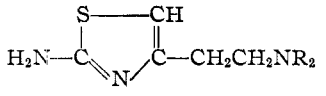
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME INC.]

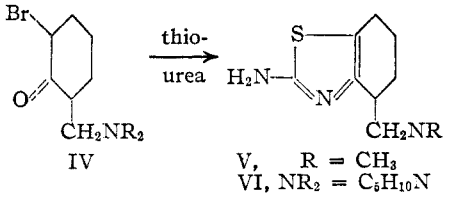
t-Aminoalkyl Derivatives of 2-Aminothiazole

BY A. H. LAND, CARL ZIEGLER AND JAMES M. SPRAGUE

2-Aminothiazole and its derivatives generally are prepared by the reaction of thiourea with α-halogen carbonyl compounds. We have shown recently that brominated *t*-aminoacetones react readily with thiourea, yielding 2-amino-4-*t*-aminomethylthiazoles.[1] The present paper describes the application of this method to halogen derivatives of several members of the large group of β-aminoketones that are obtainable by the Mannich reaction.[2]



I, R = CH_3
II, NR_2 = NC_5H_{10}
III, NR_2 = $C_9H_{10}N$



IV

V, R = CH_3
VI, NR_2 = $C_9H_{10}N$

Mannich and Golasch[3] brominated 4-dimethylamino-2-butanone hydrobromide and obtained a compound that they considered to be 1-bromo-4-dimethylamino-2-butanone hydrobromide. We found that this ketone reacted readily with thiourea to yield a 2-aminothiazole. If the structure assigned to the bromoketone is correct, the product of this reaction should be 2-amino-4-(2-dimethylaminoethyl)-thiazole (I, R_2N = $(CH_3)_2N$). The structure of the bromoketone, however, was deduced by Mannich and Golasch from a series of reactions leading to the formation of 1-methyl-3-hydroxypyrrolidine, which was an unknown compound and has not been prepared by an unequivocal synthesis.

Definite proof that the thiazole is 2-amino-4-(2-dimethylaminoethyl)-thiazole (I) was obtained in two ways: by conversion to a known compound, the N-acetyl derivative of 2-amino-4-ethylthiazole, and by direct synthesis from 2-amino-4-(2-chloroethyl)-thiazole. When an aqueous alkaline solution of the methiodide of the thiazole I was heated, trimethylamine was evolved and 2-amino-4-vinylthiazole was formed. Catalytic hydrogenation of the N-acetyl derivative of this vinylthiazole produced 2-acetamido-4-ethylthiazole. 2-Amino-4-(2-chloroethyl)-thiazole reacted with dimethylamine to give a thiazole that was identical with that prepared from the brominated Mannich ketone. Piperidine reacted similarly to yield 2-amino-4-(2-piperidinoethyl)-thiazole (II), which was prepared also through the bromination of 4-piperidino-2-butanone. These results, as well as those of Mannich and Golasch, show that bromination of the amino ketones took place, at least predominantly, on the methyl group. No evidence of bromination on the methylene group was found although the possibility that this occurred to a slight extent is not excluded. From these results the structure of 2-amino-4-[2-(1,2,3,4-tetrahydroisoquinolino)-ethyl]-thiazole (III) is assigned to the thiazole obtained from 4-(1,2,3,4-tetrahydroisoquinolino)-2-butanone.

Bromination of the Mannich bases derived from cyclohexanone also gave bromoketones that yielded 2-aminothiazoles on reaction with thiourea. Since thiazole formation is possible only when the bromoketone has the structure IV resulting from entry of the bromine into the methylene group, the thiazoles must be the 2-amino-4-*t*-aminomethyl-4,5,6,7-tetrahydrobenzothiazoles (V and VI).

