THE REACTION OF THE DISODIUM DERIVATIVE OF BENZOPHENONE WITH 2-BROMOPYRIDINE*

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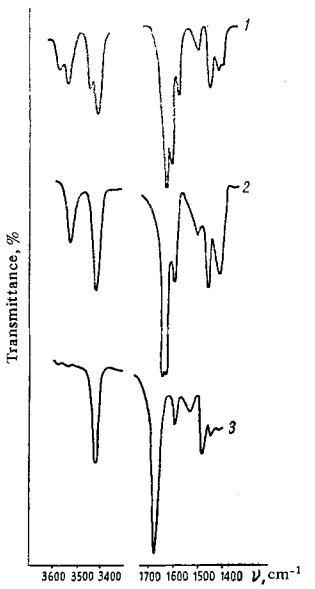
The reaction of the disodium derivative of benzophenone with 2-bromopyridine in liquid ammonia results in the introduction of a diphenylhydroxymethyl group in the γ-position of the heterocyclic ring, followed by ammonolysis of the bromine in the resulting 2-bromodihydropyridine. The anomalous nature of this reaction results from the nature of the organometallic compound.

Reaction of the disodium derivative of benzophenone with various halogen-containing compounds provides a convenient synthetic route to compounds containing the diphenylhydroxymethyl group [1]. With a view to using this method to obtain diphenylpiperidylcarbinols, which are compounds with marked physiological activity [2], we attempted to carry out the reaction between the disodium derivative of benzophenone (I) and 2-bromopyridine. It is known that the latter reacts readily with nucleophiles of various types, among them carbanions [3], to give 2-substituted pyridines. However, reaction of 2-bromopyridine with the disodium derivative of benzophenone in liquid ammonia gives, not the expected 2-diphenylhydroxymethylpyridine, but a compound (II) which, according to the analytical figures, could be a product of the reaction of not only the starting materials, but also ammonia.



IR spectra (in chloroform): 1) 2-amino-4-diphenylhydroxymethyl-4, 5-dihydropyridine (II); 2) 2-amino-4-diphenylmethylene-4, 5-dihydropyridine (III); 3) 4-diphenylhydroxymethyl-2, 3, 4, 5-tetrahydropyrid-2-one (VI).

It is suggested that the reaction between I and 2-bromopyridine involves addition of the organometallic compound to the double bond of the ring, followed by ammonolysis of the bromine in the resulting 2-bromodihydropyridine. The IR spectrum of II (see figure) confirms the 2-amino-diphenylhydroxymethyldihydropyridine structure, since it shows

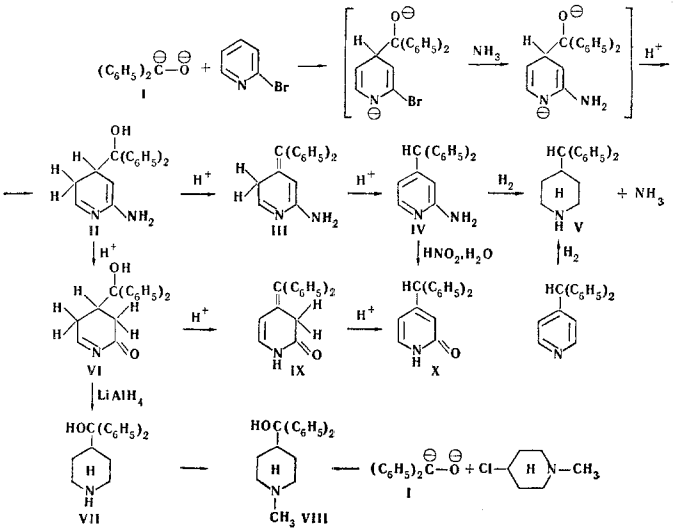
*Part X in the series "Reductive Metallation of Carbonyl Compounds". For part IX, see [20].

both the hydroxyl (3570 cm^{-1}) and the primary amino group (3420 and 3530 cm^{-1}) bands, and strong absorption at 1612 and 1635 cm^{-1} which can be attributed to the absorption of the dihydropyridine ring [4]. The chemical reactions cited below establish the position of the substituents in the heterocyclic ring, and show that the compound formed is 2-amino-4-diphenylhydroxymethyl-4, 5-dihydropyridine (II).

