[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

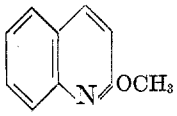
THE REACTION OF BENZYLMAGNESIUM CHLORIDE WITH CERTAIN 2-METHOXYQUINOLINES

REYNOLD C. FUSON, HAROLD L. JACKSON,[1] AND EMIL W. GRIESHABER[2]

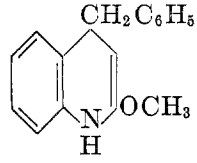
Received April 16, 1951

2-Alkoxyquinolines, because of their structural similarity to esters, might be expected to react with Grignard reagents with replacement of the alkoxyl group by the hydrocarbon radical of the Grignard reagent. Moreover, it it known that the azomethine group in pyridine and quinoline behaves toward Grignard reagents in the manner characteristic of carbonyl compounds (1). For example, quinoline reacts with the benzyl Grignard reagent to yield a mixture of 2- and 4-benzylquinoline as well as the 2,4-dibenzyl derivative (2). Of particular interest is the behavior of pyridine toward this reagent since the principal product is 4-benzylpyridine (3).

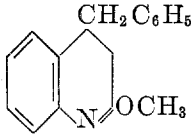
In the present work it was found that 2-methoxyquinoline (I), when treated with benzylmagnesium chloride, failed to undergo replacement of the methoxyl group. Instead, it was attacked at the 4-position, yielding 4-benzyl-2-methoxydihydroquinoline. It was assumed that the product is the 1,4-dihydro derivative (II). However, the 3,4-dihydro derivative (IIa) is also a possibility. Treatment with dilute hydrochloric acid converted the dihydroquinoline to 4-benzylhydrocarbostyril (III), a change which is similar to the conversion of 2-ethoxy-3,4-dihydroquinoline to hydrocarbostyril (4).



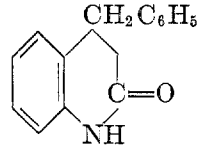
I



II



IIa



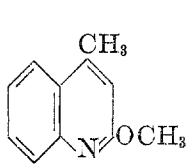
III

2-Methoxylepidine (IV), in which the 4-position is blocked, was tried next. The result was even more surprising than that with 2-methoxyquinoline; again the 4-position was the point of attack. The product was 4-benzyl-2-methoxy-4-

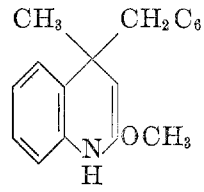
[1] Rohm and Haas Fellow, 1947–1948; Socony Vacuum Oil Company Fellow, 1948–1949; present address: E. I. duPont de Nemours and Company, Wilmington, Delaware.

[2] Present address: Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

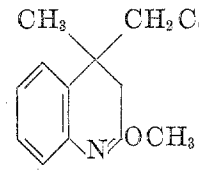
methyldihydroquinoline. Here again the 1,4-dihydro compound (V) is assumed although the 3,4-dihydro structure (Va) must be considered also.



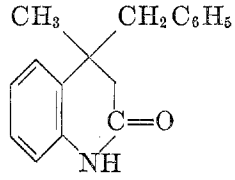
IV



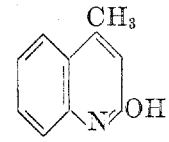
V



Va



VI



VII

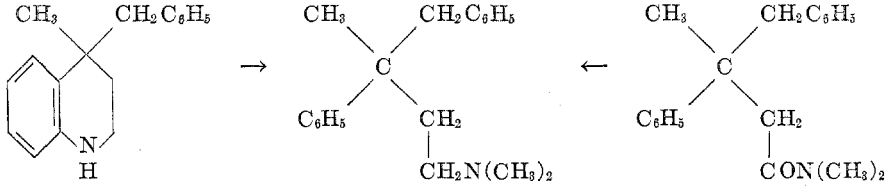
The observation that the dihydro compound was not attacked by benzylmagnesium chloride is interpreted as evidence favoring structure V, since a compound of structure Va should be reactive toward Grignard reagents.

Hydrolysis converted the dihydro methoxy compound to the corresponding lactam (VI). Both the dihydro methoxy compound and the lactam gave toluene when treated with palladium-on-carbon to yield, respectively 2-methoxylepidine (IV) and 4-methylcarbostyril (VII).

