[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

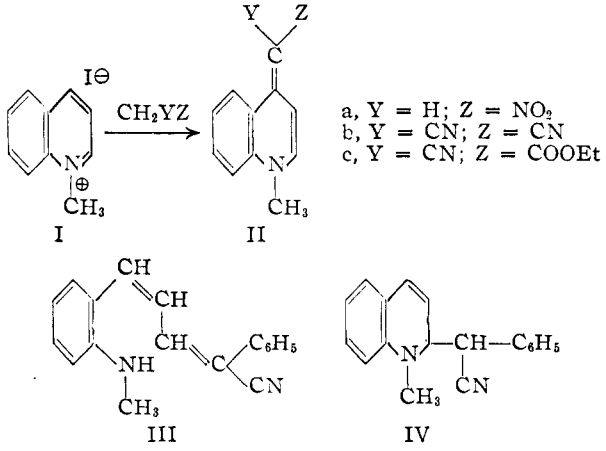
Reactions of Quinolinium Compounds with Phenylacetonitrile and Its Homologs

BY NELSON J. LEONARD AND ROBERT L. FOSTER

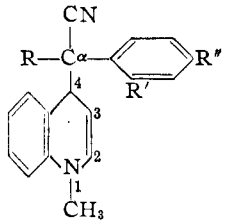
RECEIVED JANUARY 7, 1952

It has been established that 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline is produced from the condensation of 1-methylquinolinium iodide with phenylacetonitrile in the presence of base. The position of attachment of the phenylacetonitrile moiety was determined by conversion of the cyano product to the corresponding amide, followed by reduction in two stages to a substituted decahydroquinoline. The decahydroquinoline was found to be identical with that obtained by reduction of the methochloride of 4-(α-carbamylbenzyl)-quinoline, synthesized by an unequivocal method. The position of the double bond in the structure designated as 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline was assigned mainly on the basis of comparison of the ultraviolet absorption spectrum with the spectra of compounds known to possess the 1,4-dihydroquinoline nucleus. The product from 1-methylquinolinium iodide and α-phenylpropionitrile was established as 1-methyl 4-(α-cyano-α-methylbenzyl)-1,4-dihydroquinoline by its identity with the compound obtained by α-methylation of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline. 1-Methyl-4-(α-cyano-*o*-methylbenzyl)-1,4-dihydroquinoline and 1-methyl-4-(α-cyano-*p*-methylbenzyl)-1,4-dihydroquinoline were also prepared by the condensation of 1-methylquinolinium iodide with the appropriate tolylacetonitrile. 1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline and related compounds were found to undergo a number of unusual reactions, most of which were the result of extremely facile cleavage of the C_4–C_α bond.

It has been shown previously in this Laboratory that active methylene compounds of the group nitromethane,[1] malononitrile[2] and ethyl cyanoacetate[2] react with 1-methylquinolinium iodide (I) in the presence of base to give yellow products (II), which have 2,3-unsaturation and an exocyclic double bond at the 4-position. The condensation product from quinoline methosulfate and phenylacetonitrile in the presence of base has been described by Kaufmann[3] as a *colorless* solid, with the molecular formula $C_{18}H_{16}N_2$ and the postulated structure III or IV. Neither of the structures was considered by us to be correct, since all of the evidence accumulated thus far[1,2,4] indicates preferential attack by a carbanion species at the 4-position of a quinolinium compound. Our proof of the structure of the $C_{18}H_{16}N_2$ product was therefore approached as though it were 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline (Va). In the course of establishing this structure (Va) as indeed correct, some very unusual chemistry has been encountered.



In obtaining the $C_{18}H_{16}N_2$ condensation product, certain modifications of the original Kaufmann patent procedure[3] were introduced. The condensation was effected in 92% yield by stirring equimolar amounts of 1-methylquinolinium iodide, phenylacetonitrile and sodium ethoxide in absolute ethanol solution at 0°. The colorless product, m.p. 118–120°, separated directly. It remained colorless on recrystallization from petroleum ether, but became yellow when hot ethanol was used as the solvent. The excellent yield and the whiteness of the condensation product were in marked contrast to the low yield and the inherent yellow color of the products of type II obtained with the normally more active methylene compounds.[1,2] The lack of color, the analysis, which was correct for $C_{18}H_{16}N_2$, and the absence of any infrared band characteristic of a conjugated nitrile grouping were all indicative of a dihydroquinoline having no exocyclic 2,α- or 4,α-double bond. The open-chain structure III was eliminated as a possibility since the infrared spectrum also indicated the absence of an NH-grouping. On the positive side the spectrum showed a nitrile absorption band at 2240 cm.$^{-1}$ and an absorption band at 1657 cm.$^{-1}$ attributable to the double bond in the 2,3-position of Va.