Although the Mannich reaction has been applied to a large variety of ketones, the use of α-halogenated ketones has not been reported. In this investigation, it was found that ω-chloroacetophenone reacted with formaldehyde and piperidine hydrochloride without loss of the α-chlorine to yield α-chloro-β-piperidinopropiophenone. The product was contaminated with some piperidine hydrochloride, from which it could not be separated easily. Although the product was not obtained in the pure state, it reacted readily with thiourea to give 2-amino-4-phenyl-5-piperidinomethylthiazole. This same thiazole was obtained also by treating the bromination product of β-piperidinopropiophenone hydrobromide with thiourea.

Experimental[4]

All of the 2-aminothiazoles described below gave the characteristic diazo color test.[1]

2-Amino-4-(2-dimethylaminoethyl)-thiazole.—A. Forty-five grams (0.16 mole) of 1-bromo-4-dimethylamino-2-butanone hydrobromide[3] was added to a solution of 12.2 g. (0.16 mole) of thiourea in 200 ml. of water. The solution, which had become warm, was allowed to remain at room temperature for twelve hours. After the solution had been partially decolorized by shaking it with "Norit," an excess of 20% aqueous sodium hydroxide was added, whereupon 22 g. (81%) of the amine precipitated; m. p. 128–129° after recrystallization from *i*-propyl ether.

Anal. Calcd. for $C_7H_{13}N_3S$: C, 49.11; H, 7.62; N, 24.54. Found: C, 49.42; H, 7.80; N, 24.43.

(1) Sprague, Land and Ziegler, THIS JOURNAL, **68**, 2155 (1946).

(2) Blicke, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 303.

(3) Mannich and Golasch, *Ber.*, **61**, 263 (1928).

(4) All melting points are uncorrected.

B. A mixture of 3.26 g. (0.02 mole) of 2-amino-4-(2-chloroethyl)-thiazole[5] and 5 ml. of 35% aqueous dimethylamine was placed in a pressure bottle and heated for one hour in a boiling water-bath. The cold solution was made strongly basic with 20% aqueous sodium hydroxide, the precipitated base filtered, and washed with water. The yield was 1 g. after two recrystallizations from benzene; m. p. 126–128°, mixed m. p. 125–128°.

1-Bromo-4-piperidino-2-butanone Hydrobromide.—Fifty milliliters of a 35% solution of hydrogen bromide in glacial acetic acid was added to 34 g. (0.22 mole) of 4-piperidino-2-butanone[6] dissolved in 50 ml. of the same solvent. The hot solution was stirred vigorously while 35 g. (0.22 mole) of bromine in 33 ml. of glacial acetic acid was added dropwise, at a rapid rate. The addition of 300 ml. of *i*-propyl ether precipitated a dark brown oil that soon solidified. The solid was dissolved in boiling *i*-propyl alcohol and the resulting solution was partially decolorized by treatment with "Darco." On cooling, the solution deposited 30.6 g. (44%) of brown crystals, m. p. 154–156°. After repeated recrystallization from *i*-propyl alcohol, the product melted at 157–158°.

Anal. Calcd. for $C_9H_{17}ONBr_2$: N, 3.95; Br, 50.72. Found: N, 3.97; Br, 49.79.

2-Amino-4-(2-piperidinoethyl)-thiazole.—**A.** A solution of 6.3 g. (0.02 mole) of 1-bromo-4-piperidino-2-butanone hydrobromide and 1.52 g. (0.02 mole) of thiourea in the minimum quantity of water was allowed to remain at room temperature for eighteen hours. The solution was partially decolorized by treatment with "Norit" and then made alkaline with 20% sodium hydroxide solution to precipitate 3.5 g. (83%) of yellow crystals: m. p. 134–135° after three recrystallizations from *i*-propyl ether.

Anal. Calcd. for $C_{10}H_{17}N_3S$: C, 56.91; H, 8.12; N, 19.87. Found: C, 57.41; H, 8.22; N, 19.54.

The **dihydrochloride** was precipitated by adding isopropyl ether to a solution of the base in ethanolic hydrogen chloride. After repeated recrystallization from *i*-propyl alcohol containing a little hydrogen chloride, the product melted at 188–189°.

