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THE REDUCTION OF ACID AMIDES WITH LITHIUM ALUMINUM HYDRIDE

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Since Nystrom and Brown (1) found that amines could be obtained from acid amides with lithium aluminum hydride and Uffer and Schlittler (2) gave a preparative procedure for this reaction, the reduction of amides to the corresponding amines with the same number of carbon atoms has been applied in many cases. However, this important reaction for the preparation of amines, even though a great number of reductions have been carried out, has not been sufficiently studied, either from the theoretical, or from the experimental point of view. This can probably be taken as one of the causes for the big difference in yields which various authors have reported by their reductions. Neither has the partial reduction of the carbonyl group in amides, with decomposition of the molecule, resulting in the formation of aldehydes (3–6) or alcohols (1, 7–9), been the subject of systematic research. And finally, no mechanism has yet been proposed which could explain the reduction of amides to amines, or which could formulate the course of the reductive decomposition of amides into aldehydes or alcohols.

Continuing our researches on reductions with lithium aluminum hydride (10–14) we have studied the behavior of several acid amides towards lithium aluminum hydride in view of developing a widely applicable preparatory procedure for the preparation of amines by this method. The conditions under which aldehydes or alcohols are obtained, by the reductive decomposition of amides, have also been studied and a mechanism which could explain the course of this reduction is proposed.

In reductions of amides with lithium aluminum hydride the yield of amine depends mainly upon the ratio of reactants, the time of heating, and the mode of isolation of the reduction products. We shall discuss these factors in turn.

According to Nystrom and Brown (1, 15) the reduction of one mole of a disubstituted amide requires 0.5 mole of lithium aluminum hydride, as shown by the following stoichiometrical equation,

$$2\ RCONR_2 + LiAlH_4 \rightarrow 2\ RCH_2NR_2' + LiAlO_2$$

while for monosubstituted and unsubstituted amides this amount is increased by 0.25 and 0.5 mole respectively. This is due, probably, to the action of the reducing agent on the hydrogen atoms of the amide group. However, Uffer and Schlittler (2), as well as the majority of authors after them used a big excess of lithium aluminum hydride (100 to 500 % excess). We have found that reductions of disubstituted amides occur readily and quantitatively even with a very small excess of the reducing agent (25–30 %). A larger amount of lithium aluminum

[1] This communication is taken in part from the Ph.D. dissertation of M. Lj. Mihailović.

hydride does not increase the yield in amine. It is of interest to note that, when using the theoretical amount of hydride, in some cases we have obtained, besides the corresponding amine, small quantities of alcohols. Thus, in the reduction of N-benzoylpiperidine and N,N-diethylbenzamide, benzyl alcohol was formed in 10% and 15% yield, respectively, while N,N-diethylnicotinamide (coramine) gave 18% of 3-pyridinemethanol.

For the reduction of monosubstituted amides a larger excess of reducing agent was used (200–250% excess calculated on the amount needed for the reduction of the carbonyl group), because in this case a greater excess can often shorten the time of the reduction. It is probable that these amides, as well as the unsubstituted derivatives, form certain complexes (by the action of lithium aluminum hydride on the hydrogen atoms attached to nitrogen) which are more difficult to reduce.

The time of heating of the reaction mixture, after the addition of the amide to the hydride suspended in ether, is another of the factors upon which depends the yield of the reaction. Long heating has been nearly always the practice in these reductions (12 to 20 hours and more). We have found, however, that in most cases, the reduction of disubstituted amides was complete immediately after the addition of the substance to the reducing agent, and that heating longer than one hour is not necessary in one single case. The yield by the reduction of coramine has been even noticed to decrease with longer heating; while after one hour of heating the amine was obtained in 84% yield, after 12 hours the yield fell to 60%.

If the reductions are conducted at 0°, besides the corresponding amines, alcohols are often obtained with decomposition of the molecule. Thus, N,N-diethylbenzamide and coramine gave the corresponding alcohols in yields of 13% and 19% respectively. Nystrom and Brown (1) have reported the formation of benzyl alcohol from N,N-diethylbenzamide, but they give neither the experimental conditions nor the yield of this reaction. Brown (15) has subsequently explained that this reduction was carried out in the hope of obtaining benzaldehyde as an intermediate product and not under conditions favoring the formation of the amine. Under normal conditions we have obtained from N,N-diethylbenzamide only the corresponding amine in quantitative yield.