V

a, R = R′ = R″ = H
b, R = CH₃; R′ = R″ = H
c, R = R′ = H; R″ = CH₃
d, R = R″ = H; R′ = CH₃

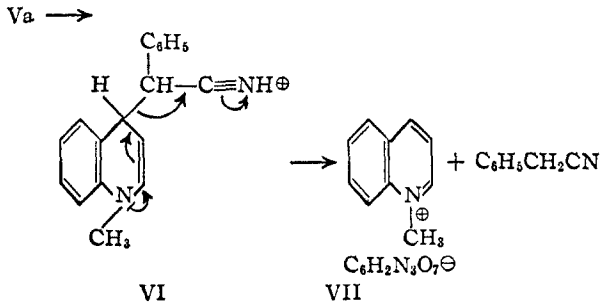
Chemical characterization of the $C_{18}H_{16}N_2$ condensation product was attempted by various methods. In practically every reaction employed, anomalous behavior was encountered; nevertheless, each abnormality finally assisted in the establishment of structure Va for the condensation product and in the understanding of its complex chemistry. For example, treatment of the 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline with picric acid in ethanol gave not the picrate of Va but 1-methylquinolinium picrate (VII), as determined by melting point and analysis. A similar elimination of an active-methylene substituent has been

(1) N. J. Leonard, H. A. DeWalt, Jr., and G. W. Leubner, THIS JOURNAL, **73**, 3325 (1951).

(2) N. J. Leonard and R. L. Foster, *ibid.*, **74**, 2110 (1952).

(3) A. Kaufmann, German Patent 250,154, July 15, 1912; *Frdl.*, **10**, 1317 (1910–1912).

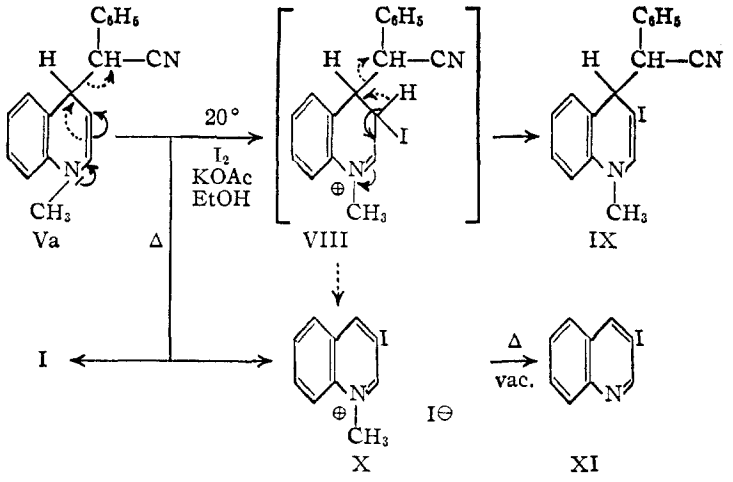
(4) (a) A. Kaufmann, *Ber.*, **51**, 116 (1918); (b) A. Kaufmann and R. Widmer, *ibid.*, **44**, 2058 (1911); (c) A. Kaufmann and A. Albertini, *ibid.*, **42**, 3776 (1909).



VI VII

observed previously in the isoquinoline series by Leonard and Leubner.[5] For example, 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline was found to eliminate phenylnitromethane when treated with picric acid, to give 2-methyl-3,4-dihydroisoquinolinium picrate. The elimination of phenylacetonitrile from the quinoline compound Va can equally well be regarded as an acid-catalyzed process (VI → VII). The 4,α-bond scission was also encountered when attempts were made to convert the nitrile Va to the corresponding carboxylic acid with 70% sulfuric acid and with concentrated hydrochloric acid. Phenylacetic acid was isolated when 70% sulfuric acid was used, and phenylacetamide, together with unreacted Va, was obtained when hydrochloric acid was employed for fifteen minutes at the reflux temperature. The fact that aqueous sodium hydroxide also effects C_4–C_α cleavage indicates that the splitting of compound Va is more than just acid-catalyzed and can be regarded more generally as being a reverse-Michael type.[6]

An attractive method of characterization of a 1-alkyl-1,4-dihydroquinoline compound would appear to be aromatization to the corresponding 1-alkylquinolinium compound. Iodine with potassium acetate in ethanol has previously been used for the oxidation of 2-methyl-1,2,3,4-tetrahydroisoquinoline to 2-methyl-3,4-dihydroisoquinolinium iodide,[5] and iodine with pyridine in ethanol, for the aromatization of 1-methyl-4-cyanoquinolane to 1-methyl-4-cyanoquinolinium iodide.[4a] When the iodine oxidation of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline (Va) was carried out in refluxing ethanol in the presence of potassium acetate, two methiodides were obtained which were separated by differential solubility in ethanol. The more soluble methiodide was identified by analysis, melting point, mixed melting point, and infrared spectrum as 1-methylquinolinium iodide (I). The less soluble methiodide melted at 289–291°, with decomposition, and had the correct analysis for an iodoquinoline methiodide. The iodoquinoline, which was freed from the methiodide by sublimation in vacuum, could be reconverted to the same methiodide. The melting point of the iodoquinoline, 61.5–62.5°, did not correspond to that of any of the known iodoquinolines; however, 3-iodoquinoline was conspicuously absent from the literature and hence our attention was directed toward this possibility. An authentic sample of 3-iodoquinoline (XI) was prepared by diazotization of 3-aminoquinoline and subsequent treatment with potassium iodide. This sample was identical with the one obtained by decomposition of the iodoquinoline methiodide of m.p. 289–291° (dec.), and the respective picrates and methiodides were likewise identical. The quinolinium products resulting from the treatment of Va with iodine and potassium acetate in refluxing ethanol were thereby fully established as 1-methylquinolinium iodide (I), obtained by a reversal of the original condensation process (I → Va), and 1-methyl-3-iodoquinolinium iodide (X), formed by iodination followed by the elimination of phenylacetonitrile. The fact that both X and I are obtained from the reaction at 80° and the knowledge that cleavage is accelerated by heating[5] (also *vide supra*) suggested that we might be able to isolate an iodinated quinoline still possessing the phenylacetonitrile moiety, if we were to operate at a lower temperature. When the reaction of iodine and potassium acetate with 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline was carried out in ethanol at 20°, there was obtained a quantitative yield of a colorless solid, m.p. 130–131.5°, having the correct analysis for $C_{18}H_{15}N_2I$. The iodine present in the compound was non-ionic, and the infrared spectrum showed a nitrile absorption band at 2247 cm.$^{-1}$ and a band at 1649 cm.$^{-1}$ presumably due to the double bond. These are comparable to those observed for compound Va. On the basis of the accumulated evidence, the structure assigned to the iodinated product is 1-methyl-3-iodo-4-(α-cyanobenzyl)-1,4-dihydroquinoline (IX). What is remarkable is the extreme ease of iodine substitution in Va. The strong affinity toward electrophilic attack at the 3-position suggests that other substitution reactions might occur under mild conditions. Formula VIII indicates one resonance form of the cation which is a possible intermediate in the formation of 1-methyl-3-iodo-4-(α-cyanobenzyl)-1,4-dihydro-