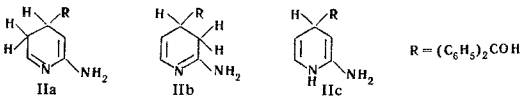
Treatment of II with dilute mineral acids converts it into two different compounds, only one of which is soluble in acid. The latter compound is a dehydration product (III), in whose spectrum the hydroxyl absorption band has disappeared. Prolonged heating of III in acid media results in transfer of the exocyclic bond into the ring and aromatization of the heterocycle (cf [5]). The structure of the resulting 2-amino-4-diphenylmethylpyridine (IV) is proved by hydrogenation. It is known [6] that hydrogenation of 2-aminopyridine hydrochloride results in removal of the amino group and the formation of piperidine. Hydrogenation of IV gave 4-diphenylmethylpiperidine (V), identical with the compound obtained by hydrogenation of 4-diphenylmethylpyridine [7], and ammonia. This confirms unambiguously the entry of the diphenylhydroxymethyl group into the γ-position of the heterocycle.

Compound II is an unusual cyclic diaminoethylene. Such compounds are known to undergo facile conversion into the amides of the corresponding acids [8]. The acid-insoluble compound VI obtained from II is also the product of such a conversion. The structure of VI as 4-diphenylhydroxymethyl-2, 3, 4, 5-tetrahydropyrid-2-one was confirmed by its IR spectrum (ν_{OH} 3420 cm^{-1}, ν_{CO} 1685 cm^{-1}, ν_{CN} 1605 cm^{-1}), and by its further reactions. Reduction of VI with lithium aluminum hydride gave 4-diphenylhydroxymethylpiperidine (VII), whose constants agreed with the literature values. Conclusive proof of this structure was obtained by conversion into its N-methyl derivative, which was obtained by an alternative route, i.e., alkylation of I with 1-methyl-4-chloropiperidine.

Dehydration of VI gave the amide (IX), which isomerized to the pyridone (X). The same pyridone was obtained by a different method, i.e., by diazotization of 2-amino-4-diphenylmethylpyridine (IV), and decomposition of the diazo compound with water.



All these reactions confirm the presence of the diphenylhydroxymethyl group in the γ-position, and the amino group in the α-position of the heterocycle. It is more difficult to assign positions to the double bonds in the dihydropyridine rings of these compounds. There is a choice between the following three structures for II, and the three corresponding structures for III and VI. The structure IIc may be excluded, since, in the absence of electron-accepting substituents, dihydropyridines exist in a form which does not have a hydrogen on the nitrogen [9]. The absence in the spectra of II and VI of bands due to the NH group supports structures IIa and VI. The latter structure is supported also by the



fact that complete reduction occurs with lithium aluminumhydride, which readily reduces the C=N bond, but not the C=C bond. In addition, the spectrum of IX shows a band at 3410 cm^{-1} characteristic of the amide group NH, identical

with the band in the pyridone X, indicating a 5–6 double in IX. However, this does not rule out the possibility of the 1–6 rearrangement of the double bond in VI and, correspondingly, in II, since the existence of an exocyclic double bond in the γ-position of IX might cause rearrangement of the double bonds in the ring.

These results, in our opinion, support structure II for the reaction product of the disodium derivative of benzophenone with 2-bromopyridine in liquid ammonia. The anomalous nature of this reaction is apparently related to the special properties of the organometallic compound. The unusual behavior of I in its reaction with iodobenzene, which results in reduction of the iodobenzene and oxidation of the organometallic compound, has been noted in the literature [10]. An examination of the reaction of I with aromatic bromo derivatives (bromobenzene and α-bromonaphthalene) has shown that in this case also, reduction of the bromo compounds occurs, with the formation of the sodium derivative of diphenylaminocarbinol. The formation of the latter compound, an intermediate in the Haller-Bayer reaction [11], was demonstrated by its further conversion into benzamide. The reaction of I with 2-bromopyridine proceeds in a similar way. This is proved by the isolation from the reaction mixture of benzophenone in significant amounts (up to 25%). It is suggested that such a reaction pathway may be connected with the spatial environment of the nucleophilic carbon atom of the dianion $(C_6H_5)_2C^-—O^-$ hindering attack on the α-carbon atom of the pyridine ring. This is also apparently connected with the reaction at the γ-carbon atom. The latter depends on reduction in the electron density on the 4-carbon atom (which is sterically more accessible than the 2-carbon atom) of 2-bromopyridine, and on the high nucleophilicity of the dianion. The increased nucleophilicity of the dianions (in comparison with the usual carbanions) from ketones is explained by the positive inductive effect of the negatively-charged oxygen atom in the α-position (the α-effect). This high nucleophilicity is manifested, as has been noted previously, in the characteristic reactions of the dimetallo derivatives of ketones with haloalkylamines [12] and aliphatic cyanides [13]. The reaction of I with 2-bromopyridine finds an analogy in the recently-described reactions [14] of 6-substituted 2-bromopyridines and of 2-bromoquinoline with sodamide, which involves the initial introduction of the amide anion into the γ-position of the heterocycle. The comparison with the amide anion stresses the high nucleophilicity of the above dianion. It would be supposed that other bromopyridines would also react anomalously with I. The reaction with 3-bromopyridine gave a mixture of 3- and 4-diphenylhydroxymethylpyridines, accompanied by oxidation of the organometallic compound. The reaction apparently proceeds via the intermediate formation of the hetaryne 3, 4-dehydropyridine, as is usually the case in the reaction of 3-bromopyridine with strong nucleophiles [15].