For complete reduction of monosubstituted amides longer heating is required, which varies from case to case. Acetanilide, after one hour of heating, gave 72%, and after five hours 93% of N-ethylaniline. From butyranilide, after one hour of heating, 77% of N-butylaniline was obtained, and after seven hours the yield was increased to 92%. N-Cyclohexylacetamide reacts even slower; one hour of heating gives only 39%, 24 hours 82%, and 36 hours 88% of the corresponding amine. N-cyclohexylbenzamide behaves similarly; 34 hours of heating were necessary to obtain 89% of N-cyclohexylbenzylamine.

The isolation of the reduction product presents another problem which affects the yield. The usual procedure hitherto used consists in dissolving the precipitate of lithium and aluminum hydroxide, after decomposition of the reduction complex and excess of hydride, in a large excess of sodium hydroxide solution

or in aqueous sodium potassium tartrate. In our hands this method did not give satisfactory results because, frequently, the inorganic precipitate could not be entirely dissolved, or else, by extraction with ether an emulsified middle layer was formed which did not clear up even after longer standing. A modified procedure, also used by many authors, consists in dissolving the inorganic residue in dilute acids followed by the addition of sodium hydroxide solution. This produces a voluminous precipitate which is filtered with difficulty and which traps some of the product. If a large amount of sodium hydroxide is added a solution is obtained which is, however, often emulsified and troublesome to extract. Also, owing to a large volume of liquid, water-soluble amines and other reduction products are difficultly extracted with ether.

We have found that the best method of hydrolysis consists in decomposing the reduction complex and excess of hydride with a calculated amount of water and 15% sodium hydroxide (n g. of lithium aluminum hydride requires the successive addition of n ml. of water, n ml. of 15% sodium hydroxide, and $3n$ ml. of water) which produces a dry, granular precipitate which absorbs very little substance and is easy to filter and wash.

According to our procedure we have obtained from the corresponding acid amides the following amines: (a) N-benzylpiperidine (93%); (b) N-ethylpiperidine (92%); (c) N-ethyl-1,2,3,4-tetrahydroquinoline (91%); (d) N,N-diethylbenzylamine (92%); (e) 3-(diethylaminomethyl)pyridine (84%) [This reduction was carried out by Uffer and Schlittler (2) in 55% yield]; (f) N-ethylaniline (93%) [Nystrom and Brown (1) have reported a yield of 60%]; (g) N-butylaniline (92%); (h) N-ethylcyclohexylamine (88%); (i) N-cyclohexylbenzylamine (90%).

The reduction of N-benzoyl-1,2,3,4-tetrahydroquinoline yielded, besides the corresponding amine (37–39%), benzyl alcohol (49–53%) and 1,2,3,4-tetrahydroquinoline (44–47%). The ratio of the products thus obtained does not depend upon the amount of lithium aluminum hydride nor upon the time of heating. However, if the reduction is run at 0° or 5° the main products obtained are benzyl alcohol (74%) and tetrahydroquinoline (72%), while the yield of N-alkylated tetrahydroquinoline is decreased to 21%.

The formation of alcohols in the reduction of amides by lithium aluminum hydride has been already reported. Thus, Karrer, Portmann, and Suter (7) obtained 2-aminobutane-1,4-diol from ethyl asparaginate and in two later cases (8, 9) similar reductions have been carried out. As already mentioned, Nystrom and Brown (1) have reported the formation of benzyl alcohol from N,N-diethylbenzamide, but later, Brown (15) proposed that the behavior of the diethyl derivative should be re-investigated.

We have found that N-acylated derivatives of heterocyclic compounds with aromatic character, namely pyrrole, indole, and carbazole, are reduced under normal conditions, with decomposition of the molecule, to alcohols and to the corresponding heterocyclic compounds. Thus, N-acetylpyrrole yielded pyrrole (83%) and ethyl alcohol; N-acetylindole gave indole (93%) and ethyl alcohol;

N-benzoylpyrrole gave benzyl alcohol (80%) and pyrrole (86%); N-benzoylindole gave benzyl alcohol (92%) and indole (90%); and N-benzoylcarbazole yielded benzyl alcohol (80%) and carbazole (90%).

Other, previously mentioned amides, are not reduced under normal conditions to alcohols (except N-benzoyl-1,2,3,4-tetrahydroquinoline). In some cases, as already stated, alcohols are formed in small yields, only when the reductions are run at low temperatures and with theoretical amounts of lithium aluminum hydride.

