1,2-Di-(3-pyridyl)-1,2-diphenylethane-1,2-diol.—A 5.0-g. (0.027 mole) sample of phenyl 3-pyridyl ketone[8] was dissolved in 50 ml. of 2-propanol contained in an 8-inch test-tube. After adding one drop of acetic acid, the tube was sealed in a flame and exposed to direct sunlight for one month. The tube was then opened and the white crystals which had deposited were separated by filtration and washed with alcohol. The resulting 3.4 g. (68%) of pinacol was sufficiently pure to be used directly for rearrangement. For analysis, a small sample was recrystallized from dioxane. The pinacol was only very slightly soluble in this solvent at the boiling point, but precipitated from the cooled solution after standing overnight. The pure pinacol melted at 187–188°.

Anal. Calcd. for $C_{24}H_{20}O_2N_2$: C, 78.23; H, 5.48; N, 7.61. Found: C, 77.92; H, 5.46; N, 7.55.

The pinacol was sparingly soluble in all the ordinary organic solvents with the exception of hot pyridine. It did not darken after prolonged storage.

Rearrangement of 1,2-Di-(3-pyridyl)-1,2-diphenylethane-1,2-diol and Scission of the Pinacolone.—The procedure used was exactly the same as that used for the 2-isomer, except that scission was effected by refluxing with a solution of 25 g. of potassium hydroxide in 100 ml. of methanol.

The 1.52-g. (62%) yield of crude 3-pyridyldiphenylmethane was recrystallized several times from petroleum ether (b.p. 60–70°) to furnish white crystals melting at 75.5–77°. There was no depression in m.p. when this material was mixed with an authentic sample of 3-pyridyldiphenylmethane.[8]

Once again no benzoic acid could be extracted from the acidified aqueous layer. Potentiometric titration of the latter, however, showed the consumption of 0.0079 mole of standard base between the two characteristic points of inflection of the curve at *p*H 3.4 and 8.5. This indicated a 79% yield of nicotinic acid. The pK_a calculated from the curve agreed within experimental error with that given for nicotinic acid.

(8) H. E. French and K. Sears, THIS JOURNAL, **73**, 469 (1951).

Phenyl 4-Pyridyl Ketone (Experiment by A. R. Casola).—A 41-g. (0.33 mole) sample of isonicotinic acid, m.p. 309°, was refluxed with 100 ml. of thionyl chloride for 20 hours. Most of the excess thionyl chloride was removed from the dark reaction mixture *in vacuo* and the residue was dissolved in a mixture of 90 ml. (1.0 mole) of dry benzene and 250 ml. of dry carbon disulfide. The solution was refluxed with stirring and 89 g. (0.67 mole) of aluminum chloride was added cautiously in small portions. Heating and stirring were continued for six hours, after which the mixture was cooled and hydrolyzed by pouring onto cracked ice. The entire mass was then subjected to distillation with steam. The residue from the steam distillation was cooled, made basic with 50% sodium hydroxide solution and extracted with 800 ml. of ether used in three portions. The combined extracts were dried over potassium hydroxide, the solvent removed and the residue distilled, b.p. 312–322°. The 40 g. (66%) of pale pink solid was recrystallized from petroleum ether to furnish phenyl 4-pyridyl ketone melting at 72–75°. A mixed m.p. with an authentic sample[9] showed no depression.

Phenyl-4-pyridylcarbinol.—A 5.0-g. (0.029 mole) portion of phenyl 4-pyridyl ketone was dissolved in 50 ml. of 2-propanol contained in an 8-inch test-tube. A drop of acetic acid was added, the tube was sealed in a flame and exposed to direct sunlight for two months. By this time, a few crystals had deposited on the walls of the tube. The tube was opened, the solution evaporated to a small volume in a steam-bath, cooled and the resulting crystals separated by filtration and washed with small amounts of 2-propanol. The product which weighed 3.6 g. (77%) melted at 123–125°. The melting point of a mixture of this substance with an authentic sample of phenyl-4-pyridylcarbinol[10] showed no depression.

(9) P. C. Teague, *ibid.*, **69**, 714 (1947).

(10) A. E. Chichibabin, *Ber.*, **37**, 1370 (1904).