Nuclear alkylation of aromatic compounds by the action of Grignard reagents is well known, but the introduction of a radical at a nuclear carbon atom already holding an alkyl group, as in the case of 2-methoxylepidine, is unusual. The only example of such a reaction with a free quinoline base is the formation of 2,2-diphenylquinoline as a by-product in the preparation of 2-phenylquinoline from quinoline and phenylmagnesium bromide (5). Similar reactions have been reported with quaternary salts of both quinoline (6) and acridine (7).

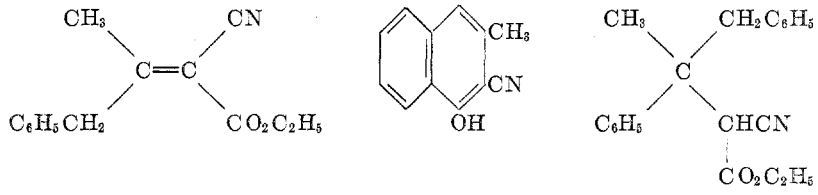
Under the conditions employed in this work both phenylmagnesium bromide and methylmagnesium iodide failed to react with either 2-methoxyquinoline or 2-methoxylepidine. The fact that the methoxyl group was unaffected by Grignard reagents stands in sharp contrast to the observation that *n*-butyllithium displaces the ethoxyl group in 2-ethoxyquinoline to give 2-*n*-butylquinoline in a yield of 58% (8).

The lactam (VI) resisted numerous attempts to effect hydrolysis or acetylation. A proof of structure was obtained by degradation of this compound to 3-benzyl-N,N-dimethyl-3-phenylbutylamine (IX), which was synthesized by an independent method. The first step in the degradation, reduction of the lactam to the corresponding tetrahydroquinoline (VIII), was accomplished with lithium aluminum hydride by a procedure which had been employed successfully by Schwartzman (9), to reduce a similar compound. The tetrahydroquinoline was converted to the methiodide and the heterocyclic ring was then opened by treatment with sodium amalgam according to the Emde method (10).

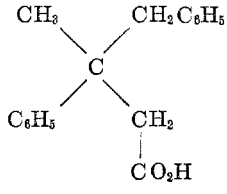


VIII IX X

The first step of the independent synthesis of the amine (IX) was the condensation of benzyl methyl ketone with ethyl cyanoacetate to give ethyl (β-phenylisopropylidene)cyanoacetate (XI). By treatment with phenylmagnesium bromide the unsaturated ester (XI) was converted in excellent yield to ethyl β-benzyl-α-cyano-β-phenylbutyrate (XIII). This ester, which proved to be very difficult to hydrolyze, was converted to the corresponding malonic acid, which readily lost carbon dioxide to yield β-benzyl-β-phenylbutyric acid (XIV). The butyric acid was transformed, by way of the acid chloride, to the N,N-dimethyl amide, which underwent reduction by lithium aluminum hydride to yield the desired amine (IX). The two samples of amine had identical physical properties and yielded the same methiodide.



XI XII XIII



XIV

The unsaturated ester showed a marked tendency to undergo cyclization to yield 2-cyano-3-methyl-1-naphthol (XII), a reaction observed earlier by Marion and McRae (11). The structure of the naphthol was confirmed by hydrolysis of the nitrile followed by decarboxylation of the resulting acid to produce 3-methyl-1-naphthol. As was to be expected, the doubly flanked cyano group was extremely resistant to hydrolysis.

EXPERIMENTAL[3]

2-Methoxyquinoline (I). 2-Chloroquinoline was prepared by heating a mixture of carbostyril and phosphorus oxychloride; m.p. 38° (12); yield 87%. A solution of the chloroquino-

[3] The microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel, and Mrs. Jean Fortney.

line (16.3 g.), dry sodium methoxide (10.8 g.), and absolute methanol (200 ml.) was heated at reflux for four hours. After the white suspension had cooled, it was poured into 300 ml. of cold water. The aqueous solution was extracted with four 50-ml. portions of ether, and the ether solution dried over solid potassium hydroxide. The mixture was filtered and the solvent evaporated; the 2-methoxyquinoline was distilled; b.p. 60–63° (0.13 mm.); n_D^{20} 1.6071; yield 67%.

A *picrate* of this compound, formed in ether and recrystallized from ethanol, separated in fine needles; m.p. 179–180°.

Anal. Calc'd for $C_{16}H_{12}N_4O_8$: C, 49.47; H, 3.12; N, 14.43.

Found: C, 49.63; H, 3.18; N, 14.48.

