The **N-benzoyl derivative** was prepared by the Schotten-Baumann reaction; m. p. 103.5–104.5°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 69.0; H, 6.1. Found: C, 69.2; H, 6.1.

γ-(3,4-Dimethoxyphenyl) γ-Hydroxypropylamine.—The reduction from ketone to alcohol and the subsequent operations were carried out as previously described. The oil, remaining after treatment with ether to remove unchanged ketoamine, could not be crystallized. An oxalate was obtained, however, by dissolving the oil in absolute alcohol and adding an alcoholic solution of oxalic acid. The resulting precipitate was recrystallized from alcohol; m. p. 185–186° (dec.).

Anal. Calcd. for $C_{24}H_{36}O_{10}N_2$: C, 56.3; H, 7.0. Found: C, 56.2; H, 7.1.

N-Benzoyl Derivative.—This derivative was prepared by the Schotten-Baumann reaction and was recrystallized from alcohol and water; m. p. 113°.

Anal. Calcd. for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.7. Found: C, 68.6; H, 6.8.

3,4-Dihydroxy-β-aminopropiophenone Hydrochloride.—This compound was prepared by demethylation of the corresponding methoxy compound in a manner already described. The product was recrystallized from water; m. p. 240° (dec.).

The **tribenzoyl derivative** was prepared in the usual manner and recrystallized with difficulty from alcohol and water; m. p. 146–147°.

Anal. Calcd. for $C_{30}H_{23}O_6N$: C, 73.0; H, 4.7. Found: C, 72.7; H, 4.6.

The **N,N-diphenylcarbamyl derivative** was prepared in a manner similar to that for the 4-hydroxy compound. On recrystallization from alcohol the compound melted at 89–90°.

Anal. Calcd. for $C_{48}H_{38}N_4O_6$: C, 75.2; H, 5.0. Found: C, 75.3; H, 5.2.

γ-(3,4-Dihydroxyphenyl) γ-Hydroxypropylamine.—The corresponding ketone was reduced as previously described. The glass obtained by evaporation of the reduced solution was partially purified by treatment with alcohol in which the ketoamine hydrochloride was insoluble. The hydrochloride of the amino-alcohol could not be isolated.

Tetra-(N,N-diphenylcarbamyl) Derivative.—This derivative was prepared by a method previously described. The compound was recrystallized from butyl and ethyl alcohols; m. p. 145° (dec.).

Anal.[10] Calcd. for $C_{61}H_{49}O_7N_5$: C, 76.0; H, 5.1. Found: C, 75.7; H, 5.0.

Summary

A number of amines have been synthesized resembling nor-adrenalone, ephedrine and epinephrine in structure, but having a three-carbon side chain with the amine group on the terminal carbon atom. The nor-adrenalone type compounds, under primary testing, were found to have vasopressor activity.

(10) For analyses reported in this paper we are indebted to Mr. Saul Gottlieb.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. V. Pyridine Compounds Analogous to Epinephrine, Adrenalene and Ephedrine

BY HARRY O. BURRUS[1] AND GARFIELD POWELL

We were interested in comparing the physiological action of compounds having a pyridine nucleus with the known activity of the corresponding compounds having a benzenoid nucleus. As pyridine is not entirely comparable with unsubstituted benzene, it seemed also necessary to make the comparison when the pyridine was substituted in the 2, 3 and 4 positions. Few such pyridine analogs of physiologically active benzenoid compounds have been prepared, even though the presence of the pyridine ring in such physiologically important types as the vitamin B complex, nucleic acids, and antibacterials included in the sulfa type drugs draws increasing attention to their potential usefulness. Even more rarely has the relative physiological activity of the isomeric 2, 3 and 4 substituted pyridine compounds been examined, in physiologically active pyridyl compounds or in pyridine analogs of other active compounds. The most notable exceptions are (1) the investigations of antipellagra activity of the various pyridine monocarboxylic acids and their derivatives,[2] (2) the pharmacological properties of the pyridyl-ethylamine dihydrochlorides,[3,4] (3) and those of the sulfa drugs.[5] In the first instance activity was found limited to the 3 position; and in the second case the 3 and the 4 ring substitutions produced compounds comparable to the phenylethylamine in pressor activity. The 2 substitution was markedly different in giving rise to an appreciable histamine-like activity. A pharmacological study in the third case has not been reported.

