REACTION OF ETHYL QUININATE DERIVATIVES WITH PHENYLLITHIUM

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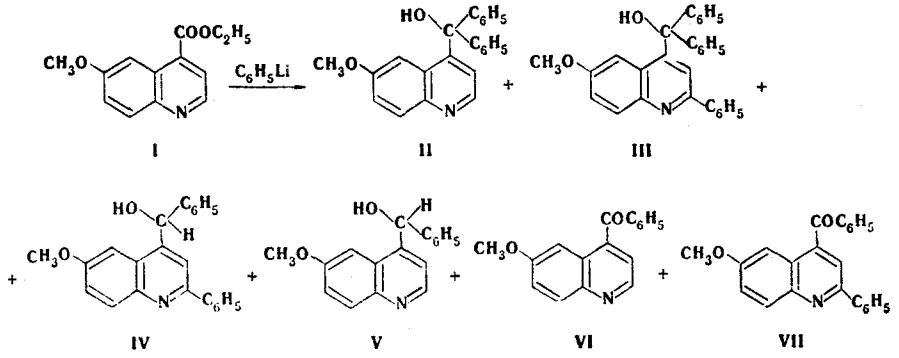
The reactions of ethyl quininate and its 1-methyl-2-oxo derivative and ethyl 1-methyl-1,2,3,4-tetrahydroquininate with phenyllithium were investigated. The structures of the products were confirmed by IR, PMR, and mass-spectroscopic data.

The high biological activity of various hetaryldiphenylcarbinols, among which effective medicinal preparations with psychostimulation (piridrol and azacyclonol), antiallergic (fenkarol and bikarfen), and other types of activity are found, has attracted the attention of researchers to this class of compounds in recent years.

In contrast to other hetaryldiphenylcarbinols and (4-quinolyl)monoaryl(hetaryl)carbinols, which are analogs of quinine alkaloids, very little study has been devoted to (4-quinolyl)-diphenylcarbinols. Only the synthesis of (4-quinolyl)diphenylcarbinol by decarboxylation of cinchoninic acid in the presence of benzophenone has been described [1], and the reaction of ethyl cinchoninate with phenylmagnesium bromide was described in [2]. Depending on the reagent ratio, 4-quinolyl phenyl ketone or (4-quinolyl)diphenylcarbinol is formed in the latter case. Similar reactions with quininic acid derivatives have not been studied.

We have investigated the reaction of ethyl quininate and its 1-methyl-2-oxo derivative and ethyl 1-methyl-1,2,3,4-tetrahydroquininate with phenyllithium. It was found that, according to the results of thin-layer chromatography (TLC), the same complex mixture of substances (II-VII) is formed in the reaction of ethyl quininate (I) with phenyllithium, regardless of the solvent [benzene–ether or ether–tetrahydrofuran (THF)] and the reaction time (5-17 h).



The quantitative ratios of II-VII depend on the synthesis conditions. To separate the principal products (II-V), the percentage of each of which in the mixture exceeds 10% of the sum of the substances, we used column chromatography with subsequent additional application of preparative chromatography in a thin layer. The purity of the substances was verified by TLC. The isolated individual compounds were characterized by elementary analysis, and their structures were confirmed by IR, PMR, and mass-spectroscopic data. Compounds VI and VII, the percentages of which in the reaction products were less than 10%, were detected in the corresponding chromatographic fractions by mass spectroscopy. Compound I undergoes reaction with phenyllithium at both the ester group and the carbon atom in the 2 position of