NEW YORK, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Mechanism of the Reaction of Chloralquinaldine with Alkali[1]

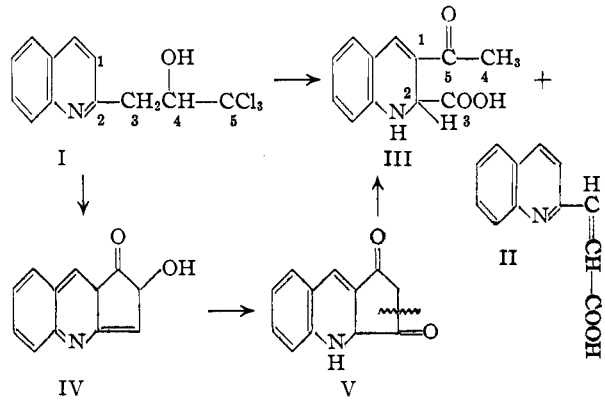
BY WILLIAM G. DAUBEN AND C. WHEATON VAUGHAN, JR.

RECEIVED MAY 23, 1953

Chloralquinaldine (I) when treated with aqueous alcoholic alkali forms in addition to the expected quinolylacrylic acid (II) a rearrangement product, 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid (III). This rearrangement has been investigated utilizing chloralquinaldine specifically labeled with carbon-14, and the mechanisms by which the reaction may proceed are discussed on the basis of the results obtained.

The reaction of chloralquinaldine (I) with aqueous alcoholic alkali forms two products, the expected quinolylacrylic acid (II) and a rearranged material[2] recently identified as 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid[3] (III). It is evident that in the latter a deep-seated rearrangement has taken place, in which not only have two carbon atoms been transferred from the two to the three position of the heterocyclic nucleus, but also the 1,2-dihydro derivative has been formed with corresponding loss of resonance energy.

Woodward and Kornfeld[3] have postulated a mechanism sequence for this rearrangement. They viewed the reaction as involving the removal of an acidic hydrogen from the methylene group of the side chain to form a carbanion, the negative charge of which, available by resonance at the three position of the nucleus, might permit attack on the trichloromethyl group with the loss of chloride ion and formation of the cyclic intermediate IV. A series of steps involving dehydration, hydration



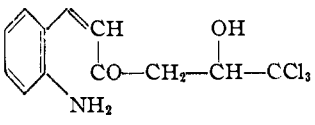
(1) Presented before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, September, 1952.

(2) (a) A. Einhorn, *Ber.*, **19**, 904 (1886); *cf.* also A. Einhorn and P. Sherman, *Ann.*, **287**, 38 (1895); (b) W. Borsche and R. Manteuffel, *ibid.*, **526**, 22 (1936).

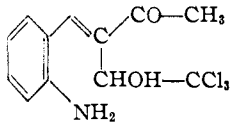
(3) R. B. Woodward and E. C. Kornfeld, THIS JOURNAL, **70**, 2508 (1948).

and prototropic change would then lead to the cyclic intermediate V, which by hydrolysis could open to the rearranged product (III).

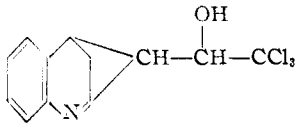
Brown, Hammick and Robinson[4] have disagreed with this hypothesis, suggesting instead a mechanism which involves the hydrolysis of the C=N bond (VI) and transfer to the resulting *o*-aminobenzylidene group from the one to the three position of the pentanone chain (VII). Two intermediates