Our results induced us to reconsider the structure of the compound obtained by the reaction of I with nicotinic acid nitrile, to which had previously been assigned the imine structure [13]. The presence in the IR spectrum of a strong band due to the CN group (2165 cm^{-1}) shows that in this case also the diphenylhydroxymethyl group has entered directly into the pyridine ring, but the exact structure of the product will require further investigation.

EXPERIMENTAL

Analyses were carried out by M. R. Simonova. IR spectra were recorded on a UR-20 spectrometer in solution in chloroform. Mp's were determined on the Koffler block.

2-Amino-4-diphenylhydroxymethyl-4, 5-dihydropyridine (II). To a solution of 0.92 g (0.04 mole) of sodium in 100 ml of liquid ammonia was added a solution of 3.64 g (0.02 mole) of benzophenone in absolute ether, followed during half an hour by a solution of 1.6 g (0.02 mole) of 2-bromopyridine in 15 ml of ether. The violet color of the solution changed to green. The ammonia was distilled off, 30 ml of water and 30 ml of ether added, and the mixture was stirred until precipitation was complete. The precipitate was filtered off and washed with ether to give 1.4–1.5 g (50–55%) of II, mp 90° C (from benzene). Found, %: C 77.6; H 6.6; N 10.0. Calculated for $C_{18}H_{18}N_2O$, %: C 77.7; H 6.5; N 10.0. If no precipitate separated, the ethereal layer was separated and washed with 10% acetic acid, with cooling. Basification of the acetic acid solution afforded II. The ether layer was washed with 5% HCl, and evaporated to give 1.8 g of a mixture of compounds, 0.3 g of which was chromatographed on a column of 8–9 g of silica gel KSK, solvent benzene: acetone (50 : 1). There was obtained 0.14 g of benzophenone and 0.14 g of benzhydrol, identified by mixed mp's. Benzophenone was detected with iodine and benzhydrol with phosphomolybdic acid.

4-Diphenylhydroxymethyl-2, 3, 4, 5-tetrahydropyrid-2-one (VI) and 2-amino-4-diphenylmethylene-4, 5-dihydropyridine (III). 0.25 g of II was suspended in 10 ml of water, and a few drops of 10% HCl added. The mixture was heated to boiling, and cooled to give 0.1 g of crystals of VI, mp 264° C (from alcohol). Found, %: C 77.4; H 6.2; N 5.3. Calculated for $C_{18}H_{17}NO_2$, %: C 77.4; H 6.1; N 5.0. The acid layer was basified, and the precipitate isolated to give 0.1 g of III, mp 197–198° C (from toluene). Found, %: C 83.3; H 6.6; N 10.5. Calculated for $C_{18}N_{16}N_2$, %: C 83.0; H 6.2; N 10.7. Hydrochloride of III, mp 249–250° C (from alcohol and ether). Found, %: Cl 11.5. Calculated for $C_{18}H_{16}N_2 \cdot HCl$, %: Cl 11.8. The proportions of III and VI obtained were dependent on the reaction conditions. Thus, on

boiling a solution of II in 10% acetic acid, the main product was VI; addition of alcoholic hydrogen chloride to an alcoholic solution of the substance followed by addition of ether gave a quantitative yield of III hydrochloride. The same hydrochloride was formed on treatment of the product of the reaction of I with 2-bromopyridine, not with acetic, but with HCl, which also serves as a method of preparation of III.

2-Amino-4-diphenylmethylpyridine (IV). A solution of 1 g of III in 20 ml of 10% HCl was boiled for 5 hr. Water was added in order to dissolve completely the oil which separated on boiling, and the solution was washed with ether and basified to give 0.8 g (80%) of IV, mp 168° C (from benzene). Found, %: C 82.8; H 6.6; N 10.8. Calculated for $C_{18}H_{16}N_2$, %: C 83.0; H 6.2; N 10.7.