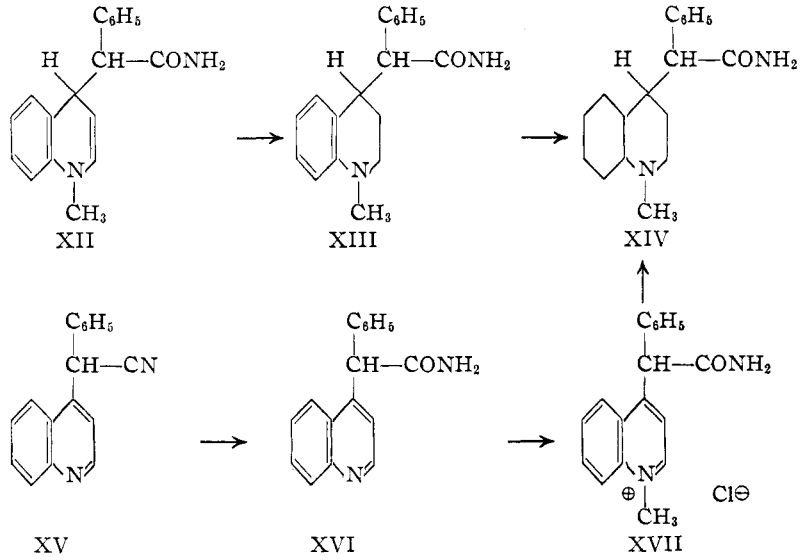
(5) N. J. Leonard and G. W. Leubner, THIS JOURNAL, **71**, 3408 (1949).

(6) For an example of C_{ar}–C_{al} scission in the presence of dilute *acid*, see M. S. Kharasch and J. Porsche, *J. Org. Chem.*, **1**, 265 (1936). An example of Michael condensation and dismutation in the presence of *alkali* is found in the work of L. A. Pinck and G. E. Hilbert, THIS JOURNAL, **68**, 2014 (1946).

quinoline (IX) by elimination of a proton, and in the formation of 1-methyl-3-iodoquinolinium iodide (X) by elimination of a proton followed by the anion of phenylacetonitrile.

Although the nitrile group in Va could not be converted to a carboxyl group without attendant C_4–C_α cleavage, the use of concentrated sulfuric acid permitted its conversion to an amide group. When an attempt was made to form the picrate of the 1-methyl-4-(α-carbamylbenzyl)-1,4-dihydroquinoline (XII) thus obtained, cleavage resulted, as in the case of the parent compound Va, and 1-methylquinolinium picrate was isolated. Numerous catalytic reduction conditions were applied to XII, and finally one set of conditions was successful in providing a reduced form of XII satisfactory for structure authentication by comparison. From the hydrogenation of 1-methyl-4-(α-carbamylbenzyl)-1,4-dihydroquinoline in glacial acetic acid over platinum oxide were obtained phenylacetamide and *cis*-1-methyldecahydroquinoline (isolated as the picrate). Hydrogenation of XII over platinum oxide in ethanol solution did not proceed until hydrochloric acid was added to the solution. Then, three products were found after the system no longer absorbed hydrogen: phenylacetamide, 1-methyl-1,2,3,4-tetrahydroquinoline (isolated as the picrate) and 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII). We then turned to hydrogenation over palladium chloride on charcoal, since this catalyst would provide a trace amount of hydrochloric acid. The yield of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII) was thereby increased to 33%, but again cleavage was a side reaction, yielding phenylacetamide (27% isolated) and 1-methyl-1,2,3,4-tetrahydroquinoline (19%).[7] The substituted tetrahydroquinoline XIII formed a hydrochloride salt, from which it could be regenerated. This fact indicates the presence of the 2,3-double bond, as in XII, to be a necessary condition for facile C_4–C_α cleavage. 1-Methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII) was readily hydrogenated in ethanol containing hydrochloric acid, in the presence of platinum oxide, to give 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline (XIV), characterized by infrared spectrum and by picrate and hydrochloride derivatives. It was this product (XIV) which was compared and identified with a sample of 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline prepared by an unequivocal method.