In a study of amines related to epinephrine we have prepared compounds with ketoethylamine, hydroxyethylamine and ethylamine groupings substituted in the 2, 3 and 4 positions on pyridine.

Owing to the fact that nor-ephedrine derivatives (isopropylamine types) have therapeutic properties that are in some respects more desirable than those of epinephrine derivatives (ethylamine types), we have sought also a method of preparation for this type of compound with a pyridine ring as the nucleus.

The procedure which was followed is outlined.

(1) From a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

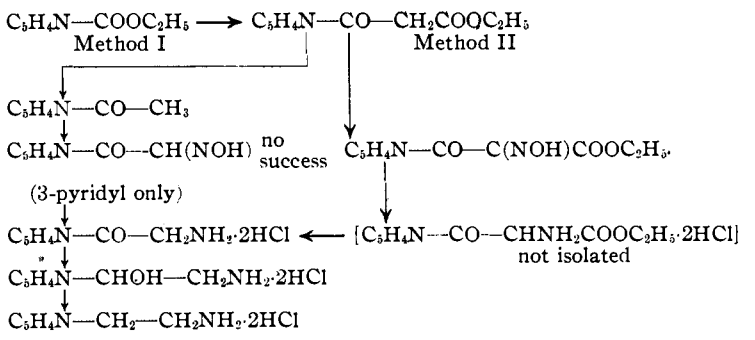
(2) Elvehjem, *Physiol. Rev.*, **20**, 249–271 (1940).

(3) Walter, Hunt and Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

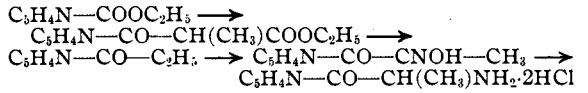
(4) Niemann and Hays, *ibid.*, **64**, 2288 (1942).

(5) Kolloff and Hunter, *ibid.*, **63**, 490 (1941).

FLOW SHEET



The preparation of the pyridine analogs of norephedrine was conducted according to the following scheme. The amine was not isolated.



Experimental

Preparation and Esterification of the Pyridine-carboxylic Acids.—The acids were esterified following the procedure of Camps,[6] that is, treatment of the acid with ethyl alcohol and sulfuric acid. It was not possible to duplicate the yields he claimed. While none of the recent articles in which this method is quoted stated the yields obtained, Pinner[7] claimed difficulty in preparing the esters. It required less time to oxidize the picolines to the acids than to recover the unreacted acids from the esterification residues. The larger yield in the case of ethyl nicotinate may be explained as a result of its greater ease of isolation from the esterification mixture.[8]

Picolinic Acid.—This was obtained by oxidizing 2-picoline following the method outlined in "Organic Syntheses."[9] However, instead of isolating picolinic acid hydrochloride, the synthesis was modified according to Clemo and Ramage[10] by precipitation of the copper complex of picolinic acid, and subsequent decomposition of the complex with hydrogen sulfide.

Isonicotinic Acid.—4-Picoline[11] was purified by recrystallization of its oxalate salt. The oxalate salt was decomposed with sodium hydroxide and the 4-picoline was steam distilled. The aqueous distillate was used directly for the oxidation to the acid. It was not necessary to form the copper complex of this acid. The aqueous solution of the acid was concentrated under vacuum until a solution saturated at room temperature was obtained. Concentrated hydrochloric acid was then added slowly with stirring and cooling until the solution was at *p*H 2.0. The solid isonicotinic acid was filtered, washed with water and dried in an oven at 120°. The yields were better than 90%.

Ethyl Nicotinate.—Commercial absolute alcohol (200 ml.) was mixed with cooling with 100 ml. of concentrated sulfuric acid, and the mixture poured over 80 g. of nicotinic acid.[12] The mixture was warmed on a steam-bath until solution was effected, then cooled at 0° and poured in a thin stream on to a mixture of 284 g. of potassium carbonate and 2000 g. of finely crushed ice in a five-liter flask equipped with a mechanical stirrer. The basic solution formed was filtered and 200 ml. of saturated sodium carbonate solution was added to the filtrate. This caused the separation of a liquid ester phase. The aqueous portion was thoroughly extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the ether distilled off. The ethyl nicotinate obtained distilled as a colorless oil at 84° at 5 mm. The average yields were 61%.

