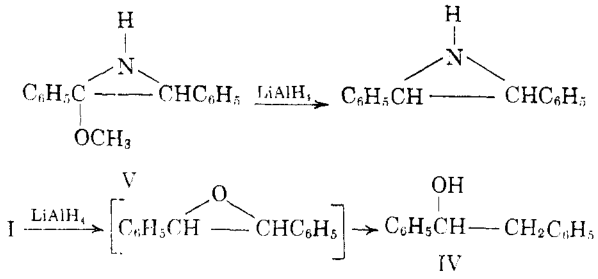
Lithium aluminum hydride reacted rapidly with I to give 75% of benzyl phenyl carbinol. In view of the fact that the nitrogen analog (V) of the epoxyether I is reduced by lithium aluminum hydride to the corresponding ethylene imine,[7] the formation of the carbinol likely involves a similar displacement of methoxide followed by further reduction of the resulting stilbene oxide.

Sodium borohydride was also unsuited as a reagent for this study since the epoxyether was not reduced by this reagent.



EXPERIMENTAL

1,2-Diphenyl-1-methoxyethylene oxide (I). The compound could be conveniently prepared in 54% yield by allowing equivalent amounts of sodium methoxide and desyl chloride to react in absolute methanol solution for two minutes at the reflux temperature. The solution was then cooled to −80° in a Dry Ice–acetone bath and the solid which precipitated was filtered and recrystallized from a petroleum ether–ether mixture, m.p. 56–57°. The product was identical with the product from the previously published procedure,[4] the yield from which was 33%.

Monomethyl ether of DL-*hydrobenzoin* (*II*) *by lithium borohydride reduction of I.* A mixture of 1.5 g. (0.068 mole) of lithium borohydride and 75 ml. of dry ether was refluxed for 6 hr. The mixture was then allowed to settle and the clear supernatant solution was decanted and cooled to −60°. The solution was stirred and another cooled solution of 6 g. (0.026 mole) of the epoxyether I in 75 ml. of ether was slowly added. The temperature was allowed to rise to room temperature and the mixture was then stirred an additional two hours. Excess saturated ammonium chloride solution was added and the ether layer separated, dried, and concentrated. The residual oil was crystallized from petroleum ether to give 1.3 g. of II, m.p. 56–57°. Alumina chromatography of the filtrate gave an additional 1.3 g. of II, m.p. 56–57°, 0.07 g. (1%) of the monomethyl ether of *meso*-hydrobenzoin III, and 0.5 g. (9%) of phenyl benzyl carbinol, m.p. 65–66°.

The total yield of II was 2.6 g. (43%) and was shown to be identical with an authentic sample made by independent synthesis.[4]

The *p*-nitrobenzoate derivative of II was prepared by the sodium dispersion method previously described.[1] From 0.5 g. of II was obtained 0.4 g. (50%) of product, m.p. 110–112°. The mixture melting point of this derivative with that obtained from the independently synthesized material was undepressed.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 70.26; H, 5.15.

The *p*-nitrobenzoate of the diastereoisomer III was prepared in 60% yield by the same method, m.p. 78–80°. The same derivative was obtained from the product of the reaction mixture or from authentic III.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 69.71; H, 5.02.

In another experiment the crude reaction mixture was converted to the *p*-nitrobenzoate derivative. Reduction of 17.6 g. (0.075 mole) of I as described above gave 16.5 g. of oil after concentration of the ether solution. Before the product began to crystallize from the oil a 2-g. aliquot was converted to the *p*-nitrobenzoate derivative. One recrystallization of the product from petroleum ether gave 2.1 g. (60%) of the *p*-nitrobenzoate of II, m.p. 105–109°. A second recrystallization gave 1.53 g., m.p. 109–111°.

Reduction of I with lithium aluminum hydride. The epoxyether I was reduced with lithium aluminum hydride in the same manner as described for lithium borohydride except that the reduction was started at 0°. From 3 g. of I was obtained 2.1 g. (75%) of phenyl benzyl carbinol, m.p. 65–66°. A mixture melting point with an authentic sample was not depressed.