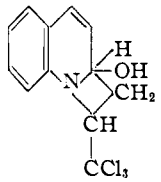
VI



VII



VIII



IX

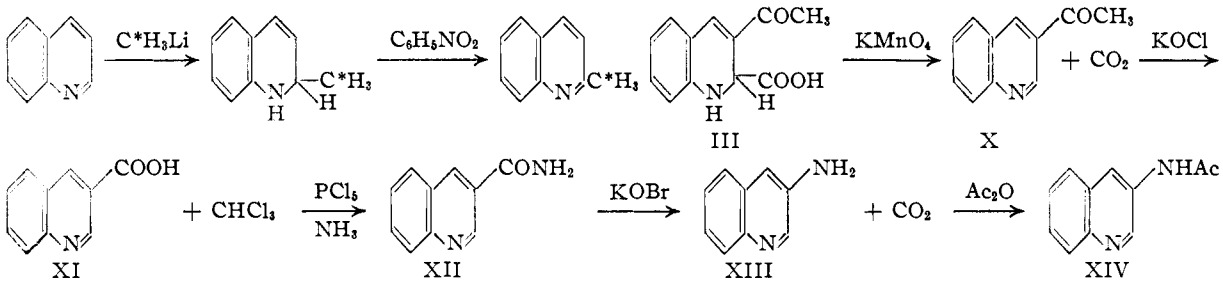
proposed to account for such a conversion are VIII and IX. As a basis for this suggestion they have shown that 2,3-dimethylquinolinechloral undergoes rearrangement in low yield to form a product which, although not isolated, upon oxidation formed 3-propionylquinoline.

Since these mechanisms fundamentally differ in the relative positions occupied by the atoms in the rearranged products as compared with the starting material, they may be distinguished by experiments in which a specific critical carbon atom is labeled with C^{14}. The synthesis of methylene-labeled chloralquinaldine was carried out by the addition of methyllithium-C^{14} across the C=N bond of quinoline, followed by hydrolysis and oxidation of the resulting 1,2-dihydroquinaldine. Base-catalyzed condensation with chloral then forms the specifically labeled I (carbon atom 3, as designated in diagram above).

Rearrangement, followed by oxidation of the resulting III-sodium salt with aqueous potassium permanganate at 0° formed 3-acetylquinoline (X), the carbon of the carboxyl group being lost as carbon dioxide. The carboxyl carbon obtained in this way was found not to be radioactive; the ketone exhibited the calculated specific activity. Since the methylene carbon atom is predicted by Woodward and Kornfeld to form the carboxyl group of III, the rearrangement does not proceed by this mechanism.

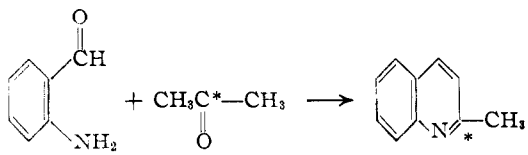
Further neutral permanganate oxidation[2b] under more vigorous conditions failed to oxidize specifically the methyl ketone, resulting instead in a mixture of products from which quinoline-3-carboxylic acid (XI) could not be isolated. Similarly, hypoiodite oxidation failed to produce a clean reaction, and, in general, only 50% of the theoretical amount of iodoform was obtained. Reaction of X with an aqueous solution of potassium hypochlorite, however, was found to afford satisfactorily the methyl group as chloroform with the formation of XI. The chloroform, counted as barium carbonate, showed negligible activity. The specific activity of the acid moiety, measured after conversion to the amide (XII), agreed with the calculated value.

When XII was treated with aqueous potassium hypobromite a Hofmann rearrangement took place, affording the carboxyl carbon atom as carbon dioxide with the formation of 3-aminoquinoline (XIII). The carboxyl carbon was found to be inactive. Since XIII had been found to decompose slowly in air, it was converted at once to the acetyl derivative (XIV) which displayed the correct specific activity. The synthetic and degradative sequence may be represented by the scheme



Thus, the radioactive carbon, originally positioned in the methylene group of the side chain, is found to rearrange into the aromatic nucleus itself. Because of the inherent difficulties involved in the selective degradation of the aromatic system and the limited amount of XIII available, it was decided that a greater amount of information might be gained by examination of rearranged material which had been labeled originally in a position predicted to migrate outside the aromatic system. The carbon chosen was in the 2-position of the aromatic nucleus, which would provide a study of the migration undergone by two atoms in adjacent positions.

The synthesis of the quinaldine was accomplished by the base-catalyzed condensation of *o*-aminobenzaldehyde with carbonyl labeled acetone, prepared by the pyrolysis of carboxyl-labeled acetates, in ethanol as a solvent. Condensation with chloral as before formed I, which was allowed to rearrange in base.