Ethyl Picolinate.—The ester, obtained as above, is a colorless oil which distils at 95° at 5 mm.; average yield 30%.

Ethyl Isonicotinate.—The ester, obtained as above, is a colorless oil which distils at 78.5° at 5 mm. It crystallizes in an ice-bath, m. p. 23°; average yield 30%.

Claisen Condensations.—The method of condensations of the esters of the pyridine monocarboxylic acids and ethyl acetate was a modification of that employed by Kolloff and Hunter.[5] The condensations proceeded smoothly and in good yield only if anhydrous, freshly prepared sodium ethoxide was used as the catalyst. In all cases it was possible to isolate the ethyl picolinoyl-, nicotinoyl- and isonicotinoylacetates and analyze their hydrochlorides, contrary to the opinion of Pinner[13] that this could not be accomplished.

The method of Pinner for the preparation of ethyl α-nicotinoyl propionate by the reaction of methyl bromide with the potassium salt of ethyl nicotinoylacetate could not be duplicated. Mixtures of ethyl and methyl pyridyl ketones which could not be separated were obtained on hydrolysis. A pure ketone was obtained by condensing ethyl propionate with the pyridine monocarboxylic ethyl esters and subsequent hydrolysis.

Ethyl Nicotinoylacetate Hydrochloride.—A mixture of 50.4 g. of ethyl nicotinate and 44 g. of ethyl acetate was added to 34 g. of freshly prepared, anhydrous sodium ethoxide[14] in a three-necked, liter flask fitted with a reflux condenser and a mechanical stirrer. The mixture was gently warmed until solution of the sodium ethoxide was completed. The condensation proceeded by itself and much heat was liberated after the reaction started. The mixture was stirred until the reaction subsided. This took approximately twenty minutes. By this time it was dark brown. It was chilled in an ice-bath and water added with cooling until solution of all solid was completed. Any unreacted ester was removed by extraction with two 50-ml. portions of ether. The solution was cooled and made neutral to nitrazine paper with hydrochloric acid. A layer of oil separated and was removed. The remaining aqueous solution was extracted with three 50-ml. portions of ether which was added to the oil.

If this oil is added to saturated potassium carbonate solution, long needles of the potassium salt of ethyl nicotinoylacetate separate. When filtered, dried and sealed in a nitrogen atmosphere this potassium salt keeps for months without decomposition.

The ether solution of the ethyl nicotinoylacetate was dried over anhydrous magnesium sulfate and filtered. Dry hydrogen chloride was bubbled into the ether solution until no more precipitate of the hydrochloride was formed on further addition. The precipitate was filtered and washed with dry ether. The crystals were hygroscopic, cream colored, and sublimed at 100° at 2 mm. to give a white sublimate. They started to decompose at 140° and melted at 154–155° with evolution of gas to a light brown liquid. The yield was 37%.

Anal. Calcd. for $C_{10}H_{12}NClO_3$: C, 52.3; H, 5.3. Found: C, 52.7; H, 5.6.

(6) Camps, *Arch. Pharm.*, **240**, 346 (1902).

(7) Pinner, *Ber.*, **33**, 1229 (1900).

(8) Kindler, *ibid.*, **69**, 2806 (1936).

(9) "Organic Syntheses," Vol. XX, John Wiley & Sons, Inc., New York, N. Y., p. 79.

(10) Clemo and Ramage, *J. Chem. Soc.*, 440 (1931).

(11) This sample was obtained from the Barrett Company, Edgewater, New Jersey, and was over 98% pure 4-picoline.

(12) The American Cyanamid Company prepares this by oxidizing nicotine.

(13) Pinner, *Ber.*, **34**, 4234 (1901).

(14) William Cumming, "Systematic Organic Chemistry," D. Van Nostrand Company, New York, N. Y., p. 505.

Ethyl Picolinoylacetate Hydrochloride.—This started to darken at 109° and turned red. It melted with evolution of gas at 117–118° and the melt decomposed. It was very hygroscopic; yield 70%.