DETROIT 2, MICH.

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[7] M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Rearrangement and Condensation of Reissert Compounds with Grignard Reagents. III

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Reissert compounds (1-acyl-1,2-dihydroquinaldonitriles and 2-acyl-1,2-dihydroisoquinaldonitriles) undergo reaction with Grignard reagents in ether-dioxane to form tertiary carbinols containing the 2-quinolyl or 1-isoquinolyl group as one of the substituents bonded to the carbinol carbon atom. The scope of this reaction has been expanded, and evidence has been uncovered which shows that the initial reaction is one between the Reissert compound and RMgX, present in the solid phase of the reaction mixture. A 1-acylisoquinoline or a 2-acylquinoline is formed as an intermediate, and this α-acyl heterocyclic derivative can undergo further reaction to form a salt of the carbinol either with R_2Mg in solution or with RMgX in the solid phase.

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) undergo reaction with Grignard reagents to form tertiary alcohols of structures III and IV, respectively.[1,2] It has been established[2] that the mechanism of the reaction in ether-dioxane solution consists of an

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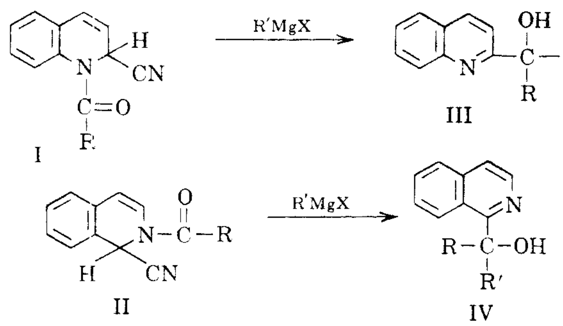
[1] W. E. McEwen, J. V. Kindall, R. N. Hazlett, and R. H. Glazier, *J. Am. Chem. Soc.*, **73**, 4591 (1951).

[2] A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

initial attack by the anion of the organometallic reagent on the α-hydrogen atom of the Reissert compound (I or II) to form the conjugate base, its intramolecular rearrangement to the α-acyl heterocyclic derivative with expulsion of a cyanide ion, and, finally, condensation of the α-acyl heterocyclic derivative with additional Grignard reagent. The scope of the reaction has now been expanded, and further details of the mechanism of reaction have been uncovered.



EXPERIMENTAL[3]

Diphenylmagnesium. An ether-dioxane solution of this material was prepared according to the procedure of Noller.[4,5] Titration experiments showed the reagent to be 0.5*N* in diphenylmagnesium and less than 0.01*N* in halide ion.

Reaction of 1-benzoylisoquinoline with diphenylmagnesium. A solution of 2.00 g. of 1-benzoylisoquinoline[6] in 15 cc. of anhydrous dioxane was added with mechanical stirring within two minutes to 35 cc. of 0.5*N* diphenylmagnesium solution, the reaction mixture being maintained in an atmosphere of dry nitrogen. An additional 15 cc. of dioxane was added to the homogeneous dark solution and the solution was stirred at room temperature for 10 min. and then heated on a steam bath for 2 hr. The solvents were removed by distillation *in vacuo*, and ice water was added to the residual cake. The mixture was extracted with ether, and the ether solution was extracted with 10% hydrochloric acid. The aqueous acid solution was made alkaline, and ether extraction provided 2.20 g. (79%) of crude diphenyl-1-isoquinolylcarbinol. After two recrystallizations from ethanol, the compound melted at 142–143°, also in admixture with a sample of the carbinol prepared by reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with phenylmagnesium bromide.[2]

Reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with diphenylmagnesium. A solution of 10.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) in 75 cc. of anhydrous dioxane was added with mechanical stirring within two minutes to 180 cc. of 0.5*N* diphenylmagnesium solution, the reaction mixture being maintained in an atmosphere of dry nitrogen. The homogeneous red solution was treated as described for the previous reaction. After the 10% hydrochloric acid extract had been made alkaline, ether extraction provided only 0.2 g. (0.2%) of crude diphenyl-1-isoquinolylcarbinol.