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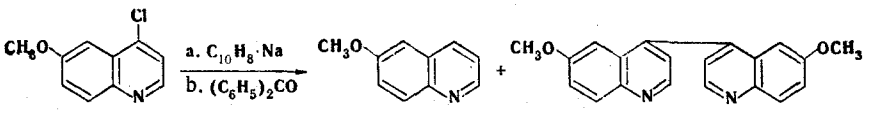
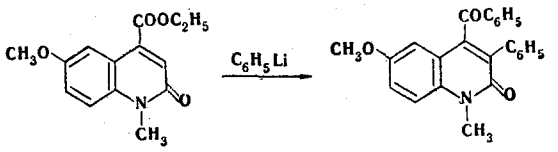
the quinoline ring; of the two possible analogous substances (II and III, IV and V, and VI and VII), the 2-phenylquinoline derivatives (III, IV, and VII) are formed in greater amounts in all cases, and the principal reaction product is (2-phenyl-6-methoxy-4-quinolyl)diphenylcarbinol (III), which was isolated in 41% yield. (6-Methoxy-4-quinolyl)diphenylcarbinol (II) was obtained in 18% yield. The formation of 2-phenylquinoline derivatives in the investigated reaction is not unexpected, since the conversion of lepidine with phenyllithium to 2-phenyl-4-methylquinoline in 54% yield has been described [3]. However, it was difficult to anticipate primary reaction in the 2 position as compared with reaction at the ester group. Insofar as organometallic synthesis through the ester group is concerned, the reaction of I with phenyllithium leads to the formation of various compounds: ketones (VI and VII), their reduction products — secondary carbinols IV and V — and finally quinolyldiphenylcarbinols II and III, with the overall yield of II and III approaching 60%.



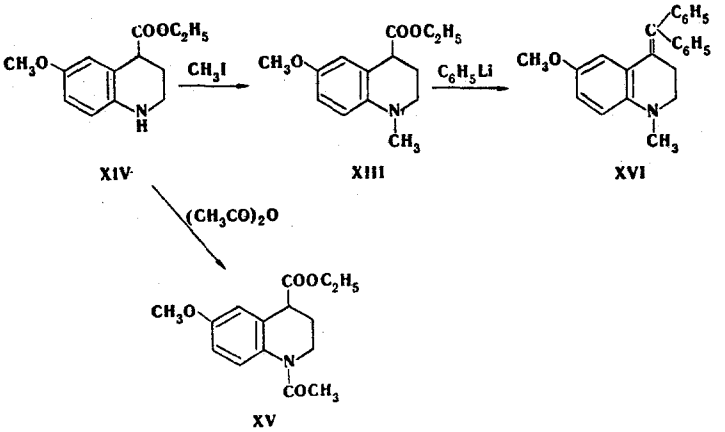
VIII IX X

Another known method for the preparation of hetaryldiphenylcarbinols based on the reaction of haloheterocycles with naphthylsodium and subsequent treatment of the hetaryllithium compounds with benzophenone [4] did not give positive results in the case of 4-chloro-6-methoxyquinoline (VIII). Instead of the expected carbinol II, dehalogenation of chloroquinoline derivative VIII to give 6-methoxyquinoline (IX) and crosslinking of two quinoline residues with the development of 6,6'-dimethoxy-4,4'-diquinolyl (X) were observed. In addition to IX and X, other minor products with molecular weights (according to the mass spectroscopic data) of 442, 430, and 386 were observed in the reaction mixture. However, not even traces of carbinol II could be detected by mass spectroscopy or chromatography.



XI XII

In contrast to I, the corresponding 1-methyl-2-oxo derivative (XI) reacts with phenyllithium simultaneously at the ester group and in the 3 position of the quinoline ring to give 1-methyl-3-phenyl-4-benzoyl-6-methoxy-2-quinolone (XII). Compound XII was obtained in 44% yield, and its structure was confirmed by IR, PMR, and mass spectroscopic data. The remaining products, which were present in the complex mixture in relatively small amounts, were not investigated. The arylation of 2-quinolones in the 3 position has not been described in the literature. This process evidently creates steric hindrance to subsequent attack by phenyllithium on the 4-benzoyl residue to give the corresponding diphenylcarbinol, and XIJ is therefore the principal product of the reaction of XI with phenyllithium.