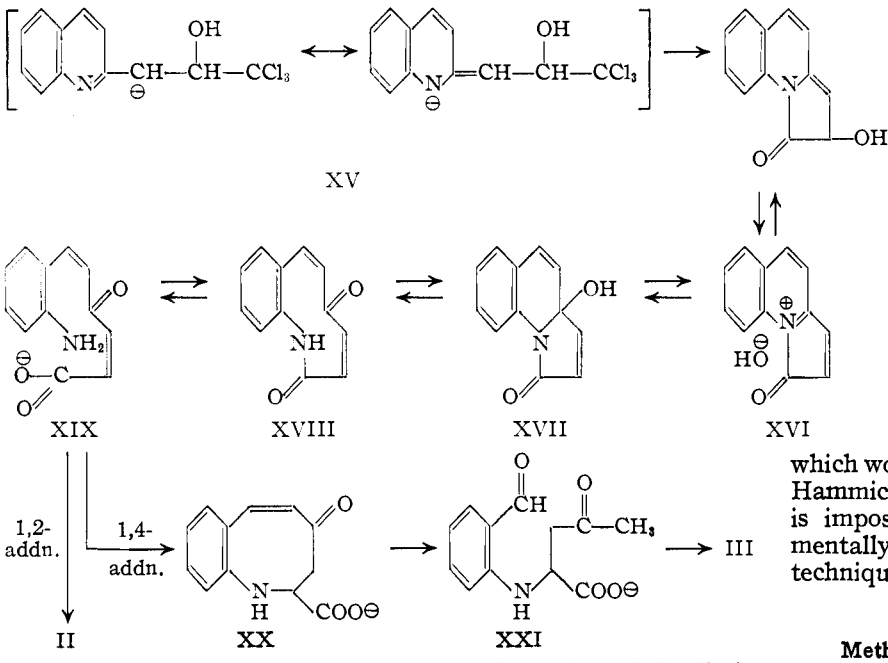


Degradation of the side chains as above revealed

(4) B. R. Brown, D. L. Hammick and R. Robinson, *J. Chem. Soc.* 780 (1950).

the carboxyl and methyl groups were devoid of activity. In this instance, however, carbon dioxide from the Hofmann oxidation was found to contain all of the radioactivity of the molecule, the remaining fragment (XIII) being inactive.

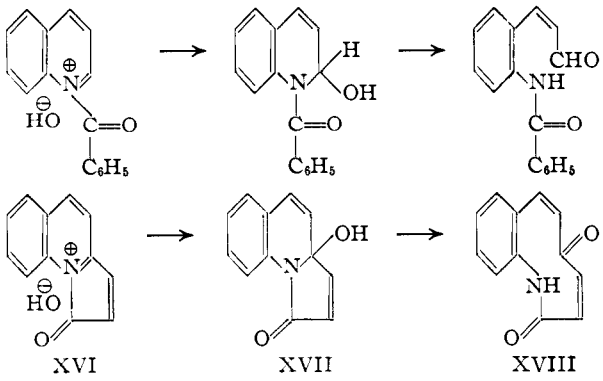
This distribution of activity is precisely that which would be expected on the basis of the mechanisms proposed by Brown, Hammick and Robinson.[4] However, their discussion of the possible intermediates by which this change might occur is only of the most general nature, and it is not felt that such mechanisms represent the most probable course of the reaction. Rather, it seems more likely that the reaction follows the route indicated



Initially, the base removes a proton from the active methylene carbon, forming the hybrid anion (XV). A nucleophilic displacement of chloride ion with the formation of a pyrrolidine ring system may then occur. It may be seen that the resulting molecule is a vinylog of a carbinol amide and will therefore be in equilibrium with the tautomeric forms, the quaternary hydroxide (XVI) and pseudo base (XVII), which may ring open by hydrolytic cleavage to give rise to XVIII. Further hydrolysis of the cyclic amide linkage forms the open-chain intermediate (XIX). The amino group may add to the unsaturated carbonyl system either by a simple 1,2-addition to the carbonyl group affording the quinolylacrylic acid (II),[5] the main reaction product, or by a 1,4-Michael type addition resulting in the formation of XX. This intermediate is the cyclic condensation product of an *o*-aminobenzaldehyde derivative with a ketone and would be in equilibrium with the product obtained by a reverse aldol condensation (XXI).[6] Ring closure on the methylene carbon adjacent to the carbonyl group, then, would form the rearrangement product observed.