Concentration of the original ether solution gave 7.5 g. of a mixture of solid and oil. The solid was separated from the oil by filtration and recrystallized from absolute ethanol. There was obtained 5.5 g. (55%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile. The oil was dissolved in ether and extracted with 6*N* hydrochloric acid. After the acid extract had been made alkaline, ether extraction afforded 1.2 g. (20%) of isoquinaldonitrile, m.p. 86–87° after recrystallization from absolute ethanol. There was no depression of melting point when this compound was mixed with authentic[7] isoquinaldonitrile.

Reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with 0.49N phenylmagnesium bromide solution. To 180 cc. of a 0.49*N* solution of phenylmagnesium bromide in ether, maintained in a dry nitrogen atmosphere, was added, with mechanical stirring, first 20 cc. of anhydrous dioxane, then a solution of 10.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 75 cc. of dioxane. The latter solution was added in a period of about two minutes. The resulting mixture was treated as described above for the diphenylmagnesium reactions. There was obtained 8.22 g. (69%) of crude diphenyl-1-isoquinolylcarbinol, and only 0.3 g. (3%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Investigation of the two phases in the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with 0.49N phenylmagnesium bromide solution. To 72 cc. of a 0.49*N* ethereal solution of phenylmagnesium bromide was added 8 cc. of anhydrous dioxane, the mixture being maintained in a pure nitrogen atmosphere. A solution of 2.00 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile in 15 cc. of dioxane was added with mechanical stirring over a period of 45 sec., the mixture being maintained at about 25°. The mixture was stirred for 10 min., then filtered in a nitrogen atmosphere. The precipitate was washed with 25 cc. of ether in two portions, and the wash solution was added to the filtrate. The deep red filtrate and the pink precipitate were each heated on the steam bath for an hour, then allowed to stand at room temperature for two hours. The solvents were removed from the filtrate by distillation *in vacuo*, and ice and water were added to the residual cake. The ether solution was treated as described for the previous reactions, and there were obtained 0.68 g. (28%) of crude diphenyl-1-isoquinolylcarbinol and 0.2 g. (10%) of unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

The original precipitate was hydrolyzed with ice water and the resulting mixture extracted with ether. By the usual procedure, 0.28 g. (12%) of crude diphenyl-1-isoquinolylcarbinol was obtained from the ethereal extract.

When the original filtrate plus wash solution was not heated on the steam bath, but instead hydrolyzed immediately, only a trace of diphenyl-1-isoquinolylcarbinol was obtained.

Phenyl-2-thienyl-2-quinolylcarbinol. To an ether solution of 2-thienylmagnesium bromide prepared from 14.2 g. (0.55 g. atom) of magnesium and 93.0 g. (0.57 mole) of freshly distilled 2-bromothiophene was added 250 cc. of anhydrous dioxane, all operations being carried out in a nitrogen atmosphere. A solution of 50.0 g. (0.191 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile[8] in 450 cc. of anhydrous dioxane was added with mechanical stirring over a period of six minutes to the Grignard mixture cooled in an ice bath. Ether was distilled from the red reaction mixture, and the residual dioxane solution was refluxed for one hour, then allowed to stand at room temperature for 12 hr. The dioxane was distilled *in vacuo*, and the residual brown cake was treated with ether, ice, and water. The mixture was extracted with ether in a continuous extractor for 20 hr. The ethereal solution was extracted with 10% hydrochloric acid. The acid solution was made alkaline by addition of sodium hydroxide

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(3) All melting points are corrected. Analyses were performed by Weiler and Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) C. R. Noller, *J. Am. Chem. Soc.*, **53**, 635 (1931).

(5) C. R. Noller and W. R. White, *J. Am. Chem. Soc.*, **59**, 1354 (1937).