Anal. Calcd. for $C_{10}H_{12}NClO_3$: C, 52.3; H, 5.3. Found: C, 52.7; H, 5.4.

Ethyl Isonicotinoylacetate.—The sodium salt of ethyl isonicotinoylacetate precipitated when water was added to the condensation mixture. It was dissolved in the minimum amount of water at 5° and the solution was neutralized with hydrochloric acid. The oil which separated was induced to crystallize by scratching the walls of the container with a glass rod. Recrystallized from 50% ethyl alcohol, the crystals melted at 57.5–58.0°; yield 80%.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7. Found: C, 62.0; H, 5.7.

Ethyl Isonicotinoylacetate Hydrochloride.—The hygroscopic crystals were cream-colored, m. p. 170–174° (dec.).

Anal. Calcd. for $C_{10}H_{12}NClO_3$: C, 52.3; H, 5.3. Found: C, 52.6; H, 5.3.

Nicotinoylmethane.—The following modification of the method of Kolloff and Hunter[5] was used. The method of preparation of ethyl nicotinoylacetate hydrochloride was followed, but the ether extraction to remove the unreacted esters was omitted. The aqueous solution was made 7% acid with hydrochloric acid and refluxed for three hours. The unreacted ethyl acetate was distilled off along with any acetone and ethyl alcohol that was formed. The solution was cooled, made alkaline with 50% sodium hydroxide solution and extracted with ether. The ether solution was dried over anhydrous potassium carbonate. The ether was distilled off. The residue distilled as a colorless oil at 80° at 5 mm.; yield 85%.

Picolinoylmethane.—This distilled as a colorless oil at 53° at 5 mm.

Isonicotinoylmethane.—This distilled as a colorless oil at 77° at 5 mm.

Nicotinoylethane.—Ethyl nicotinate (75.5 g.) and 100 g. of ethyl propionate were condensed in the presence of 59 g. of freshly prepared, anhydrous sodium ethoxide. Best results were obtained when this mixture was refluxed for a half hour. The nicotinoylethane distilled as a colorless oil at 78° at 5 mm.

Ethyl α-Nicotinoylpropionate.—This compound was isolated by neutralizing the aqueous solution containing the condensed products and extracting the oil which separated. The ethyl α-nicotinoylpropionate distilled at 58° at 2 mm. It was very hygroscopic. The corresponding hydrochloride was prepared by dissolving ethyl α-nicotinoylpropionate in dry ether and passing in dry hydrogen chloride. The hydrochloride was filtered and washed with dry ether; cream colored crystals m. p. 126–127° (dec.). They were very hygroscopic, photosensitive and oxidized in air. They decomposed on standing.

Oximation.—The method first attempted for the conversion of the esters to the required keto and hydroxy amines is labelled Method I on the flowsheet. Kaufmann, Kunkler and Peyer[15] report the successful use of this method in the case of 4-quinolyl methyl ketone. By this method nicotinoylisonitrosomethane was prepared, but the isonitroso derivatives of the picolinoyl and isonicotinoylmethanes were found to be too unstable for satisfactory work. In general these isonitroso ketones are photosensitive, oxidize in air and hydrolyze easily in acid solution.

The second method involved the preparation of the isonitroso keto esters rather than the isonitroso ketones. It was not surprising to find that an attempted hydrolysis of the isonitroso keto ester directly to the isonitroso ketone failed when attempting the method of Charrier,[16] given in the case of isonitroso ethyl acetate. Perkin[17] reports similarly that he failed to get the Charrier hydrolysis in the case of ethyl α-benzoyl-α-isonitrosoacetate.

(15) Kaufmann, Kunkler and Peyer, *Ber.*, **46**, 63 (1913).

(16) Charrier, *Gazz. chim. ital.*, **37**, II, 145-148 (1907).

(17) Perkin, *J. Chem. Soc.*, **47**, 240 (1885).

We, therefore, attempted a direct reduction from the isonitroso keto ester to the required amines and found that the method was applicable to all the pyridylisonitroso keto esters. This method has been previously reported as a method of synthesis of ketoamine hydrochlorides, although Gabriel and Posner[18] reduced isonitrosoacetoacetic ethyl ester with stannous chloride and concentrated hydrochloric acid to an impure ethyl α-aminoacetoacetate hydrochloride. There is no report on a ketonic decomposition of this product.