XIV XIII XVI XV

The previously described [5] ethyl 1,2,3,4-tetrahydroquininate (XIV), which was subjected to methylation with methyl iodide, was used for the conversion to the 1-methyltetrahydro-

quininic acid ester (XIII). The resulting 1-methyl derivative XIII was separated from the unchanged XIV by conversion of the latter to the 1-acetyl derivative (XV) with acetic anhydride and separation of XIII and XV by means of their different basicities. The degree of separation of the products was monitored by gas–liquid chromatography (GLC). The principal process in the reaction of XIII with phenyllithium was evidently the formation of an inner salt of the betaine type that was insoluble in organic solvents. The only substance that was extracted (in ∿ 16% yield) from the reaction mixture was the product of dehydration of (1-methyl-6-methoxy-1,2,3,4-tetrahydro-4-quinolyl)diphenylcarbinol — 1-methyl-4-diphenylmethylene-6-methoxy-1,2,3,4-tetrahydroquinoline (XVI). A similar case of dehydration of diphenylcarbinols has been noted in the quinuclidine series [6]. However, in contrast to (3-quinuclidyl)diphenylcarbinol, the corresponding tetrahydroquinoline derivative, which has an extremely labile proton of the benzyl type, splits out a molecule of water considerably more readily, and the final product is immediately dehydrated XVI.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer equipped with a direct inlet into the source at ionizing-voltage energies of 30 and 12 eV; the composition of the mixture was studied with variation of the ionizing voltage and the temperature. All of the molecular weights were determined by mass spectrometry. Thin-layer chromatography was carried out on Silufol UV-254 plates; the R_f values are presented for a chloroform–methanol system (30:1) (development in UV light). Analytical GLC was carried out with a Pye–Unicam series 104 chromatograph with a catharometer as the detector and a helium flow rate of 30 ml/min and the following columns: 1) a 2100 by 4 mm column with SE-30 silicone elastomer (10%) on silanized diatomaceous earth C (100-120 mesh) as the stationary phase at 250°C (for IX); 2) a 900 by 4 mm column with XE-60 silicone elastomer on Chromosorb W (80 by 100 mesh) as the stationary phase at 200°C (for XIII and XV).

Reaction of Ethyl Quininate with Phenyllithium. A solution of 2.31 g (10 mmole) of ethyl quininate [7] in 30 ml of anhydrous THF was added with stirring at ∿ 5°C in the course of 1 h to a solution of 2.52 g (30 mmole) of phenyllithium in 27 ml of anhydrous ether, and the mixture was refluxed (50°C) for 10 h. The solvent was then removed *in vacuo*, and the residue was acidified with respect to Congo Red with hydrochloric acid and extracted with benzene. The aqueous layer was made alkaline to pH 9 with 50% potassium carbonate solution and extracted with chloroform. The chloroform solution was dried with magnesium sulfate and vacuum evaporated. A suspension of the residue (3.28 g) in 10 ml of benzene was applied to a column (1200 by 24 mm) filled with 200 g of silica gel (L 40/100 μ) washed with benzene. Thin-layer chromatography on Silufol was used to monitor the separation of the substances. Elution with ether–benzene (1:100) gave 1.69 g (41%) of (2-phenyl-6-methoxy-4-quinolyl)-diphenylcarbinol (III) as colorless crystals with mp 213-214.5°C (from absolute alcohol) that were soluble in hot alcohols, ethyl acetate, and acetone but insoluble in water and had R_f 0.78. PMR spectrum (d_6-DMSO): 3.47 (s, OCH_3), 7.15 (s, 3-H), 7.25-7.91 [m, s (OH), $(C_6H_5)_2$, 2-C_6H_5, 5-H, 7-H], and 7.96 ppm (d, 8-H). The molecular weight was 417. Found, %: C 83.4; H 5.9; N 3.2. $C_{29}H_{23}NO_2$. Calculated, %: C 83.6; H 5.6; N 3.4. The hydrochloride of III was obtained as yellow crystals with mp 250-252°C (from absolute alcohol) that were soluble in hot alcohol but insoluble in water. Found, %: C 76.6; H 5.2; Cl 7.6; N 3.0. $C_{29}H_{23}NO_2 \cdot HCl$. Calculated, %: C 76.7; H 5.3; Cl 7.8; N 3.1.

