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CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS.

12.* DIPHENYLHYDROXYMETHYLATION OF QUINOLINE N-OXIDE WITH BENZOPHENONE

KETYLS AND DIANIONS

A. S. Kurbatova, Yu. V. Kurbatov, and V. K. Yu

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Diphenylhydroxymethylation of the pyridine ring to give diphenyl(2-quinolyl)carbinol or its N-oxide occurs in the reaction of quinoline N-oxide with benzophenone ketyls and dianions. The best results are obtained when the lithium ketyl is used. A reduction product, viz., quinoline, is formed simultaneously in all of the reactions.

We have found [2] that a diphenylhydroxymethyl group enters the pyridine ring to give diphenyl(2-pyridyl)carbinol N-oxide or the deoxy base in the reaction of pyridine N-oxide with benzophenone ketyls and dianions [2]. The reaction opens up new possibilities for the synthesis of heterocyclic alcohols and their N-oxide.

In order to further develop the proposed method, in the present research we studied the reaction of quinoline N-oxide (I) with benzophenone ketyls and dianions. Diphenylhydroxy-methylation of the heteroring in the 2 position to give diphenyl(2-quinolyl)carbinol N-oxide (III) and small amounts of quinoline (IV) as a side product occurs in the reaction of oxide I with an equimolar amount of lithium diphenylketyl (II). The use of stoichiometric amounts of ketyl II leads to a product of reduction of oxide IIII, viz., the deoxycarbinol (V), in 83% yield due to intramolecular oxidation of intermediate dihydroquinoline IIIa. An attempt to avoid deoxidation by decreasing the reaction temperature to 0°C did not give positive results: Traces of oxide III and deoxycarbinol V were obtained. The deoxidation of oxide III with iron in acetic acid or with the Hantzsch ester [3] gave diphenyl(2-quinolyl)carbinol from benzophenone and quinaldinic acid by the method in [4].



In contrast to lithium diphenylketyl, the sodium and potassium derivatives form only reductive condensation product V but in lower yields. As expected, the side deoxidation of

^{*}See [1] for Communication 11.

A. Navoi Samarkand State University, Samarkand 703004. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 249-251, February, 1983. Original article submitted June 18, 1982.

starting oxide I proceeds more intensively in this case. The reaction of diphenylketyls with oxide I probably proceeds via a scheme involving one-electron transfer, as evidenced by the formation of deoxidation product IV.

It should also be noted that the "reverse" decomposition of carbinols III and V to benzophenone, quinoline oxide, and quinoline can be observed when they are heated to 250°C.

 $HI \longrightarrow I + IV + C_6H_5COC_6H_5$

Regardless of the nature of the metal, the diamions of the lithium, sodium, and potassium derivatives of benzophenone form reductive condensation product V but in lower yields. As in the reaction with ketyls, the best results are obtained when the lithium derivative is used.

EXPERIMENTAL

The reagents and solvents used in the reactions were thoroughly dried and freshly distilled. Monitoring of the isolation of the reaction products and their identification were accomplished by paper chromatography (with "fast" paper) in the butanol—acetic acid—water system (system A) with Dragendorf's reagent as the developer and by means of thin-layer chromatography (TLC) on Al_2O_3 in ether (system B).