Ethyl Nicotinoylisonitrosoacetate.—Ethyl nicotinoylacetate hydrochloride (7.7 g.) was dissolved in 10% sodium hydroxide solution. The solution was kept cold in an ice-bath and 3.5 g. of sodium nitrate added. If the sodium salt of the oxime precipitated, it was redissolved by adding cold water. The solution was neutralized with hydrochloric acid. An oil separated which crystallized on cooling and scratching with a stirring rod. This compound was very soluble in hot alcohol and slightly soluble in water. It was recrystallized from 40% ethyl alcohol. The white crystals melted at 151–152° with evolution of gas at 154°. The melt decomposed suddenly at 163° from a clear brown liquid to a black tar; yield 80%.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.1; H, 4.5. Found: C, 54.4; H, 4.5.

This compound was also made directly from the condensation mixture of ethyl nicotinoylacetate hydrochloride as previously described, by distilling off the excess unreacted ethly acetate under vacuum and adding 500 ml. of water. Fifty grams of sodium nitrate was dissolved in this solution. It was kept cold in an ice-bath and neutralized with hydrochloric acid. An oil separated, which on shaking and scratching the sides of the flask could be induced to crystallize; yield 56%.

Ethyl Picolinoylisonitrosoacetate.—Recrystallized from 40% ethyl alcohol, the white crystals melted at 141.0–141.5° to give a clear, light brown liquid which evolved gas at 148–165° and turned dark brown at 169°.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.1; H, 4.5. Found: C, 54.0; H, 4.8.

Ethyl Isonicotinoylisonitrosoacetate.—Recrystallized from 20% ethyl alcohol; white crystals, m. p. 162.5–163° (dec.).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.1; H, 4.5. Found: C, 54.4; H, 4.6.

1-Phenyl-3-(3-pyridyl)-4-isonitrosopyrazolone-5.—Ethyl nicotinoylisonitrosoacetate (0.44 g.) was dissolved in hot alcohol and 0.22 g. of phenylhydrazine was added. The mixture was refluxed and alcohol added dropwise until a clear solution was obtained. A drop of hydrochloric acid was added to catalyze the reaction. A voluminous precipitate of orange crystals appeared within a few minutes. This was filtered off at intervals and the refluxing continued until no more crystals formed. The orange crystals turned into a dark brown, tarry mass if permitted to reflux too long. The product was recrystallized from 80% acetic acid. It was soluble in acetic acid and 5% hydrochloric acid, and insoluble in water, alcohol, ether, hot saturated sodium hydroxide solution and hot 10% sodium hydroxide solution; m. p. 229–230.5° (dec.); yield 90%.

Anal. Calcd. for $C_{14}H_{10}O_2N_4$: C, 63.1; H, 3.8. Found: C, 63.4; H, 4.1.

3-(3-Pyridyl)-4-isonitrosopyrazolone-5 Hemihydrate.—The method of preparation of 1-phenyl-3-(3-pyridyl)-4-isonitrosopyrazolone-5 was followed using 0.44 g. of ethyl nicotinoylisonitrosoacetate and 0.25 g. of hydrazine hydrochloride. The product was soluble in 5% hydrochloric acid and in 5% sodium hydroxide solution. It was insoluble in water, ethyl alcohol, ether and glacial acetic acid. An acid solution was yellow and an alkaline solution was orange. It crystallized in orange plates; m. p. 253–255° (dec.).

Anal. Calcd. for $C_8H_6O_2N_4 \cdot {}^1/_2H_2O$; C, 48.2; H, 3.5. Found: C, 48.4; H, 3.9.

(18) Gabriel and Posner, *Ber.*, **27**, 1141 (1894).