An excellent analogy for the primary stages of this series is the reaction undergone by quinoline when subjected to Schotten–Baumann conditions.[7] The nitrogen atom is first acylated, and the resulting quaternary hydroxide, proceeding through the pseudo-base, ring opens to form the aldehyde. The comparison to the rearrangement of I is precise, the quaternary hydroxide (XVI) ring opening through the pseudo-base (XVII) to the ketone (XVIII).

Since, however, the carbon skeleton resulting from the mechanism described above is the same as that which would be formed by the Brown, Hammick and Robinson sequence, it is impossible to distinguish experimentally between them by tracer techniques.



Experimental[8]

Methyl-labeled Quinaldine.—Methyl iodide-C^{14} (0.15 g., 1.06 mc.) was diluted with approximately 55 g. (0.387 mole) of methyl iodide and the diluted material allowed to react with lithium wire (22.6 g., 3.26 moles) in the usual manner. Aliquots of the filtered ethereal solution were added to water and titrated with standardized hydrochloric acid to determine the yield of methyllithium (65%). Quinoline (35.03 g., 0.272 mole) in 100 ml. of dry ether was added in the course of one hour at room temperature to the stirred methyllithium solution and the resulting mixture hydrolyzed with 200 ml. of water. The ether layer was separated, dried over magnesium sulfate and the solvent distilled.

The residual 1,2-dihydroquinaldine without further purification was oxidized to quinaldine by refluxing with 178 g. (a fivefold excess) of nitrobenzene for 20 minutes. The water was removed as formed. The mixture was diluted with 200 ml. of ether and extracted with 3 100-ml. portions of 3 *N* hydrochloric acid. The acidic solution was made basic with potassium hydroxide pellets while cooled in an ice-bath. The amine was extracted with 3 200-ml. portions of ether, dried and distilled through a Podbielniak Helipak

(5) Such a mechanism, however, is not essential for the formation of the non-rearranged material, since direct hydrolysis and elimination would also afford II.

(6) The reverse aldol followed by condensation to form a six-membered ring might be expected in view of the strain inherent in the eight-membered ring.

(7) K. V. Sidgwick, T. W. J. Taylor and W. Baker, "Organic Chemistry of Nitrogen," Oxford University Press, London, 1942, p. 550.

(8) Quantitative elementary analysis and oxidation of C^{14}-labeled materials to carbon dioxide were performed by the Microanalytical Laboratory of the Department of Chemistry, University of California. All melting points are corrected. All boiling points are uncorrected. All reagents in the degradative procedure were carbon dioxide free.

TABLE I

SPECIFIC ACTIVITIES OF DEGRADATION PRODUCTS FROM METHYLENE-LABELED CHLORALQUINALDINE

Substance	Wt. sample, mg.	Obsd. ct./min.[a]	Ct./min. mg. C
Chloralquinaldine (I)	11.0	959	25,600[b]
	14.8	1131	25,300
3-Acetyl-1,2-dihydroquinoline-2-carboxylic acid (III)	13.2	928	22,200
	14.4	984	22,500
CO_2 from the decarboxylation of III	14.5	45.4	85.7
3-Acetylquinoline (X)	16.3	1165	22,700
	15.2	1133	22,900
CO_2 from chloroform	7.7	59.2	167[c]
Quinoline-3-carboxamide (XII)	8.0	813	22,300
	11.9	1057	22,300
CO_2 from Hofmann reaction	19.5	74.8	121
3-Aminoquinoline (XIII)	13.6	1121	19,700[e]
	18.6	1361	20,300
3-Acetylaminoquinoline (XIV)	13.9	1041	22,100

TABLE II

SPECIFIC ACTIVITIES OF DEGRADATION PRODUCTS FROM RING-LABELED CHLORALQUINALDINE

Substance	Wt. sample, mg.	Obsd. ct./min.[a]	Ct./min. mg. C
Chloralquinaldine (I)	15.8	549	11,800[b]
	16.1	545	11,600
3-Acetyl-1,2-dihydroquinoline-2-carboxylic acid (III)			
CO_2 from the decarboxylation of III	13.4	4	6
3-Acetylquinoline (X)	19.4	626	11,200
	18.8	615	11,100
CO_2 from chloroform	13.3	0	0
Quinoline-3-carboxamide (XII)	18.1	655	11,100
	17.2	694	11,400
CO_2 from Hofmann reaction	22.0	1507[d]	10,700
	19.2	1431	10,800
3-Aminoquinoline (XIII)			
3-Acetylaminoquinoline (XIV)	15.1	0	0
	18.1	0	0