Reaction of Quinoline N-Oxide (I) with Lithium Diphenylketyl (II) (1:1). A suspension of 0.175 g (0.025 mole) of finely cut lithium in 10 ml of dioxane was added to a solution of 4.55 g (25 mmole) of benzophenone in 30 ml of absolute dioxane in a stream of purified dry nitrogen, and the mixture was stirred with a magnetic stirrer for 24 h. A solution of 2.9 g (20 mmole of oxide I in 50 ml of dioxane was added in three portions to the dark-blue solution of ketyl II, during which the color of the reaction mixture changed instantaneously from blue to red. After 24 h, water was added, and the precipitated diphenyl(2-quinolyl)carbinol N-oxide (III) was removed by filtration to give 3.4 g (52%) of a product with mp 198°C (from acetone) and Rf 0.82 (system B). Found: C 80.1; H 5.3; N 4.3%. C₂₂H₁₇NO₂. Calculated: C 80.7; H 5.2; N 4.3%. The filtrate was extracted with hexane, the solvent was removed by distillation, and cyclohexane was added to the oily residue. The mixture was filtered, and the solution was washed three times with 10% hydrochloric acid. The acidic solution was treated twice with chloroform (15-ml portions), and the cyclohexane and chloroform were removed by distillation to give 2.41 g (53%) of benzophenone with mp 42-43°C and R_f 0.94 (system B). The hydrochloric acid solution was made alkaline to pH 8-9 with potassium carbonate and extracted with chloroform. The solvent was removed by distillation to give 0.1 g (3.8%) of quinoline with Rf 0.87 (system A). The picrate had mp 202-203°C (from benzene). The aqueous mother liquor was evaporated to dryness, and the residue was mixed with Al₂O₃ and subjected to continuous extraction with benzene. The solvent was removed by distillation to give 1.23 g (42.4%) of starting oxide I with R_f 0.9 (system A) and R_f 0.03 (system B).

<u>Diphenyl(2-quinolyl)carbinol (V).</u> A) A mixture of 0.85 g (2.6 mmole) of oxide III, 0.1 g (1.8 mmole) of iron, and 10 ml of glacial acetic acid was refluxed for 3 h, after which the acetic acid was removed by vacuum distillation, and the residue was washed with water, made alkaline to pH 8-9 with potassium carbonate, and evaporated to dryness. The residue was subjected to continuous extraction with benzene, and the solvent was removed by distillation to give 0.75 g (92.6%) of diphenyl(2-quinolyl)carbinol (V) with mp 189°C (from acetone). Found: C 84.8; H 5.5; N 4.4%. $C_{22}H_7NO$. Calculated: C 84.9; H 5.5; N 4.5%. No melting-point depression was observed for a mixture of this product with a genuine sample of carbinol V obtained by method C.

B) A mixture of 0.77 g (3 mmole) of the Hantzsch ester and 1 g (3 mmole) of oxide III was heated in a distilling flask at 220-230°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 mixed with aluminum oxide, and the mixture was subjected to continuous extraction with benzene. The solvent was removed by distillation, and the residue was washed with petroleum ether in the cold. The insoluble part of the residue [0.6 g (63%)] was identified as carbinol V. The petroleum ether was removed by distillation to a small volume, and the concentrate was cooled to give 0.65 g (85.5%) of diethyl 2,6-lutidine-3,5-dicarboxylate with mp 71-72°C and R_f 0.9 (system A). Workup of the petroleum ether washings gave 0.1 g of quinoline.

C) A mixture of 5 g (28 mmole) of quinaldinic acid and 31.6 g (0.17 mole) of benzophenone in 21 ml of p-cymene was refluxed in a nitrogen atmosphere for 6 h, after which it was

cooled and treated with 10% hydrochloric acid until it gave a negative test with respect to Dragendorf's reagent. Ammonia was passed through the hydrochloric acid solution to pH 9, and the mixture was extracted with benzene. The solvent was removed by distillation to give a mixture of carbinol V and quinoline. Recrystallization from acetone gave 2.1 g (22%) of carbinol V.