(6) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

(7) J. Padbury and H. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

(8) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

solution. A solid which precipitated was collected by filtration. There was obtained 30.0 g. (49%) of crude phenyl-2-thienyl-2-quinolylcarbinol, m.p. 160.3–161.0° after several recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.41; S, 10.10. Found: C, 75.90; H, 5.01; N, 4.29; S. 10.10.

The same compound has also been prepared by reaction of 2-thienylmagnesium bromide with 2-benzoylquinoline.[9] A mixed melting point test of the two samples showed no depression, and the infrared spectra of the two samples, taken in chloroform solution, were identical.

Phenyl-2-thienyl-1-isoquinolylcarbinol. This compound, m.p. 136.3–137.8°, was prepared in 40% yield (crude product) from 2-thienylmagnesium bromide and 2-benzoyl-1,2-dihydroisoquinaldonitrile by the same procedure as described above for the preparation of phenyl-2-thienyl-2-quinolylcarbinol.

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.67; H, 4.76; N, 4.41; S, 10.10. Found: C, 75.70; H, 4.80; N, 4.55; S, 10.13.

The same compound, as shown by a mixed melting point test and the identity of the infrared spectra in chloroform solution, has been obtained by reaction of 2-thienylmagnesium bromide with 1-benzoylisoquinoline.[9]

Phenyl-p-anisyl-1-isoquinolylcarbinol. By reaction of *p*-anisylmagnesium bromide with 2-benzoyl-1,2-dihydroisoquinaldonitrile in the same manner as described above for the preparation of phenyl-2-thienyl-2-quinolylcarbinol, there was obtained a 34% yield of crude phenyl-*p*-anisyl-1-isoisoquinolylcarbinol. The purified material melted at 124.2–125.3°, also in admixture with a sample of the compound prepared[9] by reaction of *p*-anisylmagnesium bromide with 1-benzoylisoquinoline. The infrared spectra of the two samples were taken in chloroform solution and found to be identical.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.89; H, 5.75; N, 4.10.

Phenyl-p-chlorophenyl-1-isoquinolylcarbinol. This compound, m.p. 133.6–134.6°, was prepared in 43% yield by reaction of *p*-chlorophenylmagnesium bromide with 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Anal. Calcd. for $C_{22}H_{16}NOCl$: C, 76.42; H, 4.66; N, 4.05; Cl, 10.25. Found: C, 76.32; H, 4.88; N, 4.25; Cl, 10.15.

The same compound has been prepared by reaction of *p*-chlorophenylmagnesium bromide with 1-benzoylisoquinoline.[9] A mixed melting point test of the two samples showed no depression, and the infrared spectra, taken in chloroform solution, were identical.

Phenyl-2-thienyl-2-(6-methoxyquinolyl)carbinol. Very crude material was obtained in 23% yield by the reaction of 2-thienylmagnesium bromide with 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile[10] in the usual manner. A pure sample of the carbinol, m.p. 158.3– 159.0°, was obtained after two recrystallizations from toluene and five recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{21}H_{17}NO_2S$: C, 72.62; H, 4.94; N, 4.03; S, 9.23. Found: C, 72.44; H, 5.20; N, 3.81; S, 9.20.

When a portion of the very crude material cited above was subjected to distillation at 0.7-mm. pressure, a small amount of a solid, b.p. 128–132°, was obtained. After several recrystallizations from absolute ethanol, this material melted at 87.0–87.5°. It is thought that this material is probably di-2-thienyl ketone, which is reported[11] to melt at 87–88°.

Anal. Calcd. for $C_9H_6OS_2$: S, 33.00. Found: S, 33.21.