Subsequent elution with ether–benzene (1:10) gave 0.54 g (16%) of (2-phenyl-6-methoxy-4-quinolyl)phenylcarbinol (IV) as colorless crystals with mp 160-162°C. The crystals were soluble in acetone, hot alcohols, ethyl acetate, and benzene but insoluble in water and had R_f 0.60. IR spectrum: 1580, 1620(C=C, C=N); 3320 cm^{-1} (OH). The molecular weight was 341. Found, %: C 80.4; H 5.8; N 3.9. $C_{23}H_{19}NO_2$. Calculated, %: C 80.9; H 5.6; N 4.1.

Subsequent elution with ether gave 0.6 g (18%) of (6-methoxy-4-quinolyl)diphenylcarbinol (II) as colorless crystals with mp 236.5-238.5°C (from ethyl acetate). The product was soluble in hot ordinary organic solvents but insoluble in ether and water and had R_f 0.48. The molecular weight was 341 (by mass spectrometry). Found, %: C 80.7; H 5.7; N 4.0. $C_{23}H_{19}NO_2$. Calculated, %: C 80.9; H 5.6; N 4.1. The hydrochloride of II was obtained as colorless crystals with mp 250-251°C (from absolute alcohol) that were insoluble in water and ether but soluble in hot alcohol. Found, %: C 79.0; H 5.1; Cl 9.5; N 3.6. $C_{12}H_{19}NO_2 \cdot HCl$. Calculated, %: C 73.1; H 5.3; Cl 9.4; N 3.7.

Subsequent elution gave 0.39 g (15%) of (6-methoxy-4-quinolyl)phenylcarbinol (V) containing 4-benzoyl-6-methoxyquinoline (VI) (m/e 265 for V and m/e 263 for VI). Compound V was purified by preparative chromatography on 170 by 80 mm plates with a fixed (with gypsum) layer of KSK silica gel (0.16-0.2 mm particles, layer thickness 0.25 mm). A solution of 0.07 g of the substance in 0.12 ml of anhydrous chloroform was applied to two plates. The mobile phase was chloroform–methanol (30:1); the elution was monitored by irradiation with UV light. The zone with R_f 0.18-0.22, which contained carbinol V, was removed, and the substance was eluted with anhydrous chloroform to give 0.04 g of V as colorless crystals with mp 164-165°C (from chloroform). The product was soluble in acetone, alcohols, and hot chloroform but insoluble in ether, benzene, and water and had R_f 0.20 and a molecular weight of 265. Found: C 76.8; H 6.1; N 5.0. $C_{17}H_{15}NO_2$. Calculated, %: C 77.0; H 5.7; N 5.3.

Reaction of 4-Chloro-6-methoxyquinoline with Naphthylsodium and Benzophenone. A mixture of 2 g (87 mg-atom) of sodium metal, 11 g (86 mmole) of sublimed naphthalene, and 100 ml of anhydrous THF was stirred in an argon atmosphere at room temperature for 3 h, after which the solution of naphthylsodium was cooled to –15°C, and 7.56 g (39 mmole of 4-chloro-6-methoxyquinoline (VIII) [8] was added to it, and the mixture was maintained at the same temperature for another hour. A solution of 9.46 g (52 mmole) of benzophenone in 30 ml of THF was added at –15°C in the course of 15 min, and the mixture was maintained at the same temperature for 2 h. It was then stirred at room temperature for another 6 h, after which 20 ml of absolute alcohol was added, and the mixture was stirred for 30 min. The solvent was removed by vacuum distillation, 40 ml of chloroform was added to the residue, and the mixture was extracted with 18% hydrochloric acid. The chloroform was evaporated, and the residue (19.4 g) was identified as a mixture of naphthalene and benzophenone in a ratio of 1:1.1 (according to GLC data). The aqueous solution was made alkaline with 25% ammonium hydroxide and extracted with ether. The extract was dried with potassium carbonate and evaporated to dryness to give 3.18 g of a substance that did not contain carbinol II according to TLC data. Vacuum distillation gave 2.6 g (42%) of 6-methoxyquinoline (IX) [9] as a colorless mobile liquid that was soluble in ordinary organic solvents, insoluble in water, and had bp 99-100°C (0.4 mm) and n_D^{20} 1.6188. IR spectrum: 1580 and 1640 cm^{-1} (C=C and C=N). The molecular weight of the product was 159 and its retention time was 1.9 min. Found, %: C 75.0; H 6.0; N 8.9. $C_{10}H_9NO$. Calculated, %: C 75.3; H 5.7; N 8.8.