If the reductions of amides are carried out by the reverse mode of addition, *i.e.* by adding the hydride dissolved in ether to an ethereal solution of amide, at low temperatures (−15° to −10°) and with 0.25 mole of lithium aluminum hydride for one mole of disubstituted amide, aldehydes are obtained. In some cases, small amounts of alcohols are also formed. Thus, N,N-diethylbenzamide produced 37% of benzaldehyde and 11% of benzyl alcohol; N-benzoylpiperidine gave 47% of benzaldehyde and 18% of benzyl alcohol; N-benzoyl-1,2,3,4-tetrahydroquinoline formed 49% of benzaldehyde and 14% of benzyl alcohol; and coramine gave 13% of nicotinaldehyde and 28% of 3-pyridinemethanol.

Monosubstituted amides and N,N-dimethylbenzamide do not react under these conditions or give only negligible quantities of aldehydes.

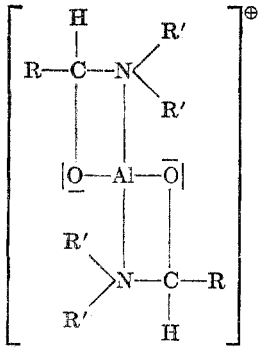
Especially good yields of aldehydes, even at higher temperatures, were obtained by the reduction of N-benzoylated pyrrole, indole and carbazole. N-benzoylpyrrole gave 54% of benzaldehyde and 82% of pyrrole at −15°, and 52% of aldehyde and 75% of pyrrole at 0°. From N-benzoylindole 56% of benzaldehyde was obtained at −15°, and 54% at 0°. N-benzoylcarbazole produced 60° of aldehyde and 83% of carbazole at −15°, and 55% of aldehyde and 80% of carbazole at 0°.

Disubstituted amides of cinnamic acid do not react like other compounds of this class. Thus, N,N-diethylcinnamamide, reduced in the usual manner, did not give the corresponding amine, but only a little cinnamyl alcohol (29%). By reverse addition at −15° or 0° this amide did not react at all. N-Cinnamoylcarbazole, which has not yet been mentioned in the literature and whose preparation is described in the experimental part, gave even under normal conditions small amounts of cinnamaldehyde. By reverse addition at −15° or 0°, the aldehyde was obtained in 45% yield.

The reduction of the carbonyl group in acid amides to a methylene group with lithium aluminum hydride can be explained by the action of a positive $AlH_2^{\oplus}$ ion on two molecules of amide, resulting in the formation of a cyclic aluminum complex (I), similar to the complex formed by the reduction of a double bond with lithium aluminum hydride (16). Upon hydrolysis, the corresponding amine would be liberated, one of the two hydrogen atoms required for the conversion being supplied by the hydrolyzing agent.

The formation of aldehydes probably proceeds through the complex (II) formed as the result of a usual nucleophilic substitution, under the attack of the hydride ion $AlH_4^{\ominus}$. Upon hydrolysis, this complex would give an unstable

amino alcohol, which would decompose, by intramolecular displacement, to the aldehyde and the starting amine. This formulation of the mechanism of the



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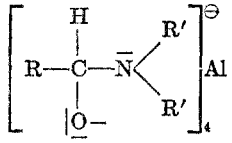
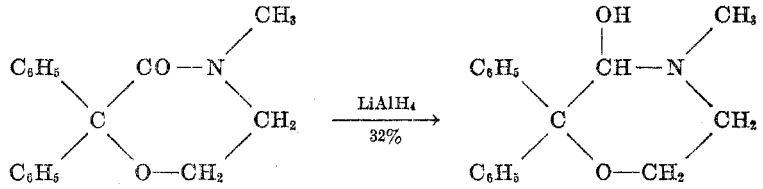


II

reduction of amides to aldehydes is supported by the fact that Morrison, Long, and Königstein (8) by the reduction of 3-keto-4-methyl-2,2-diphenylmorpholine (III) obtained, besides the expected amine, the *gem*-amino alcohol (IV), *i.e.* 3-hydroxy-4-methyl-2,2-diphenylmorpholine.

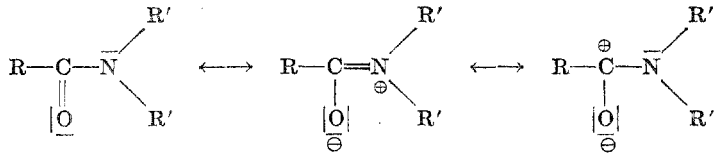


III IV

From the above proposed mechanisms it follows that the formation of aldehydes would be favored by:

(a) Steric hindrance on the nitrogen atom, which would prevent the formation of an aluminum-nitrogen bond and

(b) Increased stability of the resonance structure (VII), with an electron sextet on the carbon atom of the amide group, whose contribution, however, under normal conditions, must be very small in respect to the forms (V) and (VI) with complete octets on all atoms. In order to stabilize the electronic structure (VII), *i.e.* to eliminate the form (VI) it is necessary to introduce the unshared electron pair of nitrogen in another mesomeric system, which can be achieved by suitable substituents on the nitrogen atom of the amide group.