Anal. Calcd. for $C_{10}H_{19}N_3Cl_2S$: N, 14.78; Cl, 24.96. Found: N, 14.54; Cl, 25.18.

B. A solution of 3.45 g. (0.0213 mole) of 2-amino-4-(2-chloroethyl)-thiazole and 3.6 g. (0.0425 mole) of piperidine in 5 ml. of ethanol was refluxed for two hours. The alcohol then was evaporated and the residue was dissolved in dilute hydrochloric acid. The acid solution was poured into an excess of dilute sodium hydroxide solution and the mixture was stirred until the oily precipitate solidified. Recrystallization from benzene gave 2.5 g. of tan crystals, m. p. 130–132.5°; mixed m. p., 130–134°.

4-(1,2,3,4-Tetrahydroisoquinolino)-2-butanone Hydrochloride.—Seventeen grams (0.1 mole) of 1,2,3,4-tetrahydroisoquinoline[7] hydrochloride, 4.5 g. (0.15 mole) paraformaldehyde, 80 ml. of acetone and 20 ml. of anhydrous ethanol were refluxed for one hour. A few drops of concentrated hydrochloric acid was added to depolymerize the remaining paraformaldehyde and the refluxing was continued. When the mixture was cooled, it set to a stiff mass of crystals, which were washed with acetone: yield 14 g. (59%); m. p., 166–167° after three recrystallizations from *i*-propyl alcohol.

Anal. Calcd. for $C_{13}H_{18}ONCl$: N, 5.84; Cl, 14.80. Found: N, 5.52; Cl, 14.76.

4-(1,2,3,4-Tetrahydroisoquinolino)-2-butanone Hydrobromide.—Sixty-seven grams (0.28 mole) of 4-(1,2,3,4-tetrahydroisoquinolino)-2-butanone hydrochloride was dissolved in the minimum amount of water and the solution was made strongly alkaline with 20% sodium hydroxide. The base was extracted with two 150-ml. portions of *i*-propyl ether. The extract was dried with anhydrous sodium sulfate and then poured into an excess of a saturated solution of hydrogen bromide in *i*-propyl ether. The powdery precipitate of crude hydrobromide, m. p. 172–175° (dec.) weighed 75 g. (95%). A sample recrystallized from *i*-propyl alcohol melted at 177.5–178.5° (dec.).

Anal. Calcd. for $C_{13}H_{18}ONBr$: Br, 28.12. Found: Br, 28.02.

1-Bromo-4-(1,2,3,4-tetrahydroisoquinolino)-2-butanone Hydrobromide.—A solution of 11.2 g. (0.04 mole) of 4-(1,2,3,4-tetrahydroisoquinolino)-2-butanone hydrobromide in 50 ml. of glacial acetic acid was stirred in a flask placed directly above a 75-watt Mazda lamp while 6.4 g. (0.04 mole) of bromine in 15 ml. of glacial acetic acid was added. *i*-Propyl ether was added to the stirred solution in small portions and the suspension was stirred between each addition until the oily precipitate solidified. When precipitation was completed, the mother liquor was decanted and the solid was washed with isopropyl ether. The crude dry solid, m. p. 170–174°, weighed 12 g. Reprecipitation from boiling 80% ethanol by dilution with ethyl acetate gave 7.35 (51%) of white crystals; m. p., 171–174°. The bromine content of this material was below the theoretical value but it was satisfactory for conversion to the thiazole.

Anal. Calcd. for $C_{13}H_{17}ONBr_2$: Br, 44.03. Found: Br, 42.49, 42.95.

2-Amino-4-(2-(1,2,3,4-tetrahydroisoquinolino)-ethyl)-thiazole.—Two grams (0.02 mole) of thiourea and 7.35 g. (0.02 mole) of 1-bromo-4-(1,2,3,4-tetrahydroisoquinolino)-2-butanone hydrobromide were dissolved in 75 ml. of water containing 0.25 ml. of concentrated hydrochloric acid and left at room temperature for sixteen hours. The filtered solution was made strongly basic with 20% aqueous sodium hydroxide. The semi-solid precipitate was dissolved in isopropyl ether and the solution was dried with anhydrous sodium sulfate. Evaporation of the ether left 2.75 g. (52%) of white crystals; m. p., 92–94°, which turned brown within several days. A sample recrystallized once from hexane and twice from *i*-propyl ether melted at 93–93.5°.