Nicotinoylisonitrosomethane.—A solution of 6.9 g. of sodium in 150 ml. of commercial absolute alcohol was slowly dropped into a mixture of 12.1 g. of nicotinoylmethane and 46.8 g. of amyl nitrite.[19] As much heat was evolved the reaction vessel was cooled in an ice-bath and the contents were mechanically stirred. The solution became brick red and a finely divided precipitate of the oxime settled out. The reaction mixture was left standing in the ice-bath for a half hour after the final addition of the sodium ethoxide solution. Water was added to dissolve the sodium salt. The solution effervesced. It was kept cold and extracted with ether to remove the unreacted material. The ether was extracted with three 50-ml. portions of 10% sodium hydroxide solution to remove traces of the isonitrosoketone and was then extracted with 5% hydrochloric acid to recover the unreacted nicotinoylmethane. The sodium hydroxide extracts were added to the main solution and this was concentrated at 25° under vacuum until solid started to precipitate. Water was added to make a saturated solution at 0° and 20% acetic acid was added to precipitate the isonitrosoketone. The point of minimum solubility was reached when the solution was at *p*H 6.0. The crystals were filtered off and decolorized in water with charcoal (Norite). They were recrystallized from 20% ethyl alcohol; m. p. 166.5–167.5° (dec.); yield 50%. The substance was insoluble in chloroform, slightly soluble in water, and soluble in ether and ethyl alcohol. It decomposed in air and was photosensitive. The oxime was very easily hydrolyzed in acid solution.

Anal. Calcd. for $C_7H_6N_2O_2$: C, 56.0; H, 4.0. Found: C, 56.3; H, 4.1.

Phenylhydrazone of Nicotinoylisonitrosomethane.—This was prepared in the usual manner and recrystallized from 95% alcohol; decomposition point 201.5–202.0°.

Anal. Calcd. for $C_{13}H_{12}ON_4$: C, 65.0; H, 5.0. Found: C, 65.2; H, 5.2.

Picrate of Nicotinoylisonitrosomethane.—This was prepared in the usual manner and recrystallized from 95% ethyl alcohol; m. p. 172–173° (dec.).

Anal. Calcd. for $C_{13}H_9O_9N_5$: C, 41.2; H, 2.2. Found: C, 41.6; H, 2.7.

1-Nicotinoyl-1-isonitrosoethane.—The procedure for the preparation of nicotinoylisonitrosomethane was followed using 70.7 g. of nicotinoylethane, 204 g. of amyl nitrite and 36.2 g. of sodium dissolved in absolute alcohol. The product was recrystallized from water, decolorized with charcoal (Norite) and then recrystallized from 50% ethyl alcohol; m. p. 206–207° (dec.); yield 40%.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.8. Found: C, 58.8; H, 5.0.

Hydrogenation.—In the choice of direct reduction methods from the ester, we were guided by a study of the reduction of the nicotinoylisonitrosomethane obtained by Method I. Catalytic hydrogenation in acidified aqueous solution at low pressures demonstrated that the oxime was reduced to an amine and the ketone to a methylene group when using platinum black as catalyst. With palladium black, using the same conditions, the oxime was reduced to an amine and the ketone was reduced to an alcohol. However, when the solution contained less than five mols of acid per mol of material to be reduced, a large amount of secondary amine was formed.[20] When more acid was introduced, extensive hydrolysis of the oxime resulted. The mixtures that were formed could not be separated. When Raney nickel was used as a catalyst, a red, acid-soluble, nickel addition complex separated after approximately one mol of hydrogen had been absorbed. This was hygroscopic and easily oxidized in air. The reduction stopped at this point.

Reduction using stannous chloride dissolved in concentrated hydrochloric acid resulted in the preparation of nicotinoylaminomethane dihydrochloride. The difficulty encountered in this method was the removal of the tin salts after reduction. The solutions had to be kept acidic in order to prevent formation of dipyridyl dihydropyrazines and as a result the tin sulfides did not precipitate quantitatively. Repeated precipitations at two or more atmospheres pressure of hydrogen sulfide at 0° removed the tin salts. The ketoamines formed dipyridyl dihydropyrazines very readily. It has been observed previously that the tendency for formation of pyrazines is greater with water soluble ketoamines than with those which are difficultly soluble.[21] The dipyridyl dihydropyrazines were very hygroscopic, water soluble, and easily oxidized in air. They were not isolated.

This method of reduction was then directly employed with ethyl picolinoyl-, nicotinoyl- and isonicotinoyl, α-isonitrosoacetates, the esters being hydrolyzed during the reduction with subsequent loss of carbon dioxide.