4-Benzyl-1,4-dihydro-2-methoxyquinoline (II). A solution of 4.0 g. of 2-methoxyquinoline in 30 ml. of dry ether was added dropwise with stirring to an ice-cooled solution of benzylmagnesium chloride made from freshly distilled benzyl chloride (9.5 g.), magnesium (1.8 g.), and dry ether (100 ml.). The dark reaction mixture was heated under gentle reflux for seven hours, cooled, and poured into a mixture of ice and a saturated ammonium chloride solution. The ether solution was removed and the aqueous solution extracted with 50-ml. portions of ether. After the ether solution had been dried over potassium hydroxide, the solvent was evaporated and the product (II) was distilled through a small Vigreux column; it was a colorless viscous oil; b.p. 127–130° (0.25 mm.); n_D^{20} 1.7052; yield 71%.

Anal. Calc'd for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57.

Found: C, 81.47; H, 6.84; N, 5.52.

4-Benzyl-1,4-dihydrocarbostyril (III). When the 4-benzyl-1,4-dihydro-2-methoxyquinoline was shaken with 0.5% hydrochloric acid, a white precipitate formed. The mixture was allowed to stand at room temperature, and the product (III) which had separated was recrystallized from ethanol. It formed long white needles; m.p. 160–161°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.02; H, 6.38: N, 5.91.

Found: C, 80.29; H, 6.43; N, 6.22.

2-Methoxylepidine (IV). This compound was prepared from 2-chlorolepidine (13) by a procedure similar to that described for 2-methoxyquinoline. Purification was effected by repeated distillation through a small Vigreux column; b.p. 93–95° (0.4 mm.); n_D^{20} 1.6062; yield 69%. The *picrate*, recrystallized three times from ethanol, formed fine needles; m.p. 157.5–159°.

Anal. Calc'd for $C_{17}H_{14}N_4O_8$: C, 50.75; H, 3.51; N, 13.93.

Found: C, 50.78; H, 3.77; N, 13.72.

4-Benzyl-1,4-dihydro-2-methoxy-4-methylquinoline (V). This compound, produced by treating 2-methoxylepidine with benzylmagnesium chloride as described for 2-methoxyquinoline, was purified by distillation; b.p. 150–153° (0.8 mm.); n_D^{20} 1.6593.

Anal. Calc'd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28.

Found: C, 81.35; H, 7.01; N, 5.20.

A mixture of 3.0 g. of the benzyl derivative (V) and 0.5 g. of palladium-on-carbon (10%) was heated at 360–380° for 30 minutes. Approximately 1 ml. of toluene (n_D^{20} 1.4960; b.p. 109–114°) was caught in the distillate in a Dry Ice trap. Oxidation with dichromate converted it to a solid melting at 120–121°. When this solid was mixed with benzoic acid no depression of melting point was noted. By trituration of the residue with acetone there was obtained an oil which boiled at 93–95° (0.6 mm.) and yielded a picrate which had the melting point (158–159°) of the picrate of 2-methoxylepidine.

The benzyl derivative (V) was recovered unchanged after treatment with benzylmagnesium chloride.

4-Benzyl-4-methylhydrocarbostyril (VI). Treatment with 0.5% hydrochloric acid converted the 4-benzyl-1,4-dihydro-2-methoxy-4-methylquinoline to the corresponding hydrocarbostyril (VI), which was recrystallized from ethanol; m.p. 162.5–164°.

Anal. Calc'd for $C_{17}H_{17}NO$: C, 81.14; H, 6.82; N, 5.57.

Found: C, 81.28; H, 6.98; N, 5.50.

When heated with palladium-on-carbon this compound behaved very much like 4-benzyl-

1,4-dihydro-2-methoxy-4-methylquinoline, yielding toluene and a residual substance which was proved by the method of mixture melting points to be 4-methylhydrocarbostyril; m.p. 221–223°.

4-Benzyl-4-methyl-1,2,3,4-tetrahydroquinoline (VIII). A solution of 10 g. of 4-benzyl-4-methylhydrocarbostyril (VI) in 100 ml. of dry benzene was added dropwise over a period of 30 minutes to a cold solution of 3.8 g. of lithium aluminum hydride in dry ether. After the vigorous reaction had subsided the mixture was heated under reflux for 36 hours, cooled, and decomposed by the addition of water in slight excess. The benzene layer was removed and the aluminum hydroxide was washed with three 100-ml. portions of ether. The solid was finally treated with boiling ether under reflux. The combined ether and benzene solutions were washed with 5% hydrochloric acid. The acid layer was neutralized with 10% sodium hydroxide solution, filtered, and extracted with three 50-ml. portions of ether. The combined benzene and ether solutions yielded the tetrahydroquinoline as a yellow oil; b.p. 151–152° (0.5 mm.); n_D^{20} 1.6119; yield 65%.