The products (1.29 g) that were insoluble in chloroform and 18% hydrochloric acid were, according to the mass spectral data, a mixture in which carbinol II was absent (no molecular ion with m/e 341) but 6-methoxyquinoline dimer X (molecular ion peak with m/e 316) and other products with m/e 442, 430, and 386 were present.

Reaction of 1-Methyl-4-carbethoxy-6-methoxy-2-quinolone with Phenyllithium. A solution of 2.31 g (9 mmole) of 1-methyl-4-carbethoxy-6-methoxy-2-quinolone (XI) [7] in 30 ml of anhydrous THF was added with stirring to a solution of 2.52 g (30 mmole) of phenyllithium in 25 ml of anhydrous ether at 5°C in the course of 1 h, after which it was refluxed for 4.5 h. It was then vacuum evaporated, and 30 ml of water and 5 ml of 50% aqueous potassium carbonate solution was added to the residue. The mixture was extracted with chloroform, and the extract was dried with magnesium sulfate and vacuum evaporated. The residue (3.37 g), which, according to TLC, was a complex mixture of products, was dissolved in 25 ml of chloroform, and the solution was applied to a column (900 by 22 mm) filled with 170 g of activity II aluminum oxide previously washed with heptane. The reaction product was eluted successively with benzene, ether, and chloroform. The elution process was monitored by TLC. The chloroform eluate was evaporated to give 1.63 g (44.2%) of 1-methyl-3-phenyl-4-benzoyl-6-methoxy-2-quinolone (XII) as shiny red crystals with mp 191-194°C (from ethyl acetate). The product was soluble in benzene, hot alcohols, ethyl acetate, and acetone but insoluble in ether and water and had R_f 0.85. IR spectrum: 1655 (CON) and 1705 cm^{-1} ($COOC_2H_5$). PMR spectrum (d_6-DMSO): 3.05 (s, $N{=}CH_3$), 3.52 (s, 6-OCH_3), 6.3 (s, 5-H), 6.88 (s, C_7H_4, 8-H), and 7.45-8.05 ppm (m, 3-C_6H_5 and $C_4C(=O)C_6H_5$). The molecular weight of the product was 369. Found, %: C 78.0; H 5.6; N 3.4. $C_{24}H_{19}NO_3$. Calculated, %: C 78.0; H 5.2; N 3.8.

Ethyl 1-Methyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (XIII). A 2.3 g [16.2 mmole (1.1 ml)] sample of methyl iodide was added with external ice cooling to 3.45 g (14.8 mmole) of ethyl 6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (XIV) [5], and the mixture was allowed to stand at room temperature for 15 h. It was then treated with 5 ml of