V VI VII

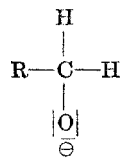
Both assumptions have been proved experimentally.

(a) There is no doubt that the yield of aldehyde depends upon the size of the substituents on the nitrogen atom. While monosubstituted amides and N,N-dimethylbenzamide do not give aldehydes, or give them only in small amounts, N,N-diethylbenzamide and the corresponding N-piperidine and N-tetrahydroquinoline derivatives produce aldehydes in good yields. In the case of large steric hindrance as shown by Weygand and Tietjen (4) with N,N,N′,N′-tetramethyl-*o*-phthalamide, the corresponding aldehyde is obtained in very good yield (70%), even by normal reduction at room temperature and with a large excess of lithium aluminum hydride.

(b) As already mentioned, N-acylated pyrroles, indoles, and carbazoles give aldehydes in good yields. The formation of these aldehydes can be explained, besides steric hindrance, by the fact that the unshared electron pair of the nitrogen atom, which is a member of the heterocyclic ring, takes part in the resonance of the aromatic system. In this way, the extreme electronic structure (VII) is stabilized to a great extent.

Three assumptions are necessary to explain the course of the reduction of amides to alcohols.

(a) The formation of the cyclic complex (I) which would decompose, upon hydrolysis, between the carbon and nitrogen atom. (b) The formation of the complex (II) with subsequent reduction and decomposition to the carbinol, and (c) Decomposition or hydrolysis of the amide molecule at the moment of reaction with lithium aluminum hydride, with simultaneous reduction to the alkoxide anion (VIII).



VIII

We shall discuss all three assumptions in turn.

(a) It is hardly probable that the formation of alcohols or amines depends upon the course of hydrolysis of the complex (I), because in that case it would not be possible to explain why small amounts of alcohols are obtained at low temperatures, besides the expected reduction products, from amides which, under normal conditions, yield only the corresponding amines, or why, by the reduction of N-benzoyl-1,2,3,4-tetrahydroquinoline the ratio of alcohol and amine obtained depends of the temperature at which the reduction was carried out. If this mechanism were correct, the formation of a certain amount of amine, by reduction of N-acylated heterocyclic compounds would be expected.

(b) It is possible that the subsequent reduction of the complex (II), with decomposition of the molecule occurs in some cases, but it cannot be adopted as the mechanism for those amides which yield alcohols as the main product. If the reduction, for instance of N,N-diethylbenzamide, is conducted at $-15°$

by the reverse mode of addition, but with 0.5 mole of lithium aluminum hydride for one mole of amide (whether the whole amount of the reducing agent is added at once, or first 0.25 mole and after one hour of stirring at room temperature the other half), benzaldehyde is again obtained in 33–35 % yield, besides a little benzyl alcohol (15–18 %) and amine, while the excess of hydride remains unchanged. This has been proven also with other amides. That means, that once formed, the complex (II) is resistant to further action of the reducing agent.

(c) Therefore it is most probable that the reduction of amides to alcohols occurs with the simultaneous decomposition of the molecule (or hydrolysis). From experimental results it appears, that in this case also, steric hindrance and especially increased stability of the resonance structure (VII) favor the formation of alcohols.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

THE REDUCTION OF AMIDES TO AMINES

General procedure. In a three-necked, round-bottomed flask, provided with a dropping-funnel, a mercury-sealed stirrer, and a reflux condenser, and protected from atmospheric moisture with $CaCl_2$ tubes there was placed the finely powdered lithium aluminum hydride (0.5 mole + 30% excess) and anhydrous ether (dried over sodium). To the stirred suspension there was added a solution of the amide (one mole) in dry ether, at such a rate, that the ether in the flask boiled gently. When the addition was complete, stirring and heating were continued for another 60 minutes (for disubstituted amide; for monosubstituted derivatives the times of heating are recorded for each special case). The mixture was then cooled in an ice-bath and the reaction product and excess of hydride were decomposed by the dropwise addition of water followed by 15% sodium hydroxide and water (n g. of lithium aluminum hydride require n ml. of water, n ml. of 15% sodium hydroxide, and $3n$ ml. of water, added in succession). After vigorous stirring for another 20 minutes the mixture was filtered with suction, the granular precipitate was washed thoroughly with ether (in some cases it is advisable to extract the precipitate with warm ether), the combined ethereal solutions were evaporated, and the cooled residue was treated with 10% hydrochloric or sulfuric acid. The acid solution was extracted with ether, in order to remove the acid and neutral products, and then made strongly alkaline (with cooling) by the addition of 15% sodium hydroxide. The liberated amine was extracted with ether, dried over potassium carbonate or potassium hydroxide, and, after removal of the solvent, distilled usually under reduced pressure.