Anal. Calc'd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.92.
Found: C, 85.78; H, 8.25; N, 5.82.

The *picrate* crystallized from ethanol in needles; m.p. 158–159°.

Anal. Calc'd for $C_{23}H_{22}NO$: C, 59.23; H, 4.76; N, 12.01.
Found: C, 59.30; H, 4.89; N, 12.01.

Methiodide of 4-benzyl-4,N-dimethyl-1,2,3,4-tetrahydroquinoline. To a cooled solution of 20 g. of the tetrahydroquinoline (VIII) in 10 ml. of absolute methanol were added 0.84 g. of sodium carbonate and a solution of 4.23 g. of methyl iodide in 10 ml. of methanol. The mixture was heated 12 hours under reflux, an additional 5 ml. of methyl iodide being added every two hours. The reaction mixture was cooled and filtered. The filtrate was diluted with an equal volume of ether and the solution chilled. The methiodide, which separated in slightly yellow needles, was washed with ether and kept in a vacuum-desiccator for 24 hours; m.p. 194–195°; yield 65%.

Anal. Calc'd for $C_{19}H_{24}IN$: C, 58.03; H, 6.15.
Found: C, 57.70; H, 6.34.

3-Benzyl-N,N-dimethyl-3-phenylbutylamine (IX). The methiodide of 4-benzyl-4,N-dimethyl-1,2,3,4-tetrahydroquinoline was reduced with 5% sodium amalgam according to the method of Emde (10). The amalgam (3.9 g.) was added slowly to a solution of the methiodide (1.54 g.) in 20 ml. of water, and the mixture was heated under reflux for ten hours. An additional 3.9 g. of the amalgam was added and the heating continued for two hours longer. Extraction of the reaction mixture with three 20-ml. portions of ether yielded the amine (IX) as a yellow oil; b.p. 139–140° (0.5 mm.); yield 40%.

Anal. Calc'd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.25.
Found: C, 85.16; H, 9.24; N, 5.13.

The *methiodide*, recrystallized from ether, melted at 192–193°.

Anal. Calc'd for $C_{20}H_{28}IN$: C, 58.68; H, 6.90.
Found: C, 58.80; H, 6.89.

Ethyl (β-phenylisopropylidene)cyanoacetate (XI). The condensation of ethyl cyanoacetate with benzyl methyl ketone was effected by a procedure similar to that described for acetone (14). A mixture of the ketone (348 g.), ethyl cyanoacetate (226 g.), chloroform (200 g.), glacial acetic acid (24 g.), and ammonium acetate (16 g.) was heated under a total reflux separator until no more water collected and for two hours longer. The total time was six hours, and 45 ml. of water was removed. The product was isolated by usual procedures and distilled through a condenser through which steam was circulated. The distillate proved to be a mixture of the unsaturated ester (XI) and a solid identified as the cyclization product, 2-cyano-3-methyl-1-naphthol (11).

The naphthol, which crystallized in the receiver, was washed thoroughly with ether; m.p. 202–204°.

Anal. Calc'd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65.
Found: C, 78.77; H, 5.15; N, 7.61.

The infrared spectrum[4] of the naphthol indicated a hydroxyl group and a conjugated nitrile group.

The infrared spectrum of the unsaturated ester indicated a conjugated nitrile group and an ester group. The extent of cyclization was usually small and in such experiments the ester was obtained in satisfactory yields. It was purified by distillation; b.p. 145–149° (0.7 mm.).

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11.

Found: C, 73.61; H, 6.43; N, 6.18.

Hydrolysis of 2-cyano-3-methyl-1-naphthol (XII). A mixture of the naphthol (3 g.), potassium hydroxide (12 g.), and ethylene glycol (150 ml.) was heated under reflux in a copper flask for five days, cooled, and diluted with water. Acidification of the solution was accompanied by copious evolution of gas. At *p*H 6.0 the color of the solution changed from orange to yellow. The 3-methyl-1-naphthol, which separated, was recrystallized three times from low-boiling petroleum ether; m.p. 90–91° (14); yield 69%.

Anal. Calc'd for $C_{11}H_{10}O$: C, 83.51; H, 6.37.

Found: C, 83.61; H, 6.48.