Phenyl-p-anisyl-2-quinolylcarbinol. A mixture of 20.0 g. (0.155 mole) of quinoline, 35.3 g. (0.166 mole) of *p*-methoxybenzophenone, 5.00 g. of aluminum foil, 5.0 g. of mercuric chloride, 5 drops of mercury, and a few mg. of iodine was heated on a steam bath with stirring for 20 min., whereupon a vigorous reaction started. The color of the mixture changed from yellow to dark green. Upon addition of 25 cc. of anhydrous dioxane, enough heat was generated to cause the reaction mixture to reflux. After the mixture had been heated on the steam bath for four hours, it was made strongly alkaline by addition of sodium hydroxide solution. The basic solution was extracted with ether, and the ether solution, in turn, was extracted with 10% hydrochloric acid. The acid extract was made alkaline by addition of sodium hydroxide solution, and unreacted quinoline was removed by steam distillation. The residual aqueous mixture was extracted with ether, and, after evaporation of the ether, there was obtained 12.0 g. (23%) of crude phenyl-*p*-anisyl-2-quinolylcarbinol, m.p. 136.5–137.3° after several recrystallizations from absolute ethanol. A mixed melting point test with the carbinol obtained[9] by reaction of *p*-anisylmagnesium bromide with 2-benzoylquinoline showed no depression. The infrared spectra of the two samples, taken in chloroform solution, were identical.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found:[9] C, 81.12; H, 5.60; N, 4.18.

No phenyl-*p*-anisyl-2-quinolylcarbinol was obtained by reaction of *p*-anisylmagnesium bromide with 1-benzoyl-1,2-dihydroquinaldonitrile under the conditions cited previously for the preparation of phenyl-2-thienyl-2-quinolylcarbinol.

2-Benzoyl-6-methoxyquinoline. To a suspension of 2.4 g. (0.1 mole) of sodium hydride in 200 cc. of anhydrous xylene (mixture of isomers), maintained at 120°, was added, with stirring, in 3–7-g. portions, a total of 29.1 g. (0.1 mole) of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile during a period of 3 hr. The dark green mixture was heated at 120° for an additional 2 hr., then filtered. The filtrate was washed with water and extracted with 5% hydrochloric acid. A small amount of polymeric material precipitated on addition of the hydrochloric acid, and this material was removed by filtration. The hydrochloric acid solution was made alkaline by addition of sodium hydroxide solution, and a solid which precipitated was collected by filtration. There was obtained 2.9 g. (11%) of crude 2-benzoyl-6-methoxyquinoline, m.p. 116.3–116.7° after several recrystallizations from absolute ethanol. The infrared spectrum of the material was taken in chloroform solution and showed a pronounced carbonyl group absorption peak at 1655 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{13}O_2N$: C, 77.54; H, 4.98; O, 12.61; N, 5.32. Found: C, 77.40; H, 4.85; O, 12.44; N, 5.31.

Although 2-benzoylquinoline and 1-benzoylisoquinoline are not soluble in 5% hydrochloric acid, 2-benzoyl-6-methoxyquinoline is readily soluble in acid of this concentration, this undoubtedly being due to the base-strengthening effect of the methoxyl group in the 6-position of the quinoline ring.

DISCUSSION

The general procedure for the preparation of 2-quinolylcarbinols of type III and 1-isoquinolylcarbinols of type IV from Grignard reagents and Reissert compounds is to add a dioxane solution of the Reissert compound to the Grignard reagent. It is well known that addition of dioxane to an ether solution of a Grignard reagent causes the precipitation of halide salts, leaving the dialkylmagnesium or diarylmagnesium in solution.[12,13] This poses the question as to which organometallic

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(9) K. E. Werth, Master's thesis, Kansas University, 1955.

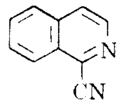
(10) A. Gassman and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

(11) L. Gattermann, *Ber.*, **18**, 3012 (1885).

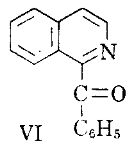
(12) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954.

