

Alumina-Catalyzed Condensation of 2-Methylquinoline with Methanol (1)

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The alumina-catalyzed reaction of 2-methylquinoline with excess methanol at 500° produced a mixture of 2-ethyl-, 2-isopropyl-, and 2-isopropenylquinolines in yields of 10%, 7%, and 2%, respectively. A mechanistic interpretation of this reaction is presented.

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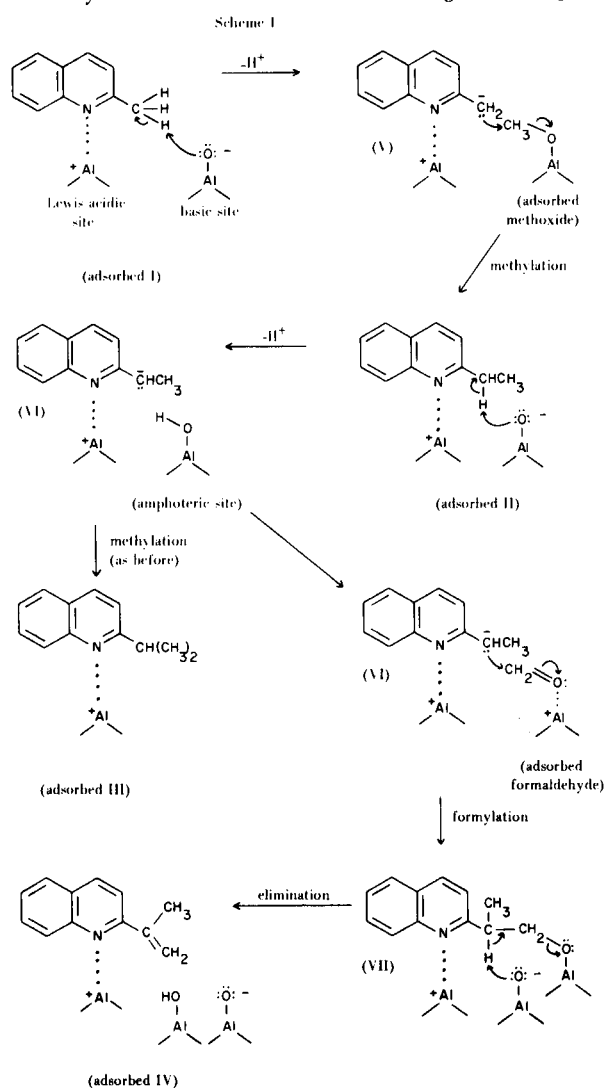
In a previous study Cullinane, *et al.*, (3) found that the vapor-phase reaction of pyridine plus methanol at 400-500° in the presence of an alumina catalyst gives a mixture of methylpyridines and dimethylpyridines (combined yield, 8 mole%). In connection with our studies on reductive methylation of aromatic compounds by means of alumina-methanol (4), we now report that passing a mixture of 2-methylquinoline (I) and excess methanol over a "weakly acidic" alumina catalyst (5) at 500° gives reaction on the 2-methyl substituent but apparently does not effect ring methylation.

Distillation of the combined basic effluent from reaction of I yielded 58 weight% of yellow liquid. Fractionation of this liquid into seven components was accomplished by means of thick-layer chromatography on silica gel (with benzene as eluent) to give recovered I (28%, R_f 0.15), 2-ethylquinoline (II, 10 mole%, R_f 0.25), 2-isopropylquinoline (III, 7 mole%, R_f 0.38), 2-isopropenylquinoline (IV, 2 mole%, R_f 0.57), and three smaller, unidentified fractions. Compounds II and III were purified through their picrates (melting points consistent with literature values) and identified further by mass and pmr spectra. Compound IV was identified by pmr, exact mass analysis, and catalytic hydrogenation to III (31%).

The R_f values found for I-IV fall in the order expected for adsorption of the compounds by means of hydrogen bonding between silica gel and the heterocyclic nitrogen atom (6), wherein steric hindrance to adsorption should increase in the order (of 2-substituents) methyl, ethyl, isopropyl, and isopropenyl (7).

Adapting the Peri model for the surface structure of γ -alumina (8) and our own stereochemical mechanistic proposals for reductive methylations of hydroxyarenes with alumina-methanol (4,9) to the present case, one can easily rationalize the transformation of I into II-IV under

the reaction conditions (Scheme 1). In this Scheme, I is adsorbed by coordination of the non-bonding electron pair



on the heterocyclic nitrogen atom to a Lewis acidic site on the catalyst. Abstraction of a proton from the 2-methyl group is effected by means of a basic site to form an adsorbed carbanion (V) [*cf.* metalation products of I and 2-methylpyridine (10,11)], which undergoes a surface S_N2 -type displacement on methoxide ion to yield II. Repetition of these processes gives adsorbed anion VI and 2-isopropylquinoline (III). Alternatively, VI reacts with formaldehyde (available from dehydrogenation of methanol) (12) to produce adsorbed alkoxide VII, precursor to IV. Only the neutral quinoline compounds I-IV are desorbed and carried into the effluent traps as isolable (and identified) compounds. [Loss of water (*e.g.* between two amphoteric sites) and other surface processes which do not involve the quinoline entity directly are not shown.]

At this time we are unable to rationalize the marked differences in the types of products isolated from I and from pyridine (3) as substrates. Any appreciable amounts of dimethylquinolines formed from I should have been detected by our isolation procedure. However, the combined yields of I-IV already represent 84% (by weight) of the total distilled product.