N-Benzoylpiperidine (9.5 g., 0.05 mole) in 150 ml. of ether was reduced with 1.25 g. of lithium aluminum hydride in 100 ml. of ether to yield 8.2 g. (93.3%) of *N-benzylpiperidine*, b.p. 122° (15 mm.). Its *hydrochloride* melts at 178–179° (17), and its *picrate* at 178.5–179° (18).

N-Acetylpiperidine (9.5 g., 0.075 mole) in 150 ml. of ether and 1.9 g. of hydride in 150 ml. of ether gave 7.8 g. (92.3%) of *N-ethylpiperidine*, b.p. 126–128°. *Picrate*, m.p. 168–169° (19).

From *N-acetyl-1,2,3,4-tetrahydroquinoline* [8.76 g., 0.05 mole, b.p. 162–163° (13.5 mm.)], dissolved in 130 ml. of ether and 1.25 g. of lithium aluminum hydride in 100 ml. of ether there was obtained 7.3 g. (90.6%) of *N-ethyl-1,2,3,4-tetrahydroquinoline*, b.p. 130–132° (15 mm.). Its *picrate* melts at 117–118° (20).

The reduction of 8.86 g. (0.05 mole) of *N,N-diethylbenzamide* in 150 ml. of ether with 1.25 g. of the hydride in 100 ml. of ether produced 7.5 g. (91.9%) of *N, N-diethylbenzylamine*, b.p. 84–85° (12 mm.). *Picrate*, m.p. 120° (21).

N,N-Diethylnicotinamide (coramine) (8.91 g., 0.05 mole), prepared according to the

procedure described by Oxley and Partridge (22), was dissolved in 100 ml. of ether and reduced with 1.25 g. of lithium aluminum hydride in 100 ml. of ether. After decomposition of the reaction product, the mixture was filtered and the inorganic residue was extracted 3–4 times with warm ether. After drying over potassium carbonate the solvent was evaporated and the residual oil distilled to yield 6.9 g. (84.1%) of *3-(diethylaminomethyl)pyridine*, b.p. 108–109° (14 mm.). The *dihydrochloride* was obtained by treating an ethereal solution of the amide with dry hydrogen chloride and it was recrystallized from an absolute ether-absolute alcohol mixture. White crystals, m.p. 184–185° (23).

Anal. Calc'd for $C_{10}H_{18}Cl_2N_2$: N, 11.81. Found: N, 12.07.

N-Benzoyl-1,2,3,4-tetrahydroquinoline (8.54 g., 0.036 mole) in 170 ml. of ether was reduced with 0.9 g. of hydride in 120 ml. of ether. After the evaporation of the ethereal solution the residue was treated with 30 ml. of 10% hydrochloric acid and extracted with ether. The ethereal layer, dried over magnesium sulfate, yielded 2.06 g. (52.9%) of *benzyl alcohol*, b.p. 92–92.5° (12 mm.) [which was identified by means of its *phenylurethan*,[2] m.p. 78° (24)], and 3.08 g. (38.3%) of *N-benzyl-1,2,3,4-tetrahydroquinoline*, b.p. 160° (0.8 mm.). This amine is a viscous, colorless oil which solidifies on standing in an ice-salt bath. Recrystallized from 96% ethyl alcohol it gave white needles, m.p. 36.5–37° (26). It is insoluble in water and dilute acids, and difficultly soluble in concentrated acids.

Anal. Calc'd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27.

Found: C, 86.22; H, 7.48; N, 6.49.

The cooled acidic aqueous solution was treated with 30 ml. of 15% sodium hydroxide and the liberated base was extracted with ether. There was obtained 2.2 g. (45.9%) of *1,2,3,4-tetrahydroquinoline*, b.p. 121–122° (12 mm.). Its *hydrochloride* melts at 180–181° (26).

The same reduction was carried out at 5°, followed by 10 minutes of stirring at room temperature. There was obtained 2.86 g. (73.5%) of *benzyl alcohol*, 1.72 g. (21.4%) of *N-benzyl-1,2,3,4-tetrahydroquinoline*, and 3.46 g. (72.4%) of *1,2,3,4-tetrahydroquinoline*.