(13) R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

species, RMgX (possibly better formulated as $R_2Mg \cdot MgX_2$[13]) or R_2Mg, is the effective reagent in the various steps of the rearrangement and condensation of Reissert compounds with Grignard reagents. In order to carry out experiments designed to provide information about this matter, a 0.5N solution of diphenylmagnesium in ether-dioxane was prepared by Noller's method.[4,5] When a dioxane solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, $R = C_6H_5$)[14] was added to the diphenylmagnesium solution, and the resulting *homogeneous* solution treated in a manner analogous to that used for the preparation of 1-isoquinolylcarbinols of type IV from II($R = C_6H_5$) and conventional Grignard reagents, only a 0.2% yield of diphenyl-1-isoquinolylcarbinol (IV, $R = R' = C_6H_5$) was obtained. Isoquinaldonitrile (V) was obtained in 20% yield, and not less than 55% of the starting material, 2-benzoyl-1,2-dihydroisoquinaldonitrile, was recovered. However, a 79% yield of diphenyl-1-isoquinolylcarbinol was obtained by the reaction of 0.5N diphenylmagnesium with 1-benzoylisoquinoline (VI), which is known to be an intermediate product in the rearrangement-condensation reaction,[1,2] in ether-dioxane solution under comparable conditions. It should also be stressed that, in a control experiment, the *heterogeneous* reaction mixture resulting from the addition of a dioxane solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile to a 0.49N solution of phenylmagnesium bromide in ether gave, after suitable processing, a 69% yield of diphenyl-1-isoquinolylcarbinol.



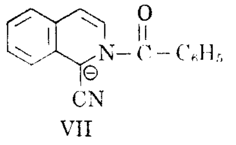
V



VI

In yet another series of experiments designed to provide evidence about the mechanism of the reaction, a solution of 2-benzoyl-1,2-dihydroisoquinaldonitrile in dioxane was added to a 0.49N solution of phenylmagnesium bromide in ether. After the reaction mixture had been stirred at room temperature for ten minutes, it was filtered. The filtrate was dark red in color and the precipitate had a pink color. When the filtrate was hydrolyzed immediately, only a trace of diphenyl-1-isoquinolylcarbinol could be isolated. However, when the filtrate was first heated on a steam bath for an hour, then hydrolyzed, diphenyl-1-isoquinolylcarbinol was obtained in 29% yield. It was also found that diphenyl-1-isoquinolylcarbinol could be obtained in 12% yield by heating the pink precipitate on the steam bath for an hour, followed by hydrolysis.

On the basis of the data cited above, plus that given in a previous manuscript,[2] it would appear that a Reissert compound, *e.g.*, 2-benzoyl-1,2-dihydroisoquinaldonitrile, first undergoes reaction with phenylmagnesium bromide in the solid phase of an ether-dioxane slurry of the reagents to form the red colored conjugate base, VII. The resulting salt, of which VII is the anion, is only partially soluble in the mixed solvent, and VII, both in the solid phase and solution, undergoes intramolecular rearrangement to give 1-benzoylisoquinoline (VI) only when heated for an appreciable period of time. Once the intermediate product, 1-benzoylisoquinoline, has been formed, it can undergo reaction with either diphenylmagnesium in solution or with phenylmagnesium bromide present in the solid phase to produce a salt of diphenyl-1-isoquinolylcarbinol



VII

Partly to increase the scope of the rearrangement and condensation reaction between Reissert compounds and Grignard reagents, and partly to provide intermediates for the synthesis[15] of analogs of the well known antihistamine, Dacapryn, a number of new carbinols of types III and IV have been prepared. Also, some of the preparations previously reported[1,2] have been repeated, and yields of carbinols have been considerably improved. With aliphatic Grignard reagents and Reissert compounds, the improvement in yield was brought about by a modification of the older procedure,[2] namely by rapid addition of the Grignard reagent to a dioxane solution of the Reissert compound, without any attempt being made to cool the reaction mixture. In the reaction between phenylmagnesium bromide and 2-benzoyl-1,2-dihydroisoquinaldonitrile, rapid addition of a dioxane solution of the Reissert compound to the Grignard reagent without cooling of the reaction mixture led to a distinct improvement in the yield of diphenyl-1-isoquinolylcarbinol over that previously reported.[2] However, the yields of carbinols produced by reaction of 2-thienylmagnesium bromide with Reissert compounds did not change appreciably whether the reagents were brought together with external cooling in an ice bath or mixed rapidly without any attempt to control the reaction temperature. Attempts to prepare phenyl-*p*-anisyl-2-quinolylcarbinol and phenyl-*p*-anisyl-2-(6-methoxyquinolyl)carbinol by the reaction of *p*-anisylmagnesium bromide with the appropriate Reissert compound failed. There was isolated from both reaction mixtures a compound, m.p. 144.3–144.9°, which had a strong carbonyl absorption peak at 1648 cm.$^{-1}$ in the infrared spectrum taken in chloroform solution. This compound was probably

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[14] A. Reissert, Ber., **38**, 3415 (1905).