EXPERIMENTAL (13)

To a pyrex reactor tube (3.0 cm. outside diameter), packed with Harshaw A1-0104 T 1/8" alumina catalyst (5) (100 g., 26 cm. in length, pre-activated *in situ* in a stream of nitrogen gas for 12 hours at the reaction temperature) and heated by means of a vertically mounted, thermally controlled (at $500 \pm 15^\circ$) combustion furnace (30 cm. long), was added dropwise (20-25 drops/minute) over a period of 8 hours in a stream of nitrogen carrier gas (flow rate of 25 ml./minute) a solution of freshly distilled 2-methylquinoline (8.5 g., Aldrich) in methanol (240 ml., reagent grade). Effluents (trapped in ice- and dry ice-acetone-cooled baths) were extracted with ether. The ether solution was extracted with 50 ml. of 5% hydrochloric acid. Basification (with sodium hydroxide) of the aqueous layer, extraction with ether (solution dried with anhydrous sodium sulfate), and evaporation of solvent left a brown liquid residue -- distilled at 60-80° (0.05 mm.) to yield 4.96 g. (58 weight% yield) of light-yellow, mixed basic products.

Fractionation of the distillate was effected by means of thick layer chromatography (8 plates, 20 x 20 cm., 2 mm. thickness) with silica gel GF-254-benzene (plates developed and dried thrice) and detection of bands (7 observed) by means of ultraviolet light. Extraction of separate bands with ether gave the following products: bottom band (#1), 2.36 g. (28%) of recovered 2-methylquinoline (I); #2, 0.93 g. (10 mole%) of 2-ethylquinoline (II); #3, 0.67 g. (7 mole%) of 2-isopropylquinoline (III); #4, 0.07 g. (0.8 weight%) -- unidentified; #5, 0.19 g. (2 mole%) of 2-isopropenylquinoline (IV); #6 (0.09 g.) and #7 (0.05 g.) -- unidentified. Initial identifications of components I-IV were made by pmr and mass spectral analyses on the crude fractions. Further identifications were made as indicated in the following paragraphs.

Fraction #1 was evaporatively distilled (50°, 0.01 mm.) to

give a liquid, identified as I by direct comparison (pmr, tlc) with an authentic sample.

Fraction #2 was converted into a picrate [recrystallized from ethanol to give yellow prisms, m.p. 146.5-148.5°; lit. (14) m.p. 151-153°] which was dissociated with 5% aqueous lithium hydroxide plus ether. The residue from evaporation of the ether layer was purified by vpc (1.3 m. of carbowax 20M, 200°) to give liquid II: pmr δ 1.28 (t, 3, J = 7.5 Hz, methyl group), 2.90 (q, 2, methylene), 7.1-8.2 ppm (m, 6 aromatic protons); Exact mass: Calcd. for M ($C_{11}H_{11}N$) and (M-1), 157.089 and 156.081; Found: 157.088 and 156.079; mass spectrum quantitatively identical to that previously reported for 2-ethylquinoline (14).

Fraction #3 was purified in the same manner as used for #2 [picrate obtained as yellow needles, m.p. 157.5-159°; lit. (14,15) m.p. 154-155°] to give liquid III: pmr δ 1.24 (d, 6, J = 7 Hz, methyl groups), 3.12 (septet, 1, methinyl group), 7.0-8.1 ppm (m, 6 aromatic protons) (14); Exact mass: Calcd. for M ($C_{12}H_{13}N$) and (M-1), 171.105 and 170.097; Found: 171.104 and 170.096; mass spectrum quantitatively identical to that previously reported for 2-isopropylquinoline (14).

Fraction #5 was rechromatographed, first on silica gel (thick layer) with dichloromethane and then on carbowax (vapor phase) at 150°, to give IV (16): pmr δ 2.37 (s, 3, methyl group), 5.49 and 5.92 (two slightly split s, 1 each, methyldene group), and 7.4-8.3 ppm (m, 6 aromatic protons); ir (carbon tetrachloride) 1595, 1500, 1425, 1260, 1140, 1100, 900, 830 cm^{-1} (17,18); Exact mass: Calcd. for M ($C_{12}H_{11}N$) and (M-1), 169.089 and 168.081; Found: 169.088 and 168.084.

Hydrogenation of 2-Isopropenylquinoline (IV).

To the reaction chamber of a Brown hydrogenator (19) were added a solution (4 ml., 0.05 M) of sodium borohydride in 2-propanol and then a solution of 0.1 g. of IV in a mixture (0.75 ml., 10%) of hydrochloric acid and 2-propanol. Hydrogenation was conducted for 1 hour. The reaction mixture was filtered, evaporated, basified with aqueous sodium hydroxide, and extracted with ether. The residue from evaporation of the ether was chromatographed (thick layer) with silica gel-benzene to give 31 mg. (31%) of III, identified by direct comparison (pmr, tlc, MS) with previously isolated product.

REFERENCES AND NOTES

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- (2) Undergraduate research assistant, summer, 1976.
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- (5) This catalyst has been designated as catalyst B in previous publications; see L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968). B contains about 0.4% sodium ion.
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(12) See reference in note 5.

(13) Pmr spectra were determined on deuteriochloroform solutions by means of a Varian Associates T-60 or XL-100 instrument. Infrared spectra were determined by means of a Beckman IR-7 spectrophotometer. Dr. Richard Wielesek obtained

mass spectral data with a CEC model 21-110 instrument.

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(16) Compound IV was previously synthesized by G. B. Bachman and D. D. Micucci [*J. Am. Chem. Soc.*, **70**, 2381 (1948)], but no spectral or chromatographic data were given. It was noted that IV is stable in hot concentrated sulfuric acid and is not susceptible to homopolymerization.

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