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]

Acknowledgment. This investigation was supported by a research grant, H-2155, from the National Institutes of Health, Public Health Service.

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(16) H. Schnackenberg and R. Scholl, *Ber.*, **36**, 654 (1903).

(17) B. Emmert and E. Pirat, *Ber.*, **74**, 714 (1941).

[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.

(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.

(2) B. Idson, *Chem. Revs.*, **47**, 307 (1950).

(3) I. A. Kaye, *J. Am. Chem. Soc.*, **71**, 2322 (1949).

(4) I. A. Kaye, U. S. Patent **2,652,398**; *Chem. Abstr.*, **48**, 10781 (1954).

(5) C. F. Geschickter and M. I. Ruben, U. S. Patent **2,594,418**; *Chem. Abstr.*, **47**, 1193 (1953).

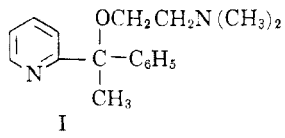
(6) C. F. Geschickter and M. I. Rubin, U. S. Patent **2,549,419**; *Chem. Abstr.*, **47**, 1193 (1953).

(7) S. Ohki, *J. Pharm. Soc. Japan*, **70**, 92 (1950); *Chem. Abstr.*, **44**, 5867 (1950).

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

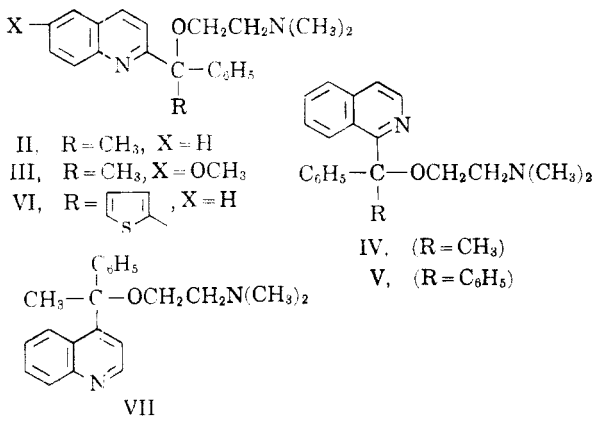
(9) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

(10) N. C. Rose and W. E. McEwen, *J. Org. Chem.*, **23**, 337 (1958).



I

Each of four aminoethers, methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II), methylphenyl-2-(6-methoxyquinolyl)-carbinyl β-dimethylaminoethyl ether (III), methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV), and diphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (V), was prepared in quantity sufficient for pharmacological screening. Two additional ethers, phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (VI) and methylphenyl-4-quinolylcarbinyl β-dimethylaminoethyl ether (VII), have also been prepared, but these compounds have not yet been screened.



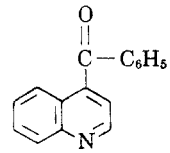
II, R = CH_3, X = H
III, R = CH_3, X = OCH_3
VI, R = , X = H

IV, (R = CH_3)
V, (R = C_6H_5)

VII

Each of the ethers was prepared by a Williamson reaction. It was found that yields were highest when the sodium or potassium salt of the tertiary carbinol was prepared by addition of the metal to a hot solution of the carbinol in anhydrous toluene, followed by dropwise addition of a toluene solution of β-dimethylaminoethyl chloride to the suspension of the sodium or potassium salt at the reflux temperature of the solvent. The use of sodium amide to form the salts of the carbinols at lower temperatures did not generally give as good results as the procedure cited above.

The carbinols used in the synthesis of ethers II–VI were prepared by the reaction of appropriate Reissert compounds and Grignard reagents.[8–10] The carbinol required for the preparation of VII was obtained by addition of methylmagnesium bromide to 4-benzoylquinoline (VIII), which, in turn, had been prepared by reaction of 4-cyanoquinoline with phenylmagnesium bromide by the method of Kaufmann, *et al.*[11]



VIII

When subjected to pharmacological testing, compound II, in the form of its dihydrobromide trihydrate, compound III, as the dihydrochloride dihydrate and compounds IV and V, as the monohydrochlorides, showed less than 1% "histadyl" (Thenylpyramine, Lilly) action. No outstanding pharmacologic properties of any kind were found for these four compounds.[12]

EXPERIMENTAL[13]

Methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II). To a refluxing solution of 20.00 g. (0.08 mole) of methylphenyl-2-quinolylcarbinol in 75 cc. of anhydrous toluene was added 1.84 g. (0.08 g.-atom) of sodium in the form of small chunks over a period of 15 min. The solution was heated under reflux and with mechanical stirring for an additional three hours. A toluene solution of β-dimethylaminoethyl chloride, prepared[14] from 17 g. of the hydrochloride, was added dropwise to the refluxing slurry of the sodium salt over a period of 90 min. The reaction mixture was heated under reflux, with mechanical stirring, for an additional 16 hr. After the reaction mixture had been cooled in an ice bath, it was extracted with 40 cc. of ice water. To the toluene solution was added, with vigorous shaking, sufficient 10% hydrochloric acid to lower the *p*H of the mixture to 5 (universal *p*H paper). The aqueous and toluene layers were separated. The toluene layer, containing most of the unreacted carbinol, was extracted with four 50 cc. portions of 10% hydrochloric acid. The combined 10% hydrochloric acid extract was made alkaline by addition of sodium hydroxide solution, and 8.4 g. (42%) of unreacted methylphenyl-2-quinolylcarbinol was collected by filtration.