[a] Corrected for background. [b] The specific activity of I is found to be 5–10% above the relatively constant (within experimental error) value observed for the other compounds of the series in both instances. That this result is indeed spurious is shown by the activity of the rearranged material (III) which is in agreement with the other values. It is thought that the anomaly may be caused by the reversal of the chloralquinaldine condensation during analyses with the formation of trichloroacetic acid. [c] Experiments in the ring-label series have demonstrated that contamination of inactive chloroform occurs to the extent of 1% in small scale determinations. [d] Barium carbonate diluted by a factor of 4.60 before counting. [e] Spurious values caused by decomposition of XII in air. The stable acetate derivative demonstrates the correct specific activity.

column. After a small forerun (4.24 g.), the main fraction was collected, b.p. 116–120° (15 mm.), yield 41.7 g. A small amount of quinaldine (10 g.) was added to the pot residue and distilled to minimize loss of activity in the column hold-up.

Carbonyl-labeled Acetone.—Carboxyl labeled sodium acetate (0.058 g., 1.12 mc., 0.7 mmole) was diluted with anhydrous sodium acetate (0.973 g., 11.7 mmoles) and dissolved in 50 ml. of water. *p*-Toluenesulfonic acid (3.07 g., 17.9 mmoles) was added and the solution was distilled until crystals were observed in the residue. Two 25-ml. portions of water were successively added and distilled, and the total distillate was titrated with 0.18 *N* barium hydroxide solution to a phenolphthalein end-point to determine the amount of acetic acid obtained (99.2%). The aqueous barium acetate solution was then evaporated to dryness, and the anhydrous salt obtained was pyrolyzed at 500° *in vacuo* to form carbonyl-labeled acetone.[9]

Quinaldine-2-C^{14}.—*o*-Aminobenzaldehyde[10] (3.098 g., 0.0248 mole) was dissolved in 400 ml. of 95% ethanol. The ampoule containing radioactive acetone was broken under the surface of the magnetically stirred solution to which was then added 5 g. (0.22 mole) of metallic sodium dissolved in 100 ml. of 95% ethanol.

The reaction mixture was allowed to stir at room temperature for 48 hours, at which time the ethanol solution was acidified with concentrated hydrochloric acid. The solvent then was removed under a Vigreux column and 50 ml. of 1 *N* sodium hydroxide solution added to generate the amine from the hydrochloride salt. The aqueous solution was extracted with ether and the extract dried over anhydrous magnesium sulfate. Quinaldine (80 g.) then was added to dilute the radioactive material and the mixture distilled, b.p. 119–121° (16 mm.), yield 74.5 g.

Chloralquinaldine-C^{14}.—Quinaldine-C^{14} (48.5 g., 0.339 mole), anhydrous chloral (52.5 g., 0.356 mole) and anhydrous pyridine (49.7 g.) were allowed to react according to the procedure of Bachman.[11] It was found that if the temperature was allowed to rise above 100°, undesirable side reactions occurred with consequent loss in yield. The crude material was recrystallized from methylene chloride–hexane, m.p. 147.1–148.0°, yield 69 g. (70%).

Anal. Calcd. for $C_{12}H_{10}ONCl_3$: C, 49.59; H, 3.48; N, 4.82; Cl, 36.60. Found: C, 49.75; H, 3.62; N, 4.83; Cl, 36.63

C^{14}-Labeled 3-Acetyl-1,2-dihydroquinoline-2-carboxylic Acid Sodium Salt.—The reaction of chloralquinaldine with aqueous alcoholic alkali and the isolation of the rearrangement product was conducted in a manner similar to the procedure described by Einhorn.[2] Chloralquinaldine (10.0 g., 0.0343 mole) was dissolved in 35 ml. of refluxing 99% ethanol in a two-liter flask equipped with a reflux condenser. The solid was precipitated by addition of 40 ml. of water and then 35 g. of 23% sodium hydroxide was added as rapidly as possible. The subsequent reaction was immediate and violent and would have resulted in a loss of material through the condenser if an oversize flask were not employed. The reaction was over in a matter of seconds; nevertheless, reflux was continued for an additional 5 minutes. At the end of the heating period the temperature was lowered by removal of approximately one-half of the solvent under reduced pressure and then an additional 50 ml. of 99% ethanol put in. The solution was cooled to −40° for several hours, the bright orange crystals of the sodium salt filtered and air-dried, yield 3.8 g. (38%).