Anal. Calcd. for $C_{14}H_{17}N_3S$: N, 16.21. Found: N, 16.01.

The **dihydrochloride,** prepared in ethanol and precipitated with *i*-propyl ether, melted at 209–210° (dec.).

Anal. Calcd. for $C_{14}H_{19}N_3Cl_2S$: N, 12.65; Cl, 21.35. Found: N, 12.47; Cl, 21.04.

2-Amino-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole.—Dry hydrogen bromide was passed into a solution of 25.5 g. (0.16 mole) of 2-dimethylaminomethylcyclohexanone[8] in 150 ml. of *i*-propyl ether. The precipitated hydrobromide (35.9 g., 93%), m. p. 165–166.5°, was dissolved in 100 ml. of hot glacial acetic acid and the solution was stirred and illuminated with a 75-watt lamp while 25 g. (0.16 mole) of bromine in 20 ml. of acetic acid was added. After a few minutes the mixture set to a mass of white crystals. The solid was stirred with 350 ml. of *i*-propyl ether, filtered, suspended in 200 ml. of acetone, and filtered again; m. p. 162–163°; yield, 44 g. (80%).

Forty grams (0.11 mole) of the crude bromoaminoketone salt and 9.8 g. (0.13 mole) of thiourea were dissolved in 100 ml. of warm water containing 0.5 ml. of concentrated hydrochloric acid. The solution then was heated on a steam-bath for one and one-half hours, cooled and made strongly alkaline with 20% sodium hydroxide solution. The resulting suspension was shaken with *i*-propyl ether and the extract was dried with anhydrous sodium sulfate. Evaporation of the ether left 21.1 g. (91% of yellow crystals; m. p. 105–107°). Repeated crystallization from *i*-propyl ether gave white crystals; m. p. 106–107.5°.

Anal. Calcd. for $C_{10}H_{17}N_3S$: C, 56.91; H, 8.12; N, 19.88. Found: C, 57.08; H, 8.37; N, 19.70.

An **acetyl derivative** was prepared by warming the aminothiazole with acetic anhydride in glacial acetic acid. The cooled solution was neutralized with sodium hy-

(5) Carrol and Smith, THIS JOURNAL, **55**, 370 (1933).

(6) Mannich and Hof, *Arch. Pharm.*, **265**, 599 (1929).

(7) Cromwell and Cram, THIS JOURNAL, **65**, 305 (1943).

(8) Mannich and Braun, *Ber.*, **52**, 1874 (1920).

droxide to precipitate the amide which melted at 179.5–180°, after repeated crystallization from 20% ethanol.

Anal. Calcd. for $C_{12}H_{19}ON_3S$: N, 16.61. Found: N, 16.41.

2-Amino-4-piperidinomethyl-4,5,6,7-tetrahydrobenzothiazole.—Eighty-three grams (0.5 mole) of piperidine hydrobromide, 200 g. (2.04 moles) of cyclohexanone and 45 g. (0.5 mole) of 35% aqueous formaldehyde solution were heated on a steam-bath for forty minutes, during which time the mixture became homogeneous. The cold, solid mixture was stirred with 300 ml. of ether, filtered and washed with ether; m. p., 183–184° (dec.) after recrystallization from isopropyl alcohol; yield, 91 g. (66%). Since further recrystallization was accompanied by darkening and a decrease in melting point, additional purification was not attempted.

Eighty-three grams (0.3 mole) of the aminoketone hydrobromide was dissolved in 300 ml. of glacial acetic acid and stirred while 48 g. (0.3 mole) of bromine in 50 ml. of glacial acetic acid was added. After the addition of a liter of *i*-propyl ether, stirring was continued until the oily precipitate of bromoketone salt solidified. The yellow solid was washed with ether; yield, 82 g. (46%); m. p., about 145° (dec.). Recrystallization from isopropyl alcohol–ethyl acetate mixture did not produce a sharply melting product.