Acetanilide (5.95 g., 0.044 mole) in 500 ml. of ether was reduced with 2.5 g. (200% excess) of lithium aluminum hydride in 120 ml. of ether. The mixture was heated for five hours, decomposed, and filtered with suction. The inorganic precipitate was extracted twice with ether and twice with chloroform, the solvents were removed, and the residue was acidified with 25 ml. of 10% hydrochloric acid. The solution was continuously extracted with ether (6 hours) and then made strongly alkaline with 30 ml. of 15% sodium hydroxide in order to liberate the amine. Yield, 4.95 g. (92.9%) of *N-ethylaniline*, b.p. 93–94° (17 mm.). *Picrate*, m.p. 137.5–138° (27).

Butyranilide (6.5 g., 0.04 mole) dissolved in 400 ml. of ether was treated with 2.3 g. (200% excess) of the hydride in 100 ml. of ether. The reaction mixture was heated for 7 hours and worked up as in the former case, to yield 5.5 g. (92.1%) of *N-butylaniline*, b.p. 118.5–119.5° (14.5 mm.). The *hydrochloride* melts at 114–115° (28).

N-Cyclohexylacetamide (5.9 g., 0.042 mole) in 300 ml. of ether was reduced with 2.4 g. (200% excess) of lithium aluminum hydride in 150 ml. of ether. Refluxing was continued for 36 hours. After removal of the solvent, the acidified solution was continuously extracted with ether (8 hours) in order to remove the unreacted amide and then treated with 15% sodium hydroxide. Yield, 4.7 g. (88%) of *N-ethylcyclohexylamine*, b.p. 159–162°. The amine was identified by means of its *substituted phenylurea*, m.p. 124–125° (29).

Because of the low solubility of *N-cyclohexylbenzamide* in ether, the reduction was carried out by means of a Soxhlet extractor arranged between the reaction flask, in which was placed 2 g. (250% excess) of lithium aluminum hydride and 400 ml. of ether, and the reflux condenser. In the extractor thimble there was placed 6.1 g. (0.03 mole) of the amide. The hydride solution was maintained at a moderate rate of boiling until all the substance in the thimble had been carried into the reaction vessel (20 hours). Gentle refluxing was continued for another 14 hours. The mixture was then treated as described for N-cyclohexylacetamide. Yield 5.1 g. (89.5%) of *N-cyclohexylbenzylamine*, b.p. 143–144° (13 mm.). Its *substituted phenylurea* melts at 121–122° (30).

[2] In all subsequent cases benzyl alcohol was identified as the phenylurethan.

THE REDUCTION OF AMIDES TO ALCOHOLS

N-Benzoylpyrrole (8.6 g., 0.05 mole) in 150 ml. of ether was reduced with 1.66 g. (75% excess) of lithium aluminum hydride in 100 ml. of ether. After one hour of heating the complex and excess of hydride were decomposed, the mixture was filtered, and the ethereal colution quickly was dried over potassium carbonate. After evaporation of the ether the residual oil was fractionated to yield 2.9 g. (85.6%) of *pyrrole*, b.p. 126–131° and 4.3 g. (80%) of *benzyl alcohol*, b.p. 201–205°.

N-Acetylpyrrole (7.6 g., 0.07 mole) in 120 ml. of ether and 2.3 g. (75% excess) of the hydride in 150 ml. of ether gave 3.9 g. (82.9%) of *pyrrole*, b.p. 127–130°. As N-ethylpyrrole has the same boiling point (129–130°), the pyrrole thus obtained was identified by means of *potassium-pyrrole*.

N-Benzoylindole (8.85 g., 0.05 mole) in 170 ml. of ether was reduced with 1.33 g. (75% excess) of the hydride in 100 ml. of ether to yield 4 g. (92.5%) of *benzyl alcohol*, b.p. 79–81° (5 mm.) and 4.2 g. (89.5%) of *indole*, b.p. 122.5–124° (5 mm.), m.p. 51°.

The reduction of *N-acetylindole* (7.96 g., 0.05 mole) dissolved in 120 ml. of ether with 1.66 g. (75% excess) of lithium aluminum hydride in 100 ml. of ether gave 5.45 g. (93.1%) of *indole*, m.p. 52° (recrystallized from hot water).