C^{14}-Labeled 3-Acetylquinoline.—The carboxyl carbon atom of 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid was obtained by oxidative decarboxylation of the sodium salt. A 2% aqueous potassium permanganate solution (20 ml.) was added dropwise at 0° under a nitrogen atmosphere to 1.0 g. (3.41 mmoles) of the sodium salt trihydrate (III) dissolved in 80 ml. of water. The reaction mixture was transferred by pipet to a nitrogen-filled centrifuge bottle and the manganese dioxide centrifuged and washed with 25 ml. of water. To the combined supernatants in a nitrogen-swept carbon dioxide collection train containing a reflux condenser was added 5 ml. of 6 *N* sulfuric acid, and the solution was heated under reflux for 30 minutes. The carbon dioxide evolved was collected in a bubble-tower containing a fourfold excess of 1 *N* sodium hydroxide (35 ml.) diluted to a total volume of 150 ml. At the end of the sweeping period the solution was buffered with 70 ml. of 1 *N* ammonium chloride solution and the barium carbonate precipitated by the addition of 70 ml. of 2 *N* barium chloride. The precipitate was washed successively with water, alcohol and ether, yield 0.571 g. (85%).

The aqueous solution containing the amine salt was made basic with 5 ml. of 6 *N* sodium hydroxide and extracted with methylene chloride. The 3-acetylquinoline was recrystallized from methylene chloride–hexane, yield 0.35 g. (60%), m.p. 99.2–99.6°.

(9) A. V. Grosse and S. Weinhouse, *Science*, **104**, 402 (1946).

(10) L. I. Smith and J. W. Opie, "Organic Syntheses," Vol. 28, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 11.

(11) A. A. Alberts and G. B. Bachman, THIS JOURNAL, **57**, 1284 (1935).

Anal. Calcd. for $C_{11}H_9ON$: C, 77.21; H, 5.31; N, 8.18. Found: C, 77.43; H, 5.05; N, 8.17.

C^{14}-Labeled Quinoline-3-carboxylic Acid.—Oxidation with potassium hypochlorite was used to obtain the activity of the methyl group of the above ketone. The hypochlorite solution was prepared by adding a warm solution of 0.30 g. of potassium carbonate and 0.105 g. of potassium hydroxide in 1.4 ml. of water to 0.427 g. of commercial HTH partially dissolved in 1.7 ml. of water. The calcium carbonate was filtered and to the magnetically stirred filtrate was added 200 mg. (1.17 mmoles) of 3-acetylquinoline. In 15 minutes the reaction was complete and the mixture was heated to 70° with a nitrogen sweep. The evolved chloroform was collected in a cold-trap at −70°.

The excess hypochlorite was destroyed with 20% sodium bisulfite (until a negative test with starch–iodide paper was obtained) and the solution acidified with glacial acetic acid. The precipitate of quinoline-3-carboxylic acid was centrifuged, washed and recrystallized from glacial acetic acid. A white, micro-crystalline product was obtained, m.p. 272–275°, yield 160 mg. (79%).

The acid was converted into its amide by grinding 125 mg. (0.723 mmole) of it with 150 mg. of phosphorus pentachloride in a glass-stoppered vial. The mixture was heated on a steam-bath for one hour. The acid chloride was then added in portions to 5 ml. of concentrated ammonium hydroxide at 0° and allowed to stand for one hour. The crude amide was recrystallized from water to give slender, white needles, m.p. 197.5–198.5°, yield 70 mg. (57%).

Anal. Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.69; N, 16.27. Found: C, 69.47; H, 4.63; N, 16.49.

C^{14}-Labeled 3-Aminoquinoline.—Quinoline-3-carboxamide (70 mg., 0.407 mmole) was added in one portion to a magnetically stirred solution consisting of 65 mg. of bromine (0.021 ml., 0.41 mmole), potassium hydroxide (0.3 g., 5.36 mmoles) and 6 ml. of water. The solution was stirred for 10 minutes by which time almost all of the amide had dissolved. The reaction mixture was then heated to 70° for 15 minutes, acidified with glacial acetic acid and the evolved carbon dioxide collected.