Twenty grams (0.057 mole) of the bromoketone and 4.8 g. (0.063 mole) of thiourea were dissolved in 100 ml. of water and, after two hours, the solution was heated on a steam-bath for one-half hour. The solution then was cooled, made basic with 20% aqueous sodium hydroxide. After the gummy yellow precipitate had solidified to a hard resinous mass, it was pulverized and washed with water. It then was suspended in boiling water and dissolved by the gradual addition of ethanol. The solution was treated with "Darco" and, upon cooling, deposited 9.1 g. (64%) of crystals, m. p. 146–148°. A second crop weighing 1.6 g., m. p. 145.5–146.5°, was obtained by adding water to the mother liquor. After two crystallizations from a benzene–hexane mixture, the melting point was 146.5–148°.

Anal. Calcd. for $C_{13}H_{21}N_3S$: C, 62.13; H, 8.43; N, 16.73; S, 12.76. Found: C, 62.09; H, 8.21; N, 16.98; S, 12.53.

α-Chloro-β-piperidinopropiophenone Hydrochloride.—Fifteen and four-tenths grams (0.1 mole) of ω-chloroacetophenone, 12.2 g. (0.1 mole) of piperidine hydrochloride, 4.5 g. (0.15 mole) of paraformaldehyde and 0.25 ml. of concentrated hydrochloric acid in 30 ml. of anhydrous ethanol were refluxed for three hours. The next day 2 g. of paraformaldehyde was added and the refluxing was continued for eight hours. The hot mixture was diluted with 300 ml. of boiling acetone, cooled slowly to room temperature and then placed in a refrigerator; the precipitate weighed 12.5 g. (43%); m. p. 165.5–166.5°. Repeated precipitation from ethanol solution by dilution with *i*-propyl ether did not alter the melting point.

Anal. Calcd. for $C_{14}H_{19}ONCl_2$: N, 4.86; Cl, 24.60. Found: N, 3.85; Cl, 26.85.

β-Piperidinopropiophenone Hydrobromide.—A mixture of 24 g. (0.2 mole) of acetophenone, 9 g. (0.5 mole) of paraformaldehyde, 33 g. (0.2 mole) of piperidine hydrobromide, 0.5 ml. of concentrated hydrochloric acid and 60 ml. of anhydrous ethanol was refluxed for an hour. Six grams of paraformaldehyde was added and the heating was continued for one and one-half hours. The hot mixture then was diluted with 500 ml. of boiling acetone and allowed to cool slowly. The white crystalline product, m. p. 195–197°, weighed 27 g. (48%). After two crystallizations from a water–*i*-propyl alcohol mixture, it melted at 197–197.5°.

Anal. Calcd. for $C_{14}H_{19}ONBr$: Br, 26.81. Found: Br, 26.48.

α-Bromo-β-piperidinopropiophenone Hydrobromide.—Twenty-five grams (0.084 mole) of β-piperidinopropiophenone hydrobromide was dissolved in 200 ml. of warm glacial acetic acid. The solution was heated on a steam-bath and stirred while 13.5 g. (0.084 mole) of bromine in 15 ml. of glacial acetic acid was added slowly. After one and one-half hours on the steam-bath, the solution was allowed to cool to 50° and the product was precipitated by slowly adding 500 ml. of *i*-propyl ether; yield 30 g. (95%) of pale yellow crystals; m. p. 174–178°. A sample, m. p. 184–185°, was obtained by repeated crystallization from *i*-propyl alcohol.

Anal. Calcd. for $C_{14}H_{18}ONBr_2$: Br, 42.38. Found: Br, 42.22.