water and 5 ml of 20% aqueous sodium hydroxide solution, and the mixture was extracted with ether. The ether extract was dried with magnesium sulfate and distilled at 145-150°C (0.8 mm) to give 2.3 g of mixture of XIV and III (in a ratio of 3:22 according to GLC). The products (3.29 g) that were insoluble in the aqueous layer and organic solvents (ether, benzene, and chloroform) were not subjected to further study. Acetic anhydride (23 ml) was added to the mixture of XIV and III, and the mixture was heated on a boiling-water bath for 1 h. The excess acetic anhydride was then removed by distillation, 7 ml of hydrochloric acid was added to the residue until it was acidic with respect to Congo Red, and the mixture was extracted with benzene. The benzene solution was dried with magnesium sulfate and evaporated to give 0.43 g (11%) of ethyl 1-acetyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (XV) as a colorless viscous liquid with bp 178-180°C (0.3 mm). The product was soluble in ordinary organic solvents but insoluble in water and had n_D^{20} 1.5502. IR spectrum: 1650 (CON) and 1720 cm^{-1} ($COOC_2H_5$). PMR spectrum (CCl_4): 1.26 (t, $COOCH_2\underline{CH_3}$), 1.9-2.25 (m, $3CH_2$), 2.8 (s, $N-COCH_3$), 2.9-3.3 (m, $2CH_2$), 3.55-3.65 (m, 4-H), 3.65 (s, OCH_3), 4.11 (q, $COO\underline{CH_2}CH_3$), and 6.4-6.65 ppm (m, 5-H, 7-H, 8-H). The retention time of the product was 18.0 min. Found, %: C 65.2; H 7.1; N 4.7. $C_{15}H_{19}NO_4$. Calculated, %: C 65.0; H 6.9; N 5.0.

The aqueous solution remaining after extraction of XV was made alkaline with 50% aqueous potassium carbonate solution and extracted with benzene. The extract was dried with magnesium sulfate and evaporated to give ethyl 1-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (XIII). The yield was 2.02 g (55% according to GLC data). The colorless vicous liquid had bp 138-140°C (0.6 mm) and n_D^{20} 1.5540 and was soluble in ordinary organic solvents but insoluble in water. IR spectrum: 1720 ($COOC_2H_5$); no band at 3380 cm^{-1} (NH). The retention time of the product was 4.08 min. Found, %: C 67.4; H 7.8; N 6.0. $C_{14}H_{19}NO_3$. Calculated, %: C 67.4; H 7.7; N 5.6.

Reaction of Ethyl 1-Methyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate with Phenyllithium. A solution of 7.18 g (28.8 mmole) of ethyl 1-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carboxylate (XIII) in 70 ml of anhydrous ether was added with stirring at ~ 5°C in the course of 45 min to a solution of 7.26 g (86.5 mmole) of phenyllithium in 76 ml of anhydrous ether, and the mixture was refluxed for 7 h. Absolute alcohol was added to the externally cooled (with ice) mixture, and the resulting mixture was stirred at room temperature for 30 min. The solvent was evaporated *in vacuo*, 35 ml of hydrochloric acid was added to the residue, and the mixture was extracted with benzene (six 20-ml portions).

The aqueous layer was made alkaline with 50% aqueous potassium carbonate solution and extracted with benzene. The extract was dried with magnesium sulfate and evaporated to give 1.54 g (16%) of 1-methyl-4-diphenylmethylene-6-methoxy-1,2,3,4-tetrahydroquinoline (XVI) as yellow-greenish crystals with mp 172-173.5°C (from ethyl acetate). The product was soluble in hot alcohols, acetone, ethyl acetate, and benzene but insoluble in water. IR spectrum: no absorption at 3100-3700 cm^{-1}. PMR spectrum ($CDCl_3$): 2.88 (s, $N-CH_3$), 2.65 (m, $3CH_2$), 3.15 (m, $2CH_2$), 3.15 (s, OCH_3), 6.36 (s, 5-H), 6.58 (s, 7-H), 6.58 (s, 8-H), and 7.15-7.3 ppm [m, $=C(C_6H_3)_2$]. The molecular weight of the product was 341. Found, %: C 84.0; H 6.9; N 4.0. $C_{24}H_{23}NO_2$. Calculated, %: C 84.3; H 6.8; N 4.1.

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