4-Diphenylmethylpiperidine (V). To a solution of 0.9 g (0.0025 mole) of IV in 20 ml of alcohol was added an equivalent amount of an alcoholic solution of hydrogen chloride, and the mixture hydrogenated in the presence of 0.2 g of platinum oxide at atmospheric pressure and room temperature until 300 ml of hydrogen had been taken up. The catalyst was removed, the solvent distilled off, and the residue triturated with 3 ml of acetone, giving 0.6 g of V hydrochloride, mp 278° C (from alcohol and ether). The free base V isolated from the hydrochloride was crystallized from hexane, mp 100–101° C. Compound V and its hydrochloride gave no depression of mp on mixing with authentic samples [7]. The alcohol distilled from the hydrogenation mixture was acidified and evaporated to give 0.16 g (90%) of ammonium chloride.

4-Diphenylhydroxymethylpiperidine (VII). A solution of 0.9 g (2.5 mM) of VI in 30 ml of benzene was added to a solution of 0.5 g of lithium aluminum hydride in ether, and the mixture boiled for 2 hr. After decomposing with water, the mixture was treated with 10% HCl, the ether layer separated, and a small amount of tartaric acid added to the aqueous solution. Basification gave 0.7 g of VII, mp 160° C (from benzene) [16].

1-Methyl-4-diphenylhydroxymethylpiperidine (VIII). A) To a solution of I in liquid ammonia obtained from 0.9 g (5 mM) of benzophenone was added a solution of 0.7 g (5 mM) of 1-methyl-4-chloropiperidine [17], the ammonia distilled off, the residue dissolved in 20% acetic acid, filtered and basified to give 1 g (71%) of VIII, mp 135° C (from hexane) [18]. B) A solution of 0.2 g of VII in a mixture of 3 ml of 90% formic acid and 3 ml of 40% aqueous formalin was boiled for 6 hr, basified, and the precipitated VIII filtered off. Recrystallization from hexane gave material mp 135° C, undepressed on mixing with material obtained as in A).

4-Diphenylmethylene-1, 2, 3, 4-tetrahydropyrid-2-one (IX). A solution of 0.5 g of VI in a mixture of 5 ml of glacial acetic acid and 1 ml of conc HCl was boiled for 20 min, poured into water, the precipitate isolated and crystallized from benzene. The yield of IX was theoretical, mp 200–201° C. Found, %: C 82.6; H 6.1. Calculated for $C_{18}H_{15}NO$, %: C 82.7; H 5.8.

4-Diphenylmethylpyrid-2-one (X). A) To a solution of 0.5 g (1.3 mM) of IV in a mixture of 100 ml of water and 1 ml of conc H_2SO_4 was added 0.5 g (7 mM) of sodium nitrite, and the mixture heated at 60° C for 30 min. The precipitate (0.4 g) was isolated and crystallized from benzene, mp 207° C. Found, %: C 82.5; H 6.1; N 5.5. Calculated for $C_{18}H_{15}NO$, %: C 82.7; H 5.8; N 5.4. B) A solution of 0.5 g of IX in a mixture of 5 ml of acetic acid and 2 ml of conc HCl was boiled for 8 hr and poured into water, giving 0.4 g of X, mp 207° C (undepressed on mixture with material obtained as in A. but depressed on mixture with starting material).

Reaction of I with 1-bromonaphthalene. To a solution of I in liquid ammonia, obtained from 3.6 g (0.02 mole) of benzophenone, was added a solution of 4.2 g (0.02 mole) of 1-bromonaphthalene in 100 ml of xylene. The ammonia was evaporated and the mixture boiled for 3 hr, cooled, and poured into water. The precipitate was filtered off to give 1.0–1.2 g of benzamide, mp 126–128° C (from dichloroethane). A mixed mp with authentic material gave no depression. Removal of the xylene left 0.8 g of naphthalene. The reaction with bromobenzene followed a similar course.

Reaction of I with 3-bromopyridine. To a solution of I in liquid ammonia, obtained from 1.82 g (0.01 mole) of benzophenone, was added a solution of 1 g (0.012 mole) of 3-bromopyridine in ether. The ammonia was distilled off, 30 ml of water and ether added, and the precipitated solid isolated. Yield 0.3 g of 4-diphenylhydroxymethylpyridine, mp 235° C (from alcohol). A mixed mp with an authentic sample [19] gave no depression. The ether layer was extracted with 10% HCl, basified, and extracted with ether. Removal of the ether left 0.2 g of 3-diphenylhdroxymethylpyridine, mp 114–115° C (from ethyl acetate), giving no depression on mixture with an authentic sample [19]. Chromatography of the ether layer revealed the presence of benzophenone and benzhydrol.

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