In this reduction the ketoamine esters could not be obtained as intermediates, although we could confirm that some reduction mixtures of ketoamine dihydrochloride and ketoamine ester dihydrochloride contained over 20% of the latter, the major portion of the ester in each case being hydrolyzed during the reduction with stannous chloride in concentrated hydrochloric acid.

The β-(2-, 3- and 4-pyridyl)-β-hydroxyethylamine dihydrochlorides were readily formed by reducing the corresponding pyridyl aminomethyl ketone dihydrochlorides using palladium black with hydrogen at one atmosphere pressure. The ketoamine and hydroxyamine dihydrochlorides were hygroscopic compounds which were easily oxidized in air. Reduction of either the ketoamine dihydrochlorides or the hydroxyamine dihydrochlorides using platinum black with hydrogen at one atmosphere pressure produced the corresponding β-(2-, 3-, and 4-pyridyl)-ethylamine dihydrochlorides. These pyridylethylamine dihydrochlorides have been prepared by other methods of synthesis.

Nicotinoylaminomethane Dihydrochloride.—A solution of 7.5 g. of nicotinoylisonitrosomethane in 95% alcohol was added dropwise to a solution of 45.2 g. of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid contained in a 500-ml. flask surrounded by an ice-bath. The mixture was kept cold and stirred for an hour. A precipitate of the stannous chloride addition complex of the ketoamine appeared but it was not quantitative. Water was added until all the salts were in solution and the tin salts were precipitated with hydrogen sulfide at 0° at two atmospheres pressure. The precipitate was filtered off and the filtrate was concentrated to dryness under vacuum. The residue was again dissolved in water and the remaining tin salts were reprecipitated with hydrogen sulfide at 0° at two atmospheres pressure. This procedure was repeated until no more tin sulfide precipitated. The tin sulfides were redissolved in concentrated hydrochloric acid and the above process was repeated. All the aqueous residues were combined and concentrated to dryness in a vacuum concentrator under a nitrogen atmosphere. The residue was recrystallized from absolute ethyl alcohol by addition of anhydrous ether. This compound was hygroscopic and oxidized in air. It decomposed when sublimed under vacuum. The crystals were light orange; m. p. 24–25° (dec.); yield 70%.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.5; H, 5.0.

The above procedure was followed also using 35 g. of ethyl nicotinoylisonitrosoacetate and 135.4 g. of stannous chloride dihydrate. After all the tin salts were removed, the ester which remained was hydrolyzed by refluxing in 10% hydrochloric acid. It was then worked up as indicated above. It was also possible to recrystallize this compound by dissolving it in the minimum amount of hot water, then cooling and adding ten times its volume of absolute alcohol.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.3; H, 5.1.

(19) Noyes, THIS JOURNAL, **55**, 3888 (1933).

(20) Hartung, *ibid.*, **53**, 2248 (1931).

(21) Tota and Elderfield, *J. Org. Chem.*, **7**, 314 (1942).

N-(Nicotinoylmethane)-*p*-chlorobenzamide.—This compound was prepared using a modified Schotten–Baumann reaction with saturated sodium bicarbonate solution as the alkalizing medium. Nicotinoylaminomethane dihydrochloride (0.418 g.) was dissolved in water and 0.350 g. of *p*-chlorobenzoyl chloride was added dropwise. The solution was kept alkaline with additions of sodium bicarbonate solution. The solid which separated was washed with 10 ml. of cold 7% hydrochloric acid. This solution was then made alkaline with cold 10% sodium hydroxide solution and extracted with three 10-ml. portions of chloroform. This was dried over anhydrous potassium carbonate, filtered and cooled. Dry hydrogen chloride was passed into the solution. The hygroscopic hydrochloride was filtered and washed with cold, saturated sodium bicarbonate solution. The free base was filtered off and recrystallized from 50% ethyl alcohol; white crystals, m. p. 152.0–152.5°.

Anal. Calcd. for $C_{14}H_{11}N_2O_2Cl$: C, 61.2; H, 4.0. Found: C, 61.4; H, 4.2.

Picolinoylaminomethane Dihydrochloride.—This was recrystallized from absolute ethyl alcohol by the addition of dry ether. The tan crystals were hygroscopic, exceedingly water soluble, and darkened in air; m. p. 178–180° (dec.); yield 60%.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.6; H, 5.1.