The aqueous layer which had been separated from the mixture of *p*H 5 was made alkaline by addition of sodium hydroxide solution. The resulting mixture was extracted with a single 125-cc. portion of low-boiling petroleum ether. Removal of the petroleum ether by distillation left 13.7 g. (93% based on unrecovered carbinol) of crude methylphenyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (II), m.p. 75.3–76.4° after several recrystallizations from 1-butanol and ethanol, respectively.

Anal. Calcd. for $C_{21}H_{24}ON_2$: C, 78.73; H, 7.55; N, 8.75. Found: C, 79.02; H, 7.56; N, 9.01.

Both the hydrochloride and hydrobromide of II proved to be very hygroscopic. Even after the hydrobromide, prepared in ether-ethanol solution, had been dried in a vacuum desiccator over anhydrous calcium chloride, it had a wide decomposition range, 70–95°, and analyzed as a dihydrobromide trihydrate.

Anal. Calcd. for $C_{21}H_{32}N_2O_4Br_2$: C, 47.03; H, 6.02; N, 5.23; Br, 29.81. Found: C, 46.96; H, 5.70; N, 5.10; Br, 30.66.

(11) A. Kaufmann, H. Peyer, and M. Kunkler, *Ber.*, **45**, 3090 (1912).

(12) We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the screening of these compounds.

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

(14) C. Tilford, R. Shelton, and M. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

Methylphenyl-2-(6-methoxyquinolyl)carbinyl β-dimethylaminoethyl ether (III). This compound, a liquid, b.p. 196–197° (0.25 mm.), was prepared in the same manner as described above for the preparation of II, except that the potassium salt of methylphenyl-2-(6-methoxyquinolyl)-carbinol was used in the reaction with β-dimethylaminoethyl chloride rather than the sodium salt.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.39; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.21; N, 7.68.

The yield of III was 83% based on unrecovered carbinol, or 63% based on starting quantities of reagents.

All attempts to prepare a completely satisfactory solid derivative of III met with failure. Only oils could be isolated on attempted preparation of the chlorobenzylate, picrate, succinate, 2-hydroxy-α-naphthoate, 3-hydroxy-β-naphthoate, methiodide, or bis-1-(2-hydroxy-3-carboxynaphthalene)methylene salt. It was possible to obtain a solid, but extremely hygroscopic, hydrochloride, which, after having been dried in a vacuum desiccator over anhydrous calcium chloride, analyzed moderately well as the dihydrochloride dihydrate of III. A solid chloroplatinate, m.p. 184.0–185.5°, was prepared, but it also could not be obtained in analytically pure form.

Methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV). To a mechanically stirred dispersion of 1.55 g. (0.067 g.-atom) of sodium in 85 cc. of anhydrous toluene, maintained at 60°, was added a solution of 16.00 g. (0.062 mole) of methylphenyl-1-isoquinolylcarbinol in 75 cc. of toluene during the course of 30 min. The mixture was stirred for an additional hour at 60° and then was heated to reflux. A toluene solution of β-dimethylaminoethyl chloride, prepared from 13.6 g. of the hydrochloride, was added over a period of an hour to the refluxing mixture. The reaction mixture was refluxed for an additional 15 hr., then worked up as described for the preparation of II. There was obtained 6.3 g. (39%) of recovered methylphenyl-1-isoquinolylcarbinol and 6.0 g. (89% based on unrecovered carbinol) of crude methylphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (IV), an oil. The oil was dissolved in anhydrous ether, and dry hydrogen chloride was passed into the solution. The monohydrochloride of IV precipitated and was collected by filtration. After several recrystallizations from ethanol–ethyl acetate, the salt had a m.p. of 226–228° (dec.).

Anal. Calcd. for $C_{21}H_{25}ON_2Cl$: C, 70.68; H, 7.35; N, 7.85; Cl, 9.94. Found: C, 70.84; H, 7.05; N, 8.01; Cl, 9.70.

A portion of the hydrochloride of IV was dissolved in water, and the aqueous solution was neutralized by addition of sodium bicarbonate solution. The amino-ether, IV, was extracted from the aqueous mixture with ether. Distillation of the ether left a nearly colorless oil.

Anal. Calcd. for $C_{21}H_{24}ON_2$: C, 78.73; H, 7.55; N, 8.75. Found: C, 78.79; H, 7.71; N, 8.89.