Reaction of Quinoline N-Oxide with Lithium Diphenylketyl (II) (1:2). A suspension of 0.42 g (0.06 mole) of finely cut lithium in 10 ml of dioxane was added to a solution of 10.9 g (60 mmole) of benzophenone in 100 ml of absolute dioxane in a stream of purified dry nitrogen, and the mixture was stirred with a magnetic stirrer for 24 h. A solution of 4.35 g (30 mmole) of oxide I in 80 ml of dioxane was added in three portions to the dark-blue solution of ketyl II, during which the color of the reaction mixture became dark red. After 24 h, water was added, and the precipitated diphenyl(2-quinolyl)-carbinol (V) was removed by filtration. The filtrate was extracted successively with heptane, benzene, and chloroform. Removal of the heptane by distillation gave a mixture of diphenyl(2-quinolyl)carbinol (V), with $R_{\rm f}$ 0.78, and benzophenone with $R_{\rm f}$ 0.93 (system B). A 0.7-g sample of the mixture was separated by means of TLC in system B to give 0.38 g of benzophenone and 0.23 g of carbinol V. The overall yields of carbinol V and benzophenone were, respectively, 7.8 g (84.9%) and 4.6 g (42%). Workup of the benzene extract gave 0.25 g (6.5%) quinoline, and the chloroform extract gave 0.25 g (5.7%) of starting oxide I. Trace amounts of oxide III and carbinol V, 92% benzophenone, traces of benzyhydrol, 5% quinoline, and 94% starting oxide I were obtained at 0-4°C when the benzophenone:lithium:oxide I ratio was 2:2:1.

The reaction of oxide I with sodium (potassium) diphenylketene was carried out in the same way as the experiment with ketyl II (1:2). The following results were obtained [the metal, ketone:metal:oxide I ratio, and reaction products (yields in percent) are given]: Na, 1:1:1, carbinol V (10%), benzophenone (89%), quinoline (47%), oxide I (37.5%); Na, 2:2:1, carbinol V (56%), benzophenone (32%), quinoline (18%), oxide I (25%); K, 1:1:1, carbinol (18.5%), benzophenone (20%), quinoline (13.6%), oxide I (43%); K, 2:2:1, carbinol (26.5%), benzophenone (30%), quinoline (26%), oxide I (7.8%).

Reaction of Oxide I with the Dianion of the Lithium (sodium, potassium) Derivative of Benzophenone. A suspension of 0.17 g (24 mmole) finely cut lithium in 10 ml of dioxane was added to a solution of 2.2 g (12 mmole) of benzophenone in 90 ml of absolute dioxane in a stream of dry nitrogen, after which the flask was sealed hermetically and allowed to stand with periodic stirring with a magnetic stirrer until the metal had dissolved completely. After 2 weeks, 1.7 g (12 mmole) of oxide I in 30 ml of dioxane was added to the resulting violet solution of the dianion of the lithium derivative of benzophenone in a nitrogen atmosphere, whereupon the reaction mixture became warm, and the color changed instantaneously from violet to brown. The reaction products were isolated as in the experiment with ketyl II. This procedure gave 2.16 g (59%) of carbinol V, 0.47 g (21.8%) of benzophenone, 0.35 g (23.3%) of quinoline, and 0.25 g (14.7%) of oxide I. In the case of the dianion of the sodium derivative of benzophenone this procedure gave 1.9 g (52.5%) of carbinol V, 0.75 g (34.4%) of benzophenone, 0.22 g (14.6%) of quinoline, and 0.5 g (30%) of oxide I. In the case of the dianion of the potassium derivative of benzophenone this procedure gave 0.5 g (13.7%) of carbinol V, 1.85 g (84.8%) of benzophenone, 0.3 g (20%) of quinoline, and 1.03 g (60.6%) of oxide I.

Thermal Decomposition of Carbinol N-Oxide III. A 0.1-g sample of carbinol N-oxide III was heated on a metal bath at 230-250 °C for 1.5 h, after which the reaction mass was dissolved in 3 ml of 5% hydrochloric acid, and the acidic solution was extracted with chloroform. The solvent was removed by distillation, and the residue was separated by means of TLC in system B to give 0.03 g of benzophenone (R_f 0.93) and 0.015 g of oxide I (R_f 0.03). The hydrochloric acid solution was made alkaline to pH 8-9 with potassium carbonate and extracted with chloroform to give 0.01 g of quinoline with R_f 0.87 (system B).