4-(α-Cyanobenzyl)-quinoline (XV) was made by a modification of the method of Cutler, Surrey and Cloke[8] from 4-chloroquinoline and phenylacetonitrile, with sodium amide as the condensing agent. The nitrile XV was converted to the amide XVI[8] by treatment with concentrated sulfuric acid at 20°. The methiodide was formed and was converted to the methochloride XVII by boiling an aqueous solution of the methiodide with a large excess of silver chloride. 1-Methyl-4-(α-carbamylbenzyl)-quinolinium chloride (XVII) in ethanol was hydrogenated smoothly over platinum at 3 atmospheres and 20° to the decahydroquinoline XIV, identical with the product obtained by the other route (Va → XII → XVIII → XIV). The conjunction in XIV of the two paths of synthesis, one of them unequivocal, established the position of substitution of the α-cyanobenzyl group on the quinoline moiety as the 4-position, as had been assumed (Va) throughout the preceding discussion. The location of the double bond at the 2,3-(Va) rather than at the 3,4-position is preferred because it explains more satisfactorily the ease of C_4–C_α cleavage and is consistent with the infrared absorption data. Further evidence for the 2,3-location is available from the ultraviolet absorption spectrum of the condensation product (Va). The compound in 95% ethanol has absorption maxima at 312, 236, and 207 mμ, with intensities, log ϵ, 3.80, 4.47 and 4.34, respectively. These are comparable with the maxima observed for two compounds with known 2,3-unsaturation—1-methyl-4-nitromethylenequinolane: 279, 236 and 206 mμ[1]; 1,2-dicyano-1,4-dihydroquinoline: 308, 273 and 229 mμ.[9] It should be mentioned that structure Va represents two racemates, but apparently one of these was formed almost exclusively under the alkaline equilibrating conditions of the original condensation. It might also be pointed out that we depended upon the stereospecificity of the similar hydrogenation processes, XIII → XIV and XVII → XIV, to provide essentially the same racemate of XIV among those eight theoretically possible.



(7) The splitting of Va or XII into two fragments does not appear to be due to "hydrogenolysis" although the C_4–C_α bond is weakened because of its quadruple allylic position. Compounds with a multiple benzyl bond, such as pentaphenylethane, are cleaved by hydrogen under more drastic conditions (W. Zartman and H. Adkins, THIS JOURNAL, **54**, 1668 (1932)).

(8) R. A. Cutler, A. R. Surrey and J. B. Cloke, *ibid.*, **71**, 3375 (1949).

(9) M. G. Seeley, R. E. Yates and C. R. Noller, *ibid.*, **73**, 772 (1951).

Having established the structure of the condensation product obtained from 1-methylquinolinium iodide and phenylacetonitrile in the presence of sodium ethoxide, we investigated the products of similar condensation with homologs of phenylacetonitrile. α-Phenylpropionitrile and compound I gave 1-methyl-4-(α-cyano-α-methylbenzyl)-1,4-dihydroquinoline (Vb) in 80% yield. The ultraviolet absorption spectrum was similar to that of Va, with maxima at 313, 236 and 206 mμ, and log ε 3.65, 4.20 and 4.14, respectively. The infrared absorption spectrum of Vb was also similar to that of Va, with a nitrile band at 2240 cm.$^{-1}$ and a band at 1655 cm.$^{-1}$ attributable to the 2,3-double bond. Compound Vb was less light-sensitive than Va and was not readily converted to the corresponding amide. Picric acid in ethanol cleaved the C_4–C_α bond of 1-methyl-4-(α-cyano-α-methylbenzyl)-1,4-dihydroquinoline giving 1-methylquinolinium picrate. The structure was firmly established as Vb by the identity of the α-phenylpropionitrile condensation product with the compound obtained by treatment of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline (Va) with methyl iodide in the presence of sodium amide. 1-Methyl-4-(α-cyano-*p*-methylbenzyl)-1,4-dihydroquinoline (Vc) was obtained in 88% yield by the condensation of I with *p*-tolylacetonitrile in ethanol in the presence of sodium ethoxide. The product exhibited ultraviolet absorption maxima at 312, 236 and 213 mμ and log ε 3.82, 4.33 and 4.33, respectively, similar to those of Va and Vb. The isomer Vd was obtained in 59% yield under the same conditions with *o*-tolylacetonitrile.

Experimental[10]

1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline (Va).—A mixture of 27.1 g. (0.10 mole) of 1-methylquinolinium iodide, m.p. 146°, and 11.6 g. (0.10 mole) of phenylacetonitrile in 100 ml. of absolute ethanol was cooled in an ice-bath. A solution of sodium ethoxide prepared from 2.3 g. (0.10 gram atom) of sodium and 50 ml. of absolute ethanol was added with vigorous stirring. Stirring was continued for 5 hours, after which the solid which separated was collected on a filter. The average yield of the crude product in seven runs was 92%. Recrystallized from petroleum ether (b.p. 90–110°), the colorless prisms melted at 118–120° (Kaufmann[3] reported m.p. 122–125° (uncor.)).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.00; H, 6.24; N, 10.81.