[15] N. C. Rose, L. R. Walters, and W. E. McEwen, *J. Org. Chem.*, **23**, 341 (1958).

TABLE I

Reaction of Reissert Compounds with Grignard Reagents

Reissert Compound	Grignard	Product	Yield, %
1-Benzoyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-quinolylcarbinol	81
	$2\text{-}C_4H_3SMgBr$	Phenyl-2-thienyl-2-quinolylcarbinol	49
	$p\text{-}CH_3OC_6H_4MgBr$		0
2-Benzoyl-1,2-dihydroisoquinaldonitrile	CH_3MgBr	Methylphenyl-1-isoquinolylcarbinol	83
	$2\text{-}C_6H_4SMgBr$	Phenyl-2-thienyl-1-isoquinolylcarbinol	40
	C_6H_5MgBr	Diphenyl-1-isoquinolylcarbinol	75
	$p\text{-}CH_3OC_6H_4MgBr$	Phenyl-*p*-anisyl-1-isoquinolylcarbinol	34
	$p\text{-}Cl\text{-}C_6H_4MgBr$	Phenyl-*p*-chlorophenyl-1-isoquinolylcarbinol	43
1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-(6-methoxyquinolyl)carbinol	84
	$2\text{-}C_4H_3SMgBr$	Phenyl-2-thienyl-2-(6-methoxyquinolyl)carbinol	23
	$p\text{-}CH_3OC_6H_4MgBr$		0

4,4′-dimethoxybenzophenone, which is reported[16] to have a m.p. of 144°. A compound thought to be di-2-thienyl ketone was also isolated as a by-product from the reaction of 2-thienylmagnesium bromide with 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile. Phenyl-*p*-anisyl-2-quinolylcarbinol was eventually obtained in 23% yield from quinoline and *p*-methoxybenzophenone by application of the Emmert reaction.[17] The results of the various rearrangement and condensation reactions of Grignard reagents with Reissert compounds are summarized in Table I. In each case of the preparation of a hitherto unreported carbinol, the identity of the product was confirmed by comparison with the carbinol obtained by reaction of a Grignard reagent with the appropriate 1-benzoylisoquinoline or 2-benzoylquinoline.[9]

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[Contribution from the Chemistry Department of the University of Kansas]

Synthesis of Analogs of Decapryn[1]

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Six quinoline and isoquinoline analogs of the prominent antihistamine drug, Decapryn, have been synthesized. The compounds were prepared by reaction of β-dimethylaminoethyl chloride with the sodium or potassium salts of methylphenyl-2-quinolylcarbinol, methylphenyl-2-(6-methoxyquinolyl)carbinol, methylphenyl-1-isoquinolylcarbinol, diphenyl-1-isoquinolylcarbinol, phenyl-2-thienyl-2-quinolylcarbinol and methylphenyl-4-quinolylcarbinol, respectively.

Decapryn (I) is considered[2] to be one of the prominent antihistamine drugs. Although certain compounds containing a quinoline or isoquinoline nucleus have been found to have antihistamine activity,[3-7] no analogs of Decapryn (I) containing a quinolyl or isoquinolyl group in place of the 2-pyridyl group have been reported. Because of this fact, and owing to the recent development of a very convenient synthesis of tertiary carbinols containing a 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom,[8-10] the preparation of a number of analogs of I was undertaken.

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[1] Much of the material in the present paper and all of the data from the preceding paper have been abstracted from the thesis submitted by Norman C. Rose in partial fulfillment of the requirements for the Ph.D. degree, Kansas University, 1957.

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