Thermal Decomposition of Carbinol V. A 0.1-g sample of carbinol V was heated on a metal bath at 250-300°C for 1 h, after which the reaction mass was worked up as in the experiment with carbinol N-oxide III to give carbinol V (R_f 0.78), benzophenone (R_f 0.93), and quino-line (R_f 0.87) (system B).

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REDUCTION OF QUATERNARY SALTS OF 3-AZAFLUORENE AND 3-AZAFLUORENONE AND THEIR CONVERSION TO INDENOINDOLIZINES

 N. S. Prostakov, A. T. Soldatenkov, P. K. Radzhan,
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 A. Samal'oa, V. F. Zakharov, and V. P. Zvolinskii
 543.422'51

The tetrahydro and hexahydro derivatives with respect to the nitrogen-containing ring were obtained by reduction of 3-azafluorene and 3-azafluorenone methiodides, respectively, with sodium borohydride. Indenoindolizines with linear and angular structures were synthesized from the N-phenacyl quaternary salts of 3-azafluorenones via 1,3-dipolar cycloaddition and by the Chichibabin method. 7-Nitro-3-azafluorenone and 3-azafluorenone N-oxide were obtained.

Until recently, virtually no information regarding the properties and chemical transformations of 3-azafluorene was available. In connection with the development of a relatively simple method for its preparation [1] it seemed possible to begin a study of this previously difficult-to-obtain heterocycle.

In pharmacological tests of the partially hydrogenated 1-azafluorene derivatives obtained in our laboratory we established that they have psychotropic properties [1]. It seemed of interest to synthesize similar compounds on the basis of 3-azafluorene (I) and 3-azafluorenone (II).

For this, we obtained N-methyl-3-azafluorenium iodide (III) and N-methyl-9-oxo-3-aza-fluorenium iodide (IV) from I and II. Quaternary salt V, which was obtained from ketone II and ω -bromoacetophenone, was used in the synthesis of indenoindolizines.

The reduction of salts III and IV was carried out by using a large excess of sodium borohydride; their transformations proceed ambiguously in this case. 2-Methyl-1,2,3,4-tetrahydroindeno[1,2-c]pyridine (VI) was obtained in 87% yield in the reduction of salt III, while 5hydroxy-2-methylindano[1,2-c]piperidine (VII) was obtained in 20% yield from salt IV. Intense (75 and 100%, respectively) molecular-ion peaks are present in the mass spectra of VI and VII. The PMR spectrum of tetrahydro derivative VI does not contain the signal of a vinyl proton, on the basis of which it may be concluded that the double bond is located in the C_(4a)-C_(9b) position in the nitrogen-containing ring. The fact that the mass spectrum of vii does not contain a peak corresponding to the tetrahydro derivative (m/z 201) also may serve as a confirmation of its structure. The signal of a methyl group (2.18 ppm) and a doublet at 4.97 ppm (1H) with a spin-spin coupling constant (SSCC) of 6.5 Hz, which can be assigned to the proton attached to the C₍₅₎ atom, are observed in its PMR spectrum.

Free bases VI and VII are unstable compounds. They are transformed rapidly in air. They were therefore converted to the hydrochlorides for identification and further study.

To obtain new condensed heterocycles of the indenoindolizine type we subjected N-phenacyl-9-oxo-3-azafluorenium bromide (V) to 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate. As expected, we obtained products of condensation in both the α and α' positions of the pyridine ring, viz., 6-oxo-3-benzoyl-1,3-dicarbomethoxyindeno[2,1-g]indolizine (VIII) and 5-oxo-1-benzoyl-2,3-dicarbomethoxyindeno[2,1-f]indolizine (IX), the isolation of which was accomplished by means of chromatography [3].

Patrice Lumumba Peoples' Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 252-255, February, 1983. Original article submitted June 8, 1982.