Ethyl β-benzyl-α-cyano-β-phenylbutyrate (XIII). The procedure was an adaptation of that used by Kohler (15) to prepare ethyl benzohydrylmalonate. An ice-cold solution of phenylmagnesium bromide, prepared from 4.8 g. of magnesium, 31.4 g. of bromobenzene, and 100 ml. of absolute ether, was added to an ice-cold solution of 22.9 g. of ethyl (β-phenylisopropylidene) cyanoacetate in 100 ml. of dry ether. The mixture was stirred for three hours—the last two under gentle reflux—and poured into an ice-cold saturated solution of ammonium chloride. The saturated cyano ester was purified by distillation; b.p. 167–174° (0.8 mm.); n_D^{20} 1.5371; yield 76%.

Anal. Calc'd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56.

Found: C, 78.94; H, 6.79; N, 4.68.

β-Benzyl-β-phenylbutyric acid (XIV). A mixture of 12.13 g. of the saturated cyano ester (XIII), 8.96 g. of potassium hydroxide, and 125 ml. of ethylene glycol was heated under reflux in a copper vessel until ammonia ceased to be evolved. The time required was five days. The reaction mixture was diluted with 100 ml. of water and brought to *p*H 5.0 by the addition of 1.0% hydrochloric acid. The acid, isolated by conventional methods, was recrystallized repeatedly from dilute ethanol, one solution being treated with Darco; m.p. 97°; yield 56%.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.14.

Found: C, 80.02; H, 7.12.

3-Benzyl-N,N-dimethyl-3-phenylbutylamine (IX). *Second method.* A 1-g. sample of the acid (XIV) was heated for ten minutes under reflux with 6 ml. of purified thionyl chloride and a drop of pyridine. After the excess thionyl chloride had been distilled, 5 ml. of a 25% solution of dimethylamine was added to the residual acid chloride. There was a vigorous evolution of heat. The β-benzyl-N,N-dimethyl-β-phenylbutyramide (X) was isolated by distillation; b.p. 161° (0.9 mm.). The viscous product sublimed to give a white solid; m.p. 19°. The amide, without further purification, was treated with lithium aluminum hydride.

A solution of the amide (1.0 g.) in 30 ml. of dry ether was added dropwise to a cold suspension of the hydride (2.5 g.) in dry ether. The mixture was heated under reflux for 36 hours, cooled, and decomposed with water in slight excess. The amine was purified by distillation; b.p. 137–138° (0.5 mm.).

Anal. Calc'd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.25.

Found: C, 85.34; H, 9.71; N, 5.00.

The methiodide has the same melting point (192–194°) as that of the sample prepared from the amine derived from the tetrahydroquinoline. The melting point of a mixture of the two samples was not depressed. The two samples of the methiodide have identical infrared spectra.

URBANA, ILLINOIS

[4] The infrared spectra were observed and interpreted by Miss Elizabeth Petersen.

REFERENCES

(1) BERGSTROM AND MCALLISTER, *J. Am. Chem. Soc.*, **52**, 2845 (1930).
(2) BERGMANN AND ROSENTHAL, *J. prakt. Chem.*, [2] **135**, 267 (1932).
(3) VEER AND GOLDSCHMIDT, *Rec. trav. chim.*, **65**, 793 (1946).
(4) FRIEDLÄNDER AND WEINBERG, *Ber.*, **15**, 1421 (1882).
(5) GILMAN AND GAINER, *J. Am. Chem. Soc.*, **69**, 877 (1947).
(6) CRAIG, *J. Am. Chem. Soc.*, **60**, 1458 (1938).
(7) SEMON AND CRAIG, *J. Am. Chem. Soc.*, **58**, 1278 (1936); FREUND AND BODE, *Ber.*, **42**, 1746 (1909).
(8) GILMAN AND BEEL, *J. Am. Chem. Soc.*, **73**, 32 (1951).
(9) SCHWARTZMAN, *J. Org. Chem.*, **15**, 517 (1950).
(10) EMDE, *Ann.*, **391**, 88 (1912); EMDE AND KULL, *Arch. Pharm.*, **272**, 473 (1924).
(11) MARION AND MCRAE, *Can. J. Research*, **18B**, 267 (1940).
(12) PERKIN AND ROBINSON, *J. Chem. Soc.*, **103**, 1973 (1913).
(13) KASLOW AND LAUER, *Org. Syntheses*, **24**, 28 (1944).
(14) WIDEQVIST AND BRÄNDSTRÖM, *Acta Chem. Scand.*, **3**, 303 (1949); see also COPE, HOFMANN, WYCKOFF, AND HARDENBERGH, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
(15) KOHLER, *Am. Chem. J.*, **34**, 132 (1905).