Dehydrogenation of Diethyl 1,4-Dihydro-4-phenyl-2,6-lutidine-3,5-dicarboxylate (V) with Pyridine N-Oxide (II). A mixture of 6.58 g (20 mmole) of ester V and 1.9 g (20 mmole) of oxide II was heated at 220-230°C, and the resulting distillate (1.54 g) contained, according to GLC, 58.5% pyridine, 1.8% 2-picoline, 15% acetaldehyde, 4.3% ethanol, 0.45% propanol, 0.8% isobutanol, and 0.7% isoamyl alcohol.

The resinified reaction mass was cooled, washed with water, mixed with aluminum oxide, and subjected to fractional extraction with petroleum ether (40-70°C). The fractions containing ester VI were combined, the solvent was removed by distillation, and the residue was washed in the cold with two portions of petroleum ether to give 3.76 g (57.5%) of ester VI with R_f 0.94 (system A) and mp 62-63°C (mp 63-64.5°C [6]). A total of 0.4 g (6%) of starting dihydro ester V, with mp 157-158°C, was isolated from the subsequent fractions.

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CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS.

11.* REACTION OF PYRIDINE N-OXIDE WITH METAL KETYLS AND BENZOPHENONE DIANIONS

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The reaction of pyridine N-oxide with metal ketyls of benzophenone was studied. It is shown that diphenyl(2-pyridyl)carbinol N-oxide is formed with the lithium and sodium derivatives of benzophenone, whereas diphenyl(2-pyridyl)carbinol is formed with the potassium derivative of benzophenone. Diphenyl(2-pyridyl)carbinol N-oxide is obtained in lower yields in the reaction of pyridine N-oxide with benzophenone dianions. Pyridine and 4,4'- and 2,2'-dipyridyls are simultaneously formed in all of the reactions.

The N-oxides of aromatic heterocycles have increased reactivity with respect to the action of various electrophilic, nucleophilic, and radical reagents [2]. However, up until now, reactions with anion radicals were unknown in the N-oxide series.

We have shown that the diphenylhydroxymethyl group enters the 2 position of the pyridine ring to give diphenyl(2-pyridyl)carbinol N-oxide (III) in 28% yield in the reaction of pyridine N-oxide (I) with benzophenonyllithium ketyl (II) in dioxane at a reagent ratio of 1:1.

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*See [1] for Communication 10.

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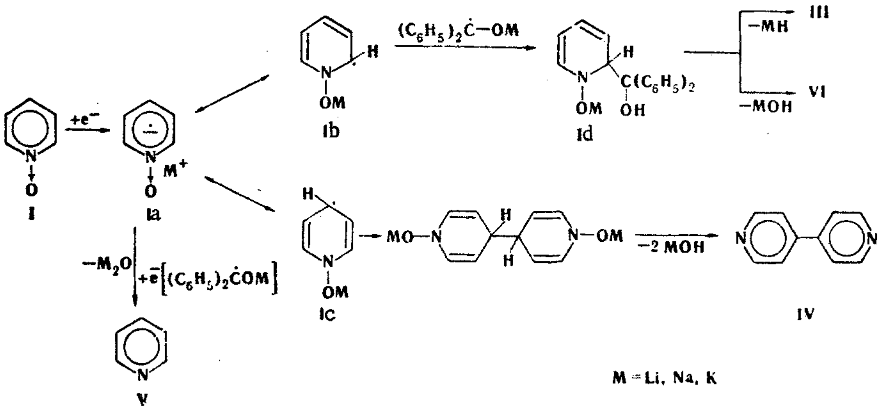
Products of reductive dimerization [10% 4,4'-dipyridyl (IV) and traces of 2,2'-dipyridyl] and deoxidation [14% pyridine (V)] are similarly obtained. Ketyl II reacts completely in this case, since otherwise the hydrolysis product (benzopinacone) would have been isolated. The high yield of benzophenone is explained by the fact that 2 moles of the ketyl undergo reaction. In fact, the ketyl is also consumed completely in the case of a reagent ratio of 1:2, and the yield of condensation product III increases sharply. The structure of the latter was confirmed by reduction to diphenyl(2-pyridyl)carbinol (VI).

Replacement of lithium by sodium in ketyl II does not have a substantial effect on the course of the reaction and also leads to the formation of oxide III but in lower yield. Like other lithium anion radicals, benzophenonyllithium (II) in ether solvents probably exists in the form of the more active separated ion pair, while benzophenonylsodium (VII) probably exists in the form of the less active contact ion pair [3].

A product of reductive condensation (VI) in 80% yield and very small amounts of pyridine, 4,4'-dipyridyl, and traces of 2,2'-dipyridyl are obtained in the reaction between oxide I and benzophenonylpotassium ketyl (VIII) under similar conditions. However the formation of oxide III does not precede the production of deoxycarbinol VI, since it is necessary additionally to use no less than 2 moles of the ketyl to realize this process.