When the compound was treated with picric acid in ethanol, a picrate formed which was recrystallized from ethanol as yellow elongated prisms, m.p. 168.5–169°, with decomposition. The melting point (Decker[11] reported m.p. 169.5°, with decomposition) and analysis indicated that the compound was **1-methylquinolinium picrate (VII).**

Anal. Calcd. for $C_{16}H_{12}N_4O_7$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.80; H, 3.32; N, 15.04.

Attempted Aromatization of 1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline.—A solution of 13.0 g. (0.05 mole) of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline and 5.4 g. (0.055 mole) of freshly fused potassium acetate in 100 ml. of absolute ethanol was heated to 80° and stirred while a solution of 12.7 g. (0.05 mole) of iodine in 120 ml. of ethanol was added during 45 minutes. Heating and stirring were continued for 1 hour. The mixture was cooled and the dark brown solid (A) which separated was removed by filtration. When ether was added to the ethanolic filtrate, yellow-orange needles were obtained which were recrystallized from ethanol–ether, m.p. 144–146°. Mixture with an authentic sample of 1-methylquinolinium iodide did not depress the melting point, and the infrared spectra of the two samples were identical. The analysis also indicated the product to be **1-methylquinolinium iodide** (I).

Anal. Calcd. for $C_{10}H_{10}NI$: C, 44.30; H, 3.72; N, 5.17. Found: C, 44.40; H, 3.64; N, 4.92.

The solid (A) was extracted with boiling water. The yellow needles which separated on cooling the filtered solution weighed 3.46 g. (27% on the basis of the established formula), m.p. 289–291°, with decomposition. The infrared spectrum showed no nitrile band. The compound gave an immediate precipitate with silver nitrate and had the composition requisite for an iodoquinoline methiodide, $C_{10}H_9NI_2$. The structure was further established (see below) as **1-methyl-3-iodoquinolinium iodide (X).**

Anal. Calcd. for $C_{10}H_9NI_2$: C, 30.25; H, 2.28; N, 3.53. Found: C, 30.21; H, 2.42; N, 3.57.

The iodoquinoline methiodide was pyrolyzed in a vacuum sublimation apparatus at 0.7 mm. pressure and a bath temperature up to 360°. The yield of iodoquinoline, collected on the cold finger, was 87%. It was purified by sublimation at 45–50° and 0.5 mm. pressure, followed by recrystallization from 55% ethanol; colorless needles, m.p. 61.5–62.5°. The analysis was satisfactory for a monoiodoquinoline, established as the **3-iodoquinoline** (see below).

Anal. Calcd. for C_9H_6NI: C, 42.38; H, 2.37; N, 5.49. Found: C, 42.56; H, 2.82; N, 5.77.

The methiodide was formed by warming the amine with excess methyl iodide in benzene solution. The yellow needles, m.p. 289–291°, with decomposition, appeared to be identical with the original iodoquinoline methiodide.

The picrate was formed in and recrystallized from ethanol, m.p. 188–188.5°.

3-Iodoquinoline (XI).[12]—To an ice-cold solution of 3.6 g. (0.025 mole) of 3-aminoquinoline (Eastman Kodak Co.) in 75 ml. of glacial acetic acid was added dropwise, with vigorous stirring, a solution of 1.7 g. (0.025 mole) of sodium nitrite in 7 ml. of water. To the red diazonium salt solution, stirred and kept at 0°, was added dropwise a solution of 20 g. of potassium iodide in 20 ml. of water. The temperature of the solution was then allowed to rise to 20°. The solution was made strongly basic by the addition of sodium hydroxide, and the product was isolated by steam-distillation. Recrystallization from 50% aqueous ethanol, with decolorization, gave colorless needles, m.p. 61–62°; yield 3.3 g. (52%). The authentic 3-iodoquinoline thus obtained did not depress the melting point of the iodoquinoline isolated as the methiodide from the attempted aromatization of Va (see above). The infrared spectra of the two samples were also identical. **The methiodide** prepared from the authentic 3-iodoquinoline melted at 288–290°, with decomposition, and did not depress the melting-decomposition point of the iodoquinoline methiodide described above. The authentic 3-iodoquinoline **picrate**, m.p. 188–188.5°, was also identical with the corresponding picrate of the same melting point.

Iodination of 1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline.—When the treatment of Va with iodine and potassium acetate in ethanol solution (quantities as described above) was carried out at 20°, a colorless solid was formed in quantitative yield. Recrystallization from ethanol gave colorless, hexagonal plates, m.p. 130–131.5°. The compound gave no precipitate with silver nitrate and had the composition calculated for **1-methyl-3-iodo-4-(α-cyanobenzyl)-1,4-dihydroquinoline (IX).**

Anal. Calcd. for $C_{18}H_{15}N_2I$: C, 55.97; H, 3.92; N, 7.26. Found: C, 56.25; H, 4.11; N, 7.34.

1-Methyl-4-(α-carbamylbenzyl)-1,4-dihydroquinoline (XII).—A solution of 10.67 g. (0.041 mole) of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline in 30 ml. of concentrated sulfuric acid (sp. gr. 1.84) was allowed to stand overnight at 20°. The acid solution was poured into ice-water containing an excess of ammonium hydroxide. The amide

(10) All melting points are corrected. The authors are indebted to Miss Elizabeth M. Petersen and Miss Helen Miklas for determination of the infrared absorption spectra, to Mr. Homer Birch for determination of the ultraviolet absorption spectra, and to Miss Emily Davis, Mrs. Jean Fortney and Mrs. Katherine Pih for the microanalyses.