Isonicotinoylaminomethane Dihydrochloride.—The orange crystals were very hygroscopic, exceedingly water soluble and oxidized in air; m. p. 240–245° (dec.); yield 65%.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.4; H, 4.7.

β-(3-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—Nicotinoylaminomethane dihydrochloride (5.50 g.) was reduced catalytically at atmospheric pressure and room temperature using 1.0 g. of palladium black[22] suspended in 100 ml. of water. The solution was acidified with 10 ml. of concentrated hydrochloric acid. The reaction ceased when one mole equivalent of hydrogen was absorbed. The palladium black was filtered off and the filtrate was concentrated under a nitrogen atmosphere in a vacuum concentrator. The residue was recrystallized from methyl alcohol; hygroscopic tan crystals, m. p. 189.5–191.0° (dec.); yield 95%.

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.2; H, 5.9.

β-(2-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—The gray crystals were very hygroscopic and oxidized in air; m. p. 198–204° (dec.).

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.1; H, 5.7.

β-(4-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—The gray crystals were hygroscopic and oxidized in air; m. p. 203–205° (dec.).

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.1; H, 5.8.

β-(3-Pyridyl)-ethylamine Dihydrochloride.—The same procedure was followed as for the preparation of β-(3-pyridyl)-β-hydroxyethylamine dihydrochloride, except that 0.50 g. of platinum black[23] was used as catalyst. The reaction ceased when two mole equivalents of hydrogen were absorbed. The product was hygroscopic white salt which was recrystallized from absolute ethyl alcohol by the addition of ether. It agreed in properties with the compound described by Niemann and Hays[4]; yield 95%.

This compound also was obtained when the above procedure was followed using 4.2 g. of β-(3-pyridyl)-β-hydroxyethylamine dihydrochloride. The reaction ceased when one mole equivalent of hydrogen was absorbed; yield 95%.

N-β-(3-Pyridyl)-ethyl-*p*-chlorobenzamide Monohydrate.—This compound was prepared by a typical Schotten–Baumann reaction using β-(3-pyridyl)-ethylamine dihydrochloride and *p*-chlorobenzoyl chloride with 10% sodium hydroxide solution as the alkalizing medium. It was dissolved in 5% hydrochloric acid and filtered. The solution was then made alkaline with 10% sodium hydroxide solution. It was recrystallized from 60% ethyl alcohol; white crystals, m. p. 173–175° (dec.).

Anal. Calcd. for $C_{14}H_{15}N_2O_2Cl$: C, 60.3; H, 5.4. Found: C, 60.4; H, 5.4.

β-(2-Pyridyl)-ethylamine Dihydrochloride.—This compound agreed in properties with the compound described by Walter, Hunt and Fosbinder.[3]

β-(4-Pyridyl)-ethylamine Dihydrochloride.—This compound agreed in properties with the compound described by Walter, Hunt and Fosbinder.[3]

The microanalyses were performed by Mr. Saul Gottlieb of these laboratories.

(22) Purchased from the American Platinum Works, Newark, N. J.

Summary

β-(2-, 3- and 4-pyridyl)-β-hydroxyethylamine dihydrochlorides and the corresponding ketones have been described. A new method of synthesis for compounds of these types is reported.

(23) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., p. 463.

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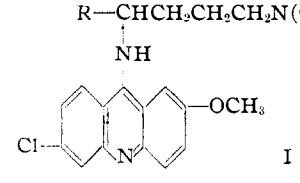
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Quinacrine Analogs Having Aromatic Groups in the Side Chain[1]

BY DAVID S. BRESLOW, HOWARD G. WALKER, ROBERT S. YOST AND CHARLES R. HAUSER

Quinacrine (I, R = CH_3) and its analogs in which R in the α-position is varied are prepared generally by coupling the appropriate diamine, $RCH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$, with 2-methoxy-6,9-dichloroacridine. The synthesis of a series of these analogs in which R is an aliphatic group higher than methyl was described recently.[2]



I

In the present investigation analogs in which R is benzyl, phenyl and certain substituted phenyl groups have been synthesized. The diamines were prepared by reduction[2] of the oximes of the

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

(2) Breslow, Yost, Walker and Hauser, THIS JOURNAL, **66**, 1921 (1944).