Diphenyl-1-isoquinolylcarbinyl β-dimethylaminoethyl ether (V). This compound was prepared from diphenyl-1-isoquinolylcarbinol and β-dimethylaminoethyl chloride in the same manner as described above for the preparation of IV, with the exception that dispersed potassium was used in place of dispersed sodium. The ether, V, was obtained in 92% yield based on unrecovered diphenyl-1-isoquinolylcarbinol, but in only 24% yield based on the starting quantity of the carbinol. After several recrystallizations from absolute ethanol, the ether, V, m.p. 99.0–99.7°, was obtained as colorless crystals.

Anal. Calcd. for $C_{26}H_{26}ON_2$: C, 81.62; H, 6.85; N, 7.33. Found: C, 81.43; H, 6.64; N, 7.25.

A portion of V was dissolved in anhydrous ether, and dry hydrogen chloride was passed into the solution. The monohydrochloride which precipitated had a m.p. of 197.6–198.4° (dec.) after several recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{26}H_{27}ON_2Cl$: C, 74.52; H, 6.50; N, 6.69; Cl, 8.46. Found: C, 74.24; H, 6.50; N, 6.58; Cl, 8.58.

Phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether (VI). The procedure used for the preparation of VI was the same as that used in the preparation of V, except that 0.30 g. of sodium iodide was added to the reaction mixture prior to the addition of the potassium dispersion to the toluene solution of phenyl-2-thienyl-2-quinolylcarbinol. In the eventual work-up of the reaction mixture, a solid precipitated before the *p*H of the mixture reached 5 during the treatment with 10% hydrochloric acid. This solid material proved to be the monohydrochloride of phenyl-2-thienyl-2-quinolylcarbinyl β-dimethylaminoethyl ether. The yield of crude product amounted to 56% based on starting carbinol, or 67% based on unrecovered carbinol. After several recrystallizations from ether-ethanol, the salt had a m.p. of 201.5–202.5° (dec.).

Anal. Calcd. for $C_{24}H_{25}N_2OSCl$: C, 67.83; H, 5.93; N, 6.59; S, 7.54; Cl, 8.34. Found: C, 67.96; H, 6.02; N, 6.50; S, 7.37; Cl, 8.28.

A portion of the salt was dissolved in water, the aqueous solution made alkaline by addition of sodium hydroxide solution, and the mixture extracted with ether. Removal of the ether by distillation left VI, an oil, as a residue.

Anal. Calcd. for $C_{24}H_{24}ON_2S$: C, 74.20; H, 6.23. Found: C, 74.02; H, 6.30.

Methylphenyl-4-quinolylcarbinol. The reaction of 4-benzoylquinoline[11] with methylmagnesium bromide in ether solution under a nitrogen atmosphere gave, after hydrolysis of the reaction mixture, a quantitative yield of crude methylphenyl-1-isoquinolylcarbinol, an oil.

The *picrate* was prepared in ethanol and recrystallized from 95% ethanol. Its m.p. was 220.5–222.0°.

Anal. Calcd. for $C_{23}H_{18}N_4O_8$: C, 57.74; H, 3.76; N, 11.71. Found: C, 57.87; H, 3.47; N, 11.94.

The picrate was decomposed by treatment with lithium hydroxide solution, and the liberated carbinol was extracted from the aqueous mixture with ether. The ether solution was washed with water, and the ether was removed by distillation. The residual, colorless, liquid carbinol was used without further purification for the preparation of VII.

Methylphenyl-4-quinolylcarbinyl β-dimethylaminoethyl ether (VII). This compound was prepared in 11% yield from methylphenyl-4-quinolylcarbinol and β-dimethylaminoethyl chloride by the same method described previously for the preparation of III. The work up was modified as follows:

After the toluene layer had been washed with water to remove salt, it was mixed with just sufficient 10% hydrochloric acid to make the mixture acid to Congo Red paper. Sufficient saturated sodium carbonate solution was then added to make the mixture just basic to Congo Red paper. The aqueous layer was separated from the toluene layer, made alkaline by addition of potassium hydroxide solution and extracted with one large portion of low-boiling petroleum ether. Evaporation of the petroleum ether left crude VII, an oil, b.p. 150–160° (0.3 mm.).

The *dipicrate* was prepared in ethanol and recrystallized from 95% ethanol. Its m.p. was 190.0–191.5°.

Anal. Calcd. for $C_{33}H_{30}N_8O_{15}$: C, 50.88; H, 3.85; N, 14.39. Found: C, 50.82; H, 3.69; N, 14.16.

A *chloroplatinate* was prepared by addition of a 10% solution of chloroplatinic acid to a solution of VII in 10% hydrochloric acid. The resulting tan precipitate had a m.p. of 212° (dec.) after having been washed with dilute hydrochloric acid and water.

Anal. Calcd. for $C_{21}H_{26}N_2OPtCl_6$: N, 3.83; Pt, 26.74. Found: N, 3.70; Pt, 26.31.

The hydrochloride proved to be very hygroscopic, and no crystalline material could be obtained on attempts to prepare the sulfate, phosphate, or succinate salts.

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