(11) H. Decker, *Ber.*, **36**, 1205 (1903).

(12) The authors wish to thank Mr. Samuel Gelfand for preparing an authentic sample of 3-iodoquinoline and for other preparative assistance.

was collected on a filter, washed with distilled water, and dried. It was recrystallized from absolute ethanol as colorless prisms, m.p. 209–210°, yield 7.59 g. (67%).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.84; H, 6.55; N, 10.16.

When the compound was treated with picric acid in ethanol, a picrate formed which was recrystallized from ethanol as yellow elongated prisms, m.p. 169–170°, with decomposition. This picrate was shown by mixed melting point and infrared analysis to be **1-methylquinolinium picrate (VII)**.

Hydrogenation of 1-Methyl-4-(α-carbamylbenzyl)-1,4-dihydroquinoline (XII). 1. Glacial Acetic Acid.—A solution of 4.7 g. (0.017 mole) of 1-methyl-4-(α-carbamylbenzyl)-1,4-dihydroquinoline in 50 ml. of glacial acetic acid was hydrogenated at 3–4 atm. and 20° in the presence of 0.15 g. of platinum oxide during 12 hours. The catalyst was removed by filtration. The acetic acid solution was poured into ice-water and neutralized by the addition of concentrated ammonium hydroxide. The solid (A) which separated was collected and recrystallized from ethanol as colorless prisms, m.p. 205°; wt. 1.03 g. Identity with the starting material was established by mixed melting point and by infrared spectrum. The alkaline filtrate obtained after removal of the starting material was extracted with ether. The extracts were combined, dried, and the ether was removed. The residue was washed with small portions of ethanol (B), and the solid (C) which remained undissolved was purified by vacuum sublimation, m.p. 156–158°.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.77; H, 6.98; N, 10.35.

The melting point and elemental analysis were suggestive of **phenylacetamide**, and the compound showed no melting point depression when mixed with an authentic sample of phenylacetamide.

The ethanol washings (B) were diluted with water. An oil separated which formed a picrate, m.p. 197–199°; wt. 0.26 g.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.26; H, 5.98; N, 14.45.

The melting point and analysis of the **picrate** indicated that the oily product was probably *cis*-**1-methyldecahydroquinoline** (reported for *cis*-1-methyldecahydroquinoline picrate, m.p. 199–200°[13]).

2. Ethanol. a. Platinum Oxide.—Hydrogenation at 3–4 atm. and 20° of 4.0 g. (0.014 mole) of XII in 150 ml. of ethanol using 0.2 g. of platinum oxide was unsuccessful, even after 16 hours. However, when 1 ml. of concentrated hydrochloric acid and 0.1 g. additional of platinum oxide were added, hydrogen was absorbed immediately. There was no further drop in pressure after 2 hours. The catalyst was removed by filtration, and the filtrate, after concentration to 25 ml., was diluted with an equal volume of water and cooled in an ice-bath. The crystals which separated were collected on a filter and washed with small portions of ether (A). The solid (B) which remained on the filter was recrystallized once from water; yield, 0.69 g. (45%) of **phenylacetamide**, m.p. 156–158°. In the recrystallization from water, 0.18 g. of less water-soluble material (C) was obtained, m.p. 235–240°. Four recrystallizations from ethanol gave colorless prisms, m.p. 247–248°, which had the correct analysis for **1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII)**.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.09; H, 7.39; N, 9.91.

From the ether washings (A) of the phenylacetamide, by treatment with picric acid in ether, a picrate was obtained, m.p. 138–139°; wt. 0.18 g. Mixtures with the **picrate** of an authentic sample of **1-methyl-1,2,3,4-tetrahydroquinoline** gave no depression.

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.06; H, 4.29; N, 14.89. Found: C, 51.29; H, 4.55; N, 14.82.

2b. Palladium Chloride.—A solution of 4.0 g. (0.014 mole) of XII in 150 ml. of absolute ethanol was hydrogenated during 18 hours using 4.0 g. of palladium chloride on charcoal (equivalent to 5% palladium). The catalyst was removed by filtration and washed with ethanol. The combined filtrates were made slightly basic with a few drops of 4 *N* sodium hydroxide and then concentrated to 25 ml. The solid which separated was recrystallized from ethanol, m.p. 246–247°; yield 1.33 g. (33%) of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII). Further concentration of the mother liquor gave 0.53 g. (27%) of phenylacetamide, colorless leaflets from water, m.p. 156–158°. A picrate was formed from the final mother liquor diluted with ether; yield 1.04 g. (19%) of 1-methyl-1,2,3,4-tetrahydroquinoline picrate, yellow needles from ethanol, m.p. 138–139°.

The hydrochloride of XIII was formed by dissolution of the base in hydrochloric acid and evaporation of the solution to dryness, m.p. 221–223°.