N-Benzoylcarbazole (4.9 g., 0.018 mole) in 150 ml. of ether was reduced with 0.6 g. (75% excess) of the hydride in 80 ml. of ether. After one hour of gentle refluxing the ice-cooled reaction mixture was decomposed with 10% hydrochloric acid 100 ml.), the ether was separated, and the aqueous solution was extracted once with ether (20 ml.). The combined ethereal layers were dried over sodium sulfate and evaporated to a small volume (*ca.* 30 ml.) when carbazole began to crystallize. The mixture was cooled to −5°, the white precipitate was filtered with suction, and washed with 10 ml. of cold chloroform. The solution was again evaporated (to 10 ml.), cooled to −5°, filtered, and washed with a little chloroform. The *carbazole* (2.7 g., 90%) thus obtained, recrystallized from ethyl alcohol, melted at 237–239°. From the remaining solution *benzyl alcohol* (1.56 g., 80.4%) was obtained upon vacuum distillation. A little carbazole remained in the flask.

The reduction of *N,N-diethylcinnamamide* (10.3 g., 0.05 mole) in 150 ml. of ether with 1.66 g. (75% excess) of lithium aluminum hydride in 100 ml. of ether was carried out as described for N-benzoylpyrrole. Yield, 1.8 g. (29.8%) of *cinnamyl alcohol*, b.p. 140–143° (13 mm.) which was identified as the *phenylurethan*, m.p. 90–90.5° (24).

THE REDUCTION OF AMIDES TO ALDEHYDES

To a solution of *N,N-diethylbenzamide* (6.38 g., 0.036 mole) in 120 ml. of anhydrous ether was added, over a period of 15 minutes, a solution of 0.34 g. (0.009 mole) of lithium aluminum hydride in 34 ml. of ether at −15° (ice-salt bath). Stirring was continued for 30 minutes at −15° and for one hour at room temperature. The reaction product was decomposed with water (3 ml.) and the inorganic precipitate was dissolved in 40 ml. of 10% sulfuric acid. The ethereal layer was separated, the aqueous solution extracted once with ether (30 ml.), and the ethereal extracts dried over sodium sulfate with the addition of a small amount of hydroquinone. Fractional distillation under reduced pressure gave 1.4 g. (36.6%) of *benzaldehyde*, b.p. 73–75° (19 mm.); 0.45 g. (11.6%) of *benzyl alcohol*, b.p. 101–104° (19 mm.); and 1.8 g. (28.2%) of unreacted amide, b.p. 152–153° (19 mm.). The benzaldehyde was identified as the *semicarbazone*, m.p. 222° (24).

N-Benzoylpiperidine (6.81 g., 0.036 mole) was reduced in the same way to yield 1.8 g. (47.1%) of *benzaldehyde*,[3] 0.7 g. (17.9%) of *benzyl alcohol*, and 1.4 g. (20.5%) of unreacted amide, b.p. 181–182° (14 mm.).

From *N-benzoyl-1,2,3,4-tetrahydroquinoline* (8.54 g., 0.036 mole) dissolved in 250 ml. of ether there was obtained 1.87 g. (49%) of *benzaldehyde* and 0.53 g. (13.7%) of *benzyl alcohol*.

N,N-Diethylnicotinamide (6.42 g., 0.036 mole) was reduced in a similar manner with the difference that the reduction complex was decomposed with moist ether, and the precipi-

[3] If not otherwise mentioned benzaldehyde was identified as the semicarbazone.

tate was extracted twice with 25 ml. of ether, and twice with 20 ml. of hot benzene. After drying over potassium carbonate the solvents were removed and the residue fractionated under reduced pressure to yield 0.5 g. (12.9%) of *nicotinaldehyde*, b.p. 83–87° (11 mm.); 0.3 g. (5.1%) of *3-(diethylaminomethyl)pyridine*, b.p. 101–105° (11 mm.); 1.1 g. (28%) of *3-pyridinemethanol*, b.p. 138–143° (11 mm.); and 1.6 g. (24.9%) of unreacted amide, b.p. 156–158° (11 mm.). Nicotinaldehyde was identified as the *thiosemicarbazone*, m.p. 213–214° (dec.) (14), and 3-pyridinemethanol as the *picrate*, m.p. 158° (14).

N-Benzoylpyrrole (6.85 g., 0.04 mole) in 100 ml. of ether was reduced by the reverse mode of addition with 0.38 g. (0.01 mole) of the hydride in 38 ml. of ether at −10°. The mixture was stirred for 30 minutes at −10° and for one hour at room temperature, decomposed with moist ether, and filtered. The inorganic residue was thoroughly washed with ether, and the combined ethereal solutions were dried quickly over potassium carbonate and evaporated. There was obtained 2.2 g. (82.1%) of *pyrrole*, b.p. 126–130° and 2.3 g. (54.1 %) of *benzaldehyde*, b.p. 175–178°.