2-Amino-4-phenyl-5-piperidinomethylthiazole.—**A.** Crude α-bromo-β-piperidinopropiophenone hydrobromide (5.6 g., 0.015 mole) was added to a solution of 2 g. (0.027 mole) of thiourea in 75 ml. of water containing 0.25 ml. of concentrated hydrochloric acid. After fifteen minutes on a steam-bath, the solution was allowed to cool to room temperature and then made strongly alkaline with 20% aqueous sodium hydroxide. The gummy precipitate was dissolved in isopropyl ether, and the solution washed with water, dried over anhydrous sodium sulfate, and then saturated with hydrogen chloride. The precipitated sticky orange aminothiazole dihydrochloride was recrystallized from 80% ethanol after treatment with decolorizing carbon; 1.9 g. of white crystalline solid; m. p. 192–196°. The base was obtained from the dihydrochloride by treatment with aqueous sodium hydroxide; m. p. 128.5–129° after three crystallizations from dilute ethanol. When the initial temperature of the melting point bath was above 80° or when the temperature was raised rapidly, the melting point was 116–120°. Samples a year old did not melt at this lower temperature.

Anal. Calcd. for $C_{15}H_{19}N_3S$: C, 65.91; H, 7.00; N, 15.37. Found: C, 65.51; H, 6.79; N, 15.16.

B. α-Chloro-β-piperidinopropiophenone hydrochloride was converted to a thiazole by the procedure described above. The product did not depress the melting point of the thiazole prepared from the bromoketone.

2-(2-Amino-4-thiazolyl)-ethyltrimethylammonium Iodide.—To a mixture of 2-amino-4-(2-dimethylaminoethyl)-thiazole (3.4 g., 0.02 mole) and 2 ml. of absolute ethanol, 3.6 g. (0.025 mole) of methyl iodide was added. After the vigorous reaction had subsided, the cooled mixture was filtered and the solid washed with ethanol; yield, 1.3 g.; m. p. 186–187° (dec.) after recrystallization from 95% ethanol.

Anal. Calcd. for $C_8H_{16}N_3IS$: N, 13.42; I, 40.52. Found: N, 13.32; I, 40.45.

2-Acetamido-4-vinylthiazole.—2-(2-Amino-4-thiazolyl)-ethyltrimethylammonium iodide (0.7 g.) was dissolved in 1 ml. of 20% aqueous sodium hydroxide and the solution was heated on a steam-bath for five minutes. The oily precipitate was extracted with ether, the extract dried with anhydrous potassium carbonate and allowed to evaporate. The residue was heated for forty-five minutes in a steam-bath with 2 ml. of acetic anhydride. After sixteen hours the excess acetic anhydride was removed by distillation *in vacuo* and the gummy residue crystallized from a boiling mixture of benzene and hexane; m. p. 136–138°.

Anal. Calcd. for $C_7H_8ON_2S$: N, 16.66. Found: N, 16.49.

Hydrogenation of 2-Acetamido-4-vinylthiazole.—A solution of 396 mg. (0.00236 mole) of 2-acetamido-4-vinylthiazole in 5 ml. of glacial acetic acid was hydrogenated in the presence of 30 mg. of platinum oxide catalyst.[9] During two and one-half hours, 0.00229 mole of hydrogen was absorbed. After removal of the catalyst, the dark solution was concentrated under diminished pressure and the black solid residue was washed with water, dried and extracted with 20 ml. of cold ether. The extract was evaporated to dryness and the crystalline residue recrystallized from 20% ethanol; yield, 110 mg.; m. p. 117–118.5°.[10]

(9) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, 2nd ed., Coll. Vol. I, page 463.

(10) Bergeim, Coy and Lott, THIS JOURNAL, **62**, 1873 (1940), give melting points of 117.5 and 185.5–187.5°, respectively, for the acetyl derivative and the hydrochloride of 2-amino-4-ethylthiazole.