Hydrogenation of 1-Methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline. 1-Methyl-4-(α-carbamylbenzyl)-decahydroquinoline (XIV).—A solution of 0.95 g. (0.0034 mole) of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline in 100 ml. of 95% ethanol made acid by adding a few drops of concentrated hydrochloric acid was hydrogenated during 8 hours at 3–4 atm. and 20° over 0.2 g. of platinum oxide. The solution was filtered and the filtrate evaporated to dryness. **The hydrochloride** was recrystallized from ethanol as colorless prisms, m.p. 327–329°; yield 0.72 g. (66%).

Anal. Calcd. for $C_{18}H_{27}N_2OCl$: C, 66.96; H, 8.43; N, 8.68. Found: C, 66.54; H, 8.58; N, 8.59.

The free base (XIV) was obtained by neutralizing an aqueous solution of the hydrochloride with ammonium hydroxide. The crude amine partially melted at 110–115° and as the temperature was raised appeared to resolidify, melting finally at 158–162°. Recrystallization from hexane gave colorless prisms, m.p. 155–162°, with the correct composition for **1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline.**

Anal. Calcd. for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.36; H, 9.33; N, 9.59.

The picrate of XIV was formed in dilute ethanol and recrystallized twice from water as yellow needles, m.p. 225–227°, with decomposition.

Anal. Calcd. for $C_{24}H_{29}N_5O_8$: C, 55.91; H, 5.67; N, 13.59. Found: C, 56.05; H, 5.87; N, 13.61.

4-(α-Cyanobenzyl)-quinoline (XV).—A modification of the method of Cutler, Surrey and Cloke[8] was used. Sodium amide was prepared by dissolving 2.53 g. (0.11 gram atom) of sodium in 100 ml. of liquid ammonia to which a crystal of ferric nitrate had been added. The solution was stirred until the blue color disappeared, and absolute ether was added to displace the ammonia. When the solution reached room temperature, a solution of 12.88 g. (0.11 mole) of phenylacetonitrile in 50 ml. of ether was added gradually with stirring. Then a solution of 8.18 g. (0.05 mole) of 4-chloroquinoline[14] in 20 ml. of ether was added dropwise, after which the reaction mixture was stirred for 30 minutes. Water (50 ml.) was added slowly. The red ether layer was separated and washed with water. The amine was extracted from the ether with four 50-ml. portions of 6 *N* hydrochloric acid. The acid solution was cooled in an ice-bath and neutralized with concentrated ammonium hydroxide. The solid which separated was collected, dried, and recrystallized from petroleum ether (b.p. 40–60°) as light yellow prisms, m.p. 88.5–90° (reported[8] 86–86.5°); yield 9.5 g. (78%).

4-(α-Carbamylbenzyl)-quinoline (XVI).—The compound was prepared from XV according to the directions of Cutler, Surrey and Cloke[8] and recrystallized from *n*-butanol as colorless prisms, m.p. 270° (reported[8] 267–268°); yield 93%.

1-Methyl-4-(α-carbamylbenzyl)-quinolinium Iodide.—An excess of methyl iodide was added to a hot solution of 3.1 g. (0.012 mole) of 1-methyl-4-(α-carbamylbenzyl)-quinoline (XVI) in dimethylformamide containing a few drops of benzyl alcohol. The methiodide crystallized when the solution was cooled, and was recrystallized from water as yellow elongated prisms, m.p. 256–257°; yield 4.4 g. (92%).

Anal. Calcd. for $C_{18}H_{17}N_2OI$: C, 53.48; H, 4.24; N, 6.93. Found: C, 53.38; H, 3.94; N, 7.02.

1-Methyl-4-(α-carbamylbenzyl)-quinolinium Chloride (XVII).—Silver chloride prepared from 3.4 g. of silver nitrate and excess hydrochloric acid was washed free of acid

(13) M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1715 (1934).

(14) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, THIS JOURNAL, **68**, 1264 (1946).

and added to a hot solution of 3.0 g. (0.0074 mole) of 1-methyl-4-(α-carbamylbenzyl)-quinolinium iodide in 200 ml. of water. The mixture was boiled for 30 minutes and then filtered to remove the silver chloride and iodide. The filtrate was evaporated to dryness. The residue was triturated with ethanol, giving 1.45 g. (63%) of colorless crystals which decomposed at approximately 177°. This material was used directly for catalytic hydrogenation.

Hydrogenation of 1-Methyl-4-(α-carbamylbenzyl)-quinolinium Chloride.—A solution of 1.0 g. (0.0032 mole) of XVII in 100 ml. of absolute ethanol was hydrogenated during 18 hours at 3–4 atm. and 20° using 0.3 g. of platinum oxide. The catalyst was removed by filtration, and the solution was concentrated to 15 ml. and cooled. The solid which separated was recrystallized from ethanol–ether as colorless prisms, m.p. 325–327°; yield 0.21 g. (21%) of 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline hydrochloride. Mixtures with the hydrochloride obtained from the hydrogenation of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII) gave no depression in melting point. The infrared spectra of the two hydrochlorides (in Nujol mulls) were identical.

The base was liberated from the hydrochloride by solution in water and addition of ammonium hydroxide. The precipitate was recrystallized from hexane as colorless prisms, m.p. 157–162°. The authentic 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline (XIV) had an infrared spectrum identical with that of the base obtained by catalytic reduction of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII). Their picrates, both m.p. 225–227°, with decomposition, were also identical.