The same reduction at 0° gave 2 g. (74.5%) of *pyrrole* and 2.2 g. (51.7%) of *benzaldehyde*.

N-Benzoylindole (8.85 g., 0.04 mole) was reduced in the same way as N-benzoylpyrrole. After evaporation of the ether to a small volume, phenylhydrazine (4.3 g., 0.04 mole) was added, the mixture was cooled to 0°, and the precipitate was filtered and recrystallized from ethyl alcohol. Yield, 4.35 g. (55.5%) of *benzaldehyde phenylhydrazone*, m.p. 157–158° (24).

The same reduction at 0° yielded 4.2 g. (535%) of the *phenylhydrazone*.

N-Benzoylcarbazole (4.9 g., 0.018 mole) in 150 ml. of ether was reduced at −15° by the dropwise addition of 0.17 g. (0.0045 mole) of lithium aluminum hydride in 17 ml. of ether. After stirring for 30 miutes at −15° and one hour at room temperature the reduction product was decomposed with water (3 ml.) and the precipitate dissolved in 50 ml. of 10% hydrochloric acid. The organic layer was separated and the aqueous solution was extracted once with ether (20 ml.). The combined ethereal extracts were dried over sodium sulfate with the addition of a small amount of hydroquinone and the solution was concentrated until a white precipitate appeared (25–30 ml.). The mixture was cooled to −5°, filtered, and the carbazole washed with a little ether. The liquid was again evaporated to 15 ml., and regardless of the small white precipitate, treated with 1.9 g. (0.018 mole) of phenylhydrazine. From the filtered and dried *benzaldehyde phenylhydrazone* the remaining carbazole was removed by vacuum sublimation (119° at 0.09 mm.) and the phenylhydrazone was recrystallized from ethyl alcohol. Yield, 2.1 g. (60%), m.p. 157–157.5°. The *carbazole* was recrystallized from ethyl alcohol; yield 2.5 g. (83.3%).

The same reduction at 0° gave 1.94 g. (55%) of *benzaldehyde* in the form of its *phenylhydrazone* and 2.4 g. (80%) of *carbazole*.

N-Cinnamoylcarbazole. Preparation. Carbazole (16.7 g., 0.1 mole) and a small excess of cinnamoyl chloride (17.5 g., 0.105 mole) were heated in an oil-bath for one hour at 185–195°, the mixture being shaken from time to time. After cooling, 50 ml. of absolute ethyl alcohol was added, and the mixture was heated for 10 minutes at 60°, and then cooled to 0°. The separated amide was recrystallized from alcohol (with the addition of a small amount of decolorizing carbon) until the melting point remained unchanged. There was obtained 19.7 g. (66.3%) of the amide, m.p. 96.5–97°.

Anal. Calc'd for $C_{21}H_{15}NO$: C, 84.82; H, 5.09; N, 4.71.

Found: C, 84.69; H, 5.25; N, 4.82.

Reduction. N-Cinnamoylcarbazole (5.9 g., 0.02 mole) in 150 ml. of ether was reduced at −10° by the addition of 0.19 g. (0.005 mole) of lithium aluminum hydride in 19 ml. of ether. Stirring was continued for 30 minutes at −10° and for one hour at room temperature. The reaction mixture was decomposed with moist ether, filtered, and the ethereal solution was dried over magnesium sulfate. The dried solution was concentrated to a small volume and treated as described for N-benzoylcarbazole. Yield, 3 g. (89.8%) of *carbazole* and 2.01 g. (45.2%) of *cinnamaldehyde phenylhydrazone*, m.p. 166–167° (24).

The same reduction was run at 0° to yield 3 g. (89.8%) of *carbazole* and 1.98 g. (45%) of *cinnamaldehyde phenylhydrazone*.

SUMMARY

1. An extensive study on the behavior of acid amides towards lithium aluminum hydride has been carried out and a general preparative procedure has been evolved for the preparation of amines from the corresponding amides. According to this method several mono- and di-substituted amides have been reduced to amines in excellent yields (84–93%).

2. Conditions have been studied under which aldehydes and alcohols are obtained by the reduction of amides with lithium aluminum hydride. It was found that N-acylated heterocyclic compounds with aromatic character, namely pyrroles, indoles, and carbazoles, are reduced under normal conditions to alcohols with decomposition of the molecule. By applying special conditions, these compounds gave, by reductive decomposition, aldehydes in good yields.

3. A mechanism has been proposed to explain the course of these reductions.

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