Electron transfer from ketyl II, VII, or VIII to oxide I to give anion radical Ia, which is mesomeric with respect to σ radical Ib, probably occurs in the first step of the reaction. As a result of recombination with the ketyl, radical Ib gives dihydro derivative Id, which is stabilized by conversion to aromatic compound III or VI due to splitting out of a metal (lithium, sodium) hydride or hydroxide (potassium). The products of dimerization (4,4'- and 2,2'-dipyridyl) and reductive deoxidation (pyridine) are also obtained from ion radical Ia, respectively, by dimerization or reduction. The results of the reaction of N-oxide I with sodium metal constitute evidence in favor of this assumption [4].

The formation of recombination products III and VI, as well as 4,4'-dipyridyl, is explained by the fact that the greater portion of the spin density in anion radical Ia is concentrated in the α and γ positions [5]. Since ketyls in solution exist in equilibrium with the dianions [6], it may be assumed that the formation of III and VI occurs as a result of nucleophilic substitution of hydrogen. However, experiments showed that the substitution of oxide I by dianions of benzophenonyllithium, benzophenonylsodium, and benzophenonylpotassium proceeds with difficulty and, regardless of the nature of the metal, leads to the formation of oxide III in low yields (21-25%). Deoxidation and reductive dimerization of oxide I become the principal reaction pathways. The elucidation of the mechanism of the reaction of oxide I with ketyls and dianions of benzophenone requires additional study and will be the subject of a separate publication.

The reaction under consideration may serve as a simple and convenient method for the synthesis of heteroaromatic alcohols and their N-oxides. It can be formally regarded as a modification of the Emmert method for the synthesis of heterocyclic alcohols [7]. However, we have established that the reaction of pyridine with benzophenone metal ketyls does not take place and that the starting base is recovered in quantitative yield.

EXPERIMENTAL

The reagents and solvents used in this research were freshly distilled and dried. The isolation of the reaction products was monitored by paper chromatography (on "fast"-grade paper) in butanol—hydrochloric acid—water (50:7:14) (system A) and butanol—acetic acid—water (50:7:14) (system B) with development with Dragendorff's reagent and by thin-layer chromatography (TLC) in an Al_2O_3—ether (system C) and silica gel—ether (system D).

Reaction of Pyridine N-Oxide (I) with Benzophenonyllithium Ketyl (II). A suspension of 1.01 g (0.14 g-atom) of finely cut up lithium in 10 ml of dioxane was added in a stream of purified dry nitrogen to a solution of 26.22 g (0.14 mole) of benzophenone in 200 ml of absolute dioxane, and the mixture was stirred with a magnetic stirrer for 30 h. A solution of 10.5 g (0.11 mole) of oxide I in 50 ml of dioxane was added in several portions to the resulting dark-blue solution of ketyl II, during which the mixture turned successively green and red-brown. After 24 h, water was added to completely dissolve the lithium hydroxide, and the aqueous mixture was extracted successively with hexane and ether. The solvents were removed by distillation to give 26.3 g of a mixture of diphenyl(2-pyridyl)carbinol N-oxide (III), with R_f 0.12, and benzophenone with R_f 0.9 (system C). A 0.7-g sample of this mixture was separated by means of TLC in system C to give 0.5 g of benzophenone and 0.2 g of oxide III with mp 192°C (from ethanol; mp 194°C [8]). Workup of the ether extract gave 4 g of a mixture of oxide III, with R_f 0.95, and 4,4'-dipyridyl with R_f 0.8 (system B), which was separated by TLC in system D to give 1.7 g (10%) of dipyridyl IV, with mp 73°C (from water), and 1.26 g of oxide III. The overall yield of oxide III was 28%.

Dry hydrogen chloride was bubbled into the hexane—dioxane and ether distillates, and 1.25 g (14%) of pyridine hydrochloride, with R_f 0.35 (system A), was obtained after removal of the solvents by distillation. The picrate had mp 159-160°C. The aqueous mother liquor was evaporated to dryness, the residue was mixed with Al_2O_3, and the mixture was subjected to continuous extraction with acetone. The solvent was removed by distillation, and the residue was chromatographed in system D to give 1.2 g (11%) of starting oxide I. When the benzophenone:lithium:oxide I ratio was 2:2:1, 64% oxide III, 5.3% dipyridyl IV, 8.8% pyridine V, and 21% starting oxide I were obtained.

The reaction of oxide I with benzophenonylsodium ketyl (VII) was carried out as in the experiment with ketyl II. Workup gave 33% oxide III, 3.2% dipyridyl IV, 7.7% pyridine, 60% benzophenone, and 23% starting oxide I. When the benzophenone:sodium:oxide I ratio was 2:2:1, 40% oxide III, 5.4% dipyridyl IV, 6.4% pyridine, 53% benzophenone, and 16% oxide I were obtained.

