 (100); 119 (50); 93 (65); 77 (53); 65 (24); 55 (28); 41 (42); 39 (35) | $C_{12}H_{17}N$ |
| Id | 1.6 | 60 | 125 (10) | 1.4840 | ν: 3350 (NH); 2850 ($CH_{aliph}$); δ:1470 ($CH_2$) | 181 (12.5); 152 (3); 138 (100); 110 (2.8); 82 (7); 56 (29.3); 44 (8); 41 (17.7); 28 (9.4) | $C_{12}H_{23}N$ |
| Ie | 2.6 | 25 | 60 – 63 (12) | 1.4473 | ν: 3350 (NH); 2800($CH_{aliph}$) | 141 (15); 126 (13.5); 112 (4); 98 (100); 85 (6); 70 (16.6); 56 (24.8); 44 (40); 41 (16.3); 28 (9) | $C_9H_{19}N$ |
| If | 2.5 | 35 | 163 – 166 | 1.4521 | ν: 3350 (NH); δ: 1480 ($CH_2$) | 127 (12.6); 112 (3); 98 (4.6); 84 (100); 71 (14.2); 55 (12); 41 (16.2); 39 (10.2); 28 (25.3); 15 (6.2) | $C_8H_{17}N$ |
| Ig | 2.0 | 30 | 106 – 110 | 1.4844 | ν: 3390 ($NH_2$); 2860 ($CH_{aliph}$); δ: 1480 ($CH_2$); 840 ($NH_2$) | 85 (12.3); 72 (2.5); 67 (2.4); 56 (100); 42 (16.3); 30 (17.2); 28 (17.6); 15 (3.7) | $C_5H_{11}N$ |
| Ih | 2.0 | 35 | 73 (10) | 1.5425 | ν: 3360, 3290 ($NH_2$); 1450, 1500, 1600 ($C{=}C_{arom.}$); δ: 840 ($NH_2$) | 106 (100); 72 (2.5); 67 (2.4); 56 (100); 42 (16.3); 30 (17.2); 28 (17.6); 15 (3.7) | $C_7H_9N$ |
| Ii | 2.1 | 30 | 73 – 75 (12) | 1.5230 | ν: 3340 (NH); 2800 ($CH_{aliph}$); 1500, 1600 ($C{=}C_{arom}$) | 120 (100); 104 (5); 91 (61); 77 (12); 65 (12.3); 51 (16); 44 (88); 42 (56.7); 30 (21); 28 (17) | $C_8H_{11}N$ |
| Ij | 2.5 | 30 | 70 – 75 (5) | 1.5115 | ν: 3350 (NH); 1500, 1600 ($C{=}C_{arom}$); δ: 700, 740 ($C{-}H_{arom}$) | 134 (16); 120 (40); 106 (4); 91 (100); 77 (6.3); 65 (10); 58 (15); 51 (6); 44 (9); 32 (7); 28(36) | $C_9H_{13}N$ |
| Ik | 2.5 | 25 | 93 – 94 (10) | 1.5022 | ν: 3340 (NH); 2800 ($CH_{aliph}$); 500, 1600 ($C{=}C_{arom}$) | 149 (3); 139 (34); 106 (4.4); 91 (100); 89 (2.3); 77 (5); 65 (13); 58 (1.8); 51 (6); 39 (8) | $C_{10}H_{15}N$ |
| Il | 1.5 | 60 | 150 – 152 (5) | – | ν: 3350 (NH); 1450, 1500, 1600 ($C{=}C_{arom}$); δ: 700, 750 ($C{-}H_{arom}$) | 183 (61); 181 (26); 106 (36); 91 (100); 77 (38.2); 65 (35); 51 (22.8); 20 (39) | $C_{13}H_{13}N$ |
| Im | 3.0 | 23 | 75 – 76 (10) | 1.5265 | ν: 3350, 3290 ($NH_2$); 2780 ($CH_{aliph}$); 1500, 1600 ($C{=}C_{arom}$) | 121 (13); 120 (26); 106 (100); 91 (13); 79 (60.1); 51 (45); 44 (7.6); 42 (47.4) | $C_8H_{11}N$ |
| In | 1.5 | 55 | 155 – 156 (2) | – | ν: 3340 (NH); 1450, 1500, 1600 ($C{=}C_{arom}$); δ: 700, 750 ($C{-}H_{arom}$) | 197 (73); 182 (100); 167 (13); 135 (26); 120 (36); 105 (79); 93 (69); 77 (70); 65 (48); 51 (44); 43 (36) | $C_{14}H_{15}N$ |

Hewlett-Packard Model 5985A chromatomass spectrometer. The course of the reactions was monitored and the purity of the reaction products was checked by TLC on Kieselgel 60F254 plates (Merck, Germany). The data of elemental analyses agree with the results of analytical calculations according to the empirical formulas.

**General method for the synthesis of compounds Ia – In**. To a 10% solution of the initial carbonyl compound (0.5 mole) in glacial acetic acid were added with stirring at 15°C the initial amine (0.55 mole) and then (gradually, over 1 h) sodium borohydride (0.55 mole). Upon keeping the reaction mass at room temperature for 0.5 – 2 h, acetic acid was evaporated. To the residue were sequentially added water (200 ml) and a 20% aqueous hydrochloric acid solution (to pH ~ 2 – 3). Finally, this acid solution was washed with ethyl ether, neutralized with a 30% sodium hydroxide solution, and extracted with ethyl ether. The combined ether extracts were dried over sodium sulfate, the solvent was evaporated, and the residue (target amine) purified by recrystallization. The yields and physicochemical characteristics of the synthesized compounds are summarized in Table 1.

## REFERENCES

1. A. V. Panfilov, Yu. D. Markovich, I. P. Ivashev, et al., *Khim.-Farm. Zh.*, **34**(2), 32 – 33 (2000).
2. A. Hajocz, *Complex Hydrides in Organic Chemistry* [Russian translation], Khimiya, Leningrad (1971).
3. R. Mathini, G. Liso, and A. Rebo, *J. Org. Chem.*, **55**, 3483 – 3485 (1975).