1-Methyl-4-(α-cyano-α-methylbenzyl)-1,4-dihydroquinoline (Vb).—This compound was made by the same method used for its homolog Va, from equimolar amounts of 1-methylquinolinium iodide (I), α-phenylpropionitrile,[15] and sodium ethoxide in ethanol at 0°. The product was recrystallized from petroleum ether (b.p. 90–110°) as colorless needles, m.p. 132–133°; yield 80%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 82.92; H, 6.92; N, 10.19.

(15) S. Wideqvist, *Svensk. Kem. Tid.*, **55**, 125 (1943).

When the compound was heated with picric acid in ethanol, a picrate formed which was recrystallized from ethanol, m.p. 169–170°, and was shown to be 1-methylquinolinium picrate (VII).

Methylation of 1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline.—Sodium amide was prepared by adding 1.15 g. (0.05 gram atom) of sodium in small pieces to 75 ml. of liquid ammonia containing a crystal of ferric nitrate. The ammonia was displaced by the dropwise addition of 100 ml. of anhydrous ether. To the suspension of sodium amide at 20° was added 13.0 g. (0.05 mole) of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline. The suspension was stirred for 15 minutes, and 7.0 g. (0.05 mole) of methyl iodide in 30 ml. of anhydrous ether was added gradually. After the addition, stirring was continued for 15 minutes. The solid material was collected on a filter and leached with hot petroleum ether (b.p. 90–110°). The combined filtrates were evaporated, and the residue was recrystallized from petroleum ether as colorless needles, m.p. 130.5–131°. Mixtures with compound Vb obtained by condensation of I with α-phenylpropionitrile gave no melting point depression, and the infrared spectra of the two samples were identical.

1-Methyl-4-(α-cyano-*p*-methylbenzyl)-1,4-dihydroquinoline (Vc).—This compound was prepared by the same method as that used for Va and Vb, from equimolar quantities of 1-methylquinolinium iodide (I), *p*-tolylacetonitrile[16] and sodium ethoxide in ethanol at 0°. Recrystallized from petroleum ether, the colorless needles melted at 133–134°; yield 88%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.27; H, 6.85; N, 10.36.

1-Methyl-4-(α-cyano-*o*-methylbenzyl)-1,4-dihydroquinoline (Vd).—Prepared in like manner from *o*-tolylacetonitrile,[17] compound Vd was recrystallized from ether, colorless prisms, m.p. 96–97°; yield 59%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.30; H, 6.60; N, 10.23.

(16) A. F. Titley, *J. Chem. Soc.*, 508 (1926).

(17) M. S. Newman, THIS JOURNAL, **62**, 2295 (1940).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Some 1-(2-Thienyl)-2-N,N-disubstituted-aminoalkanols and Their Methyl Ethers

BY IRVING ALLAN KAYE, HOWARD C. KLEIN,[1] WILLIAM J. BURLANT AND IRVING C. KOGON

RECEIVED DECEMBER 3, 1951

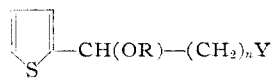
Several 1-(2-thienyl)-2-N,N-disubstituted-aminoethanols were prepared from 2-acetylthiophene without isolation of the bromo- or aminoketone intermediates. Although 1-piperidyl- and 4-morpholinylmethyl 2-thienyl ketones were stable to air and acids, di-*n*-butylaminomethyl 2-thienyl ketone could be prepared only in an inert atmosphere and decomposed in the presence of mineral acids. 1-Piperidylmethyl 2-thienyl ketone was recovered unchanged from a reaction with cyclohexylmagnesium bromide. Three aminoethers were obtained in low yield by the reaction of 2-thienylmagnesium bromide with dialkylaminoacetals.

Since aminoalkoxy and thienyl groups are each found in a number of substances which exhibit marked pharmacological activity, several 1-(2-thienyl)-2-N,N-disubstituted-aminoethanols (IA-D) and their methyl ethers (IE-G), as well as 1-(2-thienyl)-3-(4-morpholinyl)-propanol (IH) were prepared for therapeutic evaluation. Although compounds of this type are covered by a patent,[2] none have been described. A similar group of 3-amino-1,1-di-(2-thienyl)-alkan-1-ols has recently been shown to include some powerful antispasmodic and local anesthetic agents.[3]

(1) Part of this communication is taken from a thesis submitted by H. C. Klein to the Graduate Faculty of Brooklyn College, January, 1949, in partial fulfillment of the requirements for the M.A. Degree.

(2) G. J. Van Zoeren, U. S. Patent 2,367,702 (January 23, 1945).

(3) D. W. Adamson, *J. Chem. Soc.*, 885 (1950).



(IA–H)

(A) Y = diethylamino; R = H; n = 1
(B) Y = di-*n*-butylamino; R = H; n = 1
(C) Y = 1-piperidyl; R = H; n = 1
(D) Y = 4-morpholinyl; R = H; n = 1
(E) Y = diethylamino; R = CH_3; n = 1
(F) Y = di-*n*-propylamino; R = CH_3; n = 1
(G) Y = di-*n*-butylamino; R = CH_3; n = 1
(H) Y = 4-morpholinyl; R = H; n = 2

The aminoethanols (IA-D) were prepared by aluminum isopropoxide reduction of the corresponding ketones, which in turn were formed by condensing secondary amines with 2-bromoacetylthiophene. Initial attempts to prepare one of these