The aqueous solution containing the amine salt was made basic with sodium hydroxide and extracted with methylene chloride. The solvent was evaporated and the residue recrystallized from toluene, m.p. 81–82°, yield 43.4 mg. (74%).

3-Acetylaminoquinoline.—Since the amine was observed to decompose slowly in air, the acetyl derivative was used for activity determinations. 3-Aminoquinoline (0.301 g., 2.09 mmoles) was allowed to reflux for five minutes with 0.3 ml. of acetic anhydride, to which a catalytic amount of sodium acetate had been added, and the mixture was hydrolyzed with 50 ml. of water. The viscous black reaction mixture was instantly converted upon hydrolysis to a white micro-crystalline solid, which was recrystallized twice from water (charcoal), m.p. 166.2–167°, yield 0.292 g. (75%).

Anal. Calcd. for $C_{11}H_{10}ON_2$: C, 70.94; H, 5.42; N, 15.05. Found: C, 70.90; H, 5.51; N, 15.07.

Radioactivity Determinations.—All C^{14}-compounds were oxidized under reduced pressure with the oxidation mixture of Van Slyke and Folch,[12] the carbon dioxide collected in sodium hydroxide solution and precipitated in the usual fashion. The activity was determined with thin uniform layers of barium carbonate, using a thin mica-windowed Geiger–Mueller tube.[13] To correct for the dilution of the activity of a specific carbon in the compound, the observed activity obtained when the compound was combusted is always multiplied by the total number of carbon atoms in the molecule.

(12) D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 309 (1940).

(13) W. G. Dauben, J. C. Reid and P. E. Yankwich, *Anal. Chem.*, **19**, 828 (1947).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF TENNESSEE]

Syntheses of Some 2-Thiocyanoimidazoles[1]

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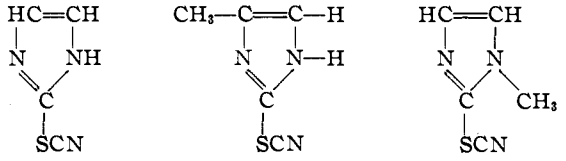
Several 2-thiocyanoimidazoles have been prepared from the corresponding mercaptoimidazoles and cyanogen bromide. Best results were obtained when the reactants were mixed in the solid state. No evidence was found for thiocyanation of imidazoles by treatment with thiocyanogen.

Thiocyano derivatives of imidazoles were desired for biological studies of this Laboratory. Such compounds have not been reported.

Since direct thiocyanation of imidazoles did not prove successful, cyanation of mercaptoimidazoles was resorted to.

Abramovitch[2] has prepared aliphatic thiocyanates by interaction of mercaptans and cyanogen halides in the presence of alkali and suitable solvents. Using a modification of this method, 2-thiocyanoimidazole (I) has been obtained in good yield from 2-mercaptoimidazole and cyanogen bromide. Efforts to convert 4(5)-methyl-2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole to the corresponding thiocyano compounds II and III by this procedure met with limited success. Although the desired products were likely produced, pure crystalline compounds were not isolated from the reaction mixtures.

Elimination of the use of alkali and solvents resulted in a procedure for synthesizing 2-thiocyanoimidazoles in pure crystalline form and satisfactory yield. The method involved the thorough mixing of solid cyanogen bromide and the mercaptoimidazole with subsequent gentle heating. The hydrobromide of the desired thiocyano compound was produced, from which the free base was readily isolated. In this manner 2-thiocyano-4(5)-methyl-2-thiocyano- and 1-methyl-2-thiocyanoimidazole have been prepared. In preliminary studies it was found that benzyl mercaptan was converted to benzyl thiocyanate by direct interaction of cyanogen bromide.



I II III

The thiocyanoimidazoles are relatively unstable. On standing at room temperature the colorless crystals gradually turn yellow. However, 2-thiocyanoimidazole, when suspended in chloroform, is stable at room temperature for several months.

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(2) B. Abramovitch, U. S. Patent 2,486,090, Oct. 25, 1949; *C. A.*, **44**, 2018 (1950).