Diphenyl(2-pyridyl)carbinol (VI). A) A mixture of 2 g (7.6 mmole) of oxide III, 0.3 g (0.005 g-atom) of iron, and 30 ml of glacial acetic acid was refluxed for 3 h, after which the acetic acid was removed by vacuum distillation, and the residue was diluted with water. The aqueous mixture was made alkaline to pH 8-9 and evaporated to dryness, and the residue was extracted continuously with benzene. The solvent was removed by distillation to give 1.7 g (95%) of carbinol VI with mp 105°C (from ethanol). No melting-point depression was observed for a mixture of this product with a genuine sample obtained by the method in [9].

B) A mixture of 0.83 g (3 mmole) of oxide III and 0.76 g (3 mmole) of the Hantzsch ester was heated in a distilling flask at 240°C for 40 min until it gave a negative test for the starting Hantzsch ester with picric acid. The reaction mixture was then cooled and washed repeatedly in the cold with petroleum ether. The solvent was then removed by distillation to give 0.7 g (93%) of diethyl 2,6-lutidine-3,5-dicarboxylate with R_f 0.9 (system A) and mp 71-72°C. The residue was recrystallized from ethanol to give 0.65 g (83%) of carbinol VI with R_f 0.15 (system C) and mp 105°C (from ethanol).

Reaction of Oxide I with Benzophenonylpotassium Ketyl (VIII). A solution of 11.4 g (0.12 mole) of oxide I in 50 ml of dioxane was added in a nitrogen atmosphere to a dark-blue solution of ketyl VIII obtained from 26.22 g (0.14 mole) of benzophenone and 5.61 g (0.14 g-atom) of potassium in 200 ml of dioxane. After 24 h, the resulting red-brown mixture was decomposed with water and extracted successively with hexane and ether. The solvents were removed by distillation, and the residue was dissolved in 20 ml of ether. The ether solution was treated four times with dilute (1:1) hydrochloric acid, the ether layer was separated, the solvent was removed by evaporation, and the oily residue was allowed to stand for crystallization. This procedure gave 1.19 g (6%) of triphenylcarbinol with mp 161°C. No melting-point depression was observed for a mixture of this product with a genuine sample. Workup of the residue gave 12.86 g (48%) of benzophenone. Ammonia was bubbled into the hydrochloric acid solution until it was alkaline, after which it was extracted with ether. The extract was dried with anhydrous Na_2SO_4, and the solvent was removed by distillation to give 10.02 g (32%) of carbinol VI with R_f 0.15 (system C) and mp 105°C (from alcohol). Workup of the ether extract of the reaction mixture gave 0.4 g (2.1%) of dipyridyl IV with R_f 0.8 (system B) and mp 73°C (from water). The aqueous mother liquor was evaporated to dryness, and the residue was mixed with Al_2O_3 and extracted continuously with benzene. Workup gave 1.4 g (12.7%) of oxide I. Dry hydrogen chloride was bubbled into the hexane—dioxane and ether distillates until they were acidic, after which the solvents were removed by distillation to give 0.6 g (6%) of pyridine hydrochloride. When the benzophenone:potassium:oxide I ratio was 2:2:1, 80% carbinol VI, 2.5% dipyridyl IV, 4% pyridine, 47% benzophenone, 34% triphenylcarbinol, and 4% oxide I were obtained.

Reaction of the Benzophenonyllithium(Sodium or Potassium) Dianion with Oxide I. A suspension of 0.17 g (0.024 g-atom) of finely cut up lithium in 10 ml of dioxane was added in a stream of dry nitrogen to a solution of 2.18 g (12 mmole) of benzophenone in 90 ml of absolute dioxane, after which the flask was sealed hermetically and allowed to stand until the metal dissolved completely and the violet benzophenonyllithium dianion formed. After 2 weeks, a solution of 1.1 g (11 mmole) of oxide I in 20 ml of dioxane was added in a nitrogen atmosphere to the resulting solution, during which the color of the reaction mixture changed to red-brown. The reaction products were isolated as in the experiment with ketyl II to give 0.81 g (25%) of oxide III, 0.25 g (13%) of dipyridyl IV (traces of 2,2'-dipyridyl), 0.23 g (25%) of pyridine, 1 g (45%) of benzophenone, and 0.1 g (9%) of oxide I.

The experiment with the benzophenonylpotassium dianion gave 0.74 g (24%) of oxide III, 0.2 g (11%) of dipyridyl IV (with traces of 2,2'-dipyridyl), 0.3 g (33%) of pyridine, 0.6 g (39%) of triphenylcarbinol, 0.85 g (39%) of benzophenone, and 0.15 g (13%) of oxide I.

The reaction with the benzophenonylsodium dianion gave 0.64 g (20%) of oxide III, traces of dipyridyls, 0.38 g (42%) of pyridine, 0.8 g (38%) of benzophenone, and 0.4 g (36%) of oxide I.

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