The acetamido compound (100 mg.) was dissolved in 1 ml. of 8 *N* ethanolic hydrogen chloride solution and allowed to remain at room temperature for sixteen hours. After evaporation of the alcohol, concentrated hydrochloric acid (0.25 ml.) was added to the residue and the solution evaporated on a steam-bath. The 2-amino-4-ethylthiazole hydrochloride was recrystallized from a mixture of ethanol and acetone; m. p. 185–187°.[10]

Summary

Several β-*t*-aminoketones ("Mannich bases") have been brominated and the resulting bromoaminoketones have been converted to 2-aminothiazoles. The structures of the bromination products of two β-aminoketones have been proved by independent syntheses of the 2-aminothiazoles derived from them. α-Chloro-β-piperidinopropiophenone has been synthesized from ω-chloroacetophenone by the Mannich reaction.

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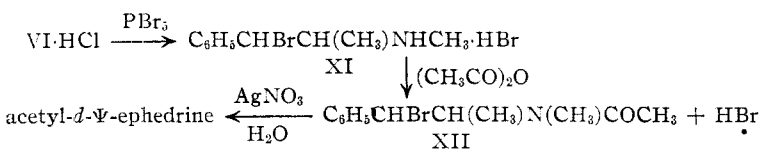
[CONTRIBUTION FROM THE U. S. FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

The Constitution of Acetylephedrine and Acetyl-Ψ-ephedrine

BY LLEWELLYN H. WELSH

Acetyl-*l*-ephedrine was first prepared by Nagai[1] by the action of acetyl chloride on an ethereal solution of *l*-ephedrine (1-phenyl-2-methylamino-1-propanol), (I). He reported that the substance formed a hydrate, melted at 87°, and that he was unable to obtain crystalline salts from acid solutions of the compound. He represented it as an amide, or N-acetyl derivative of ephedrine.

Schmidt and Calliess[2] prepared acetyl-*d*-Ψ-ephedrine hydrochloride by refluxing acetic anhydride with *d*-Ψ-ephedrine hydrochloride, (VI·HCl), or its diastereoisomer, *l*-ephedrine hydrochloride (I·HCl). On treatment with alkali the product yielded acetyl-*d*-Ψ-ephedrine which, without proof, was represented as an N-acetyl derivative. Later,[3] Schmidt carried out a series of reactions which, according to his concepts, may be formulated in the following manner



Since XII, supposedly 1-bromo-1-phenyl-2-acetylmethylaminopropane, had no basic properties and yielded acetyl-*d*-Ψ-ephedrine by what was interpreted as replacement of bromine by hydroxyl when treated with aqueous silver nitrate, the N-acetyl structure (VII) was considered to be proved, and the corresponding hydrochloride was represented as an N-acetyl salt (VIII). Recently, however, Mitchell[4] has submitted evidence that the product formed by the action of acetic anhydride on XI is acetyl-*d*-Ψ-ephedrine hydrobromide instead of the compound represented by structure XII. This fact would render inconclusive Schmidt's evidence for an N-acetyl structure.

Mitchell[4] prepared acetyl-*l*-ephedrine and acetyl-*d*-Ψ-ephedrine by heating the corresponding alkaloids with one and one-half moles of acetic anhydride at 70° for ten minutes. From the Ψ-ephedrine derivative he prepared the well defined hydrochloride, but efforts to prepare acetyl-*l*-ephedrine hydrochloride yielded a poorly defined product contaminated with the diastereoisomer. On treatment with nitrous acid the acetylated alkaloids yielded nitrosoacetyl products of which the one derived from Ψ-ephedrine was well defined, whereas that resulting from acetyl-*l*-ephedrine apparently consisted of a mixture of diastereoisomers. Mitchell considered the ready formation of nitrosoacetyl compounds to be proof that the acetyl derivatives have a replaceable amino hydrogen and that they and the salts derived from them possess an O-acetyl structure. His interpretation of the reactions is expressed structurally in the following diagram.

It seemed possible that criteria simpler than those used by Schmidt[3] and by Mitchell[4] could be employed to differentiate between N-acetyl (amide) and O-acetyl (ester) structures. If a compound under consideration is a hydroxyamide it should afford a practically neutral aqueous solution and should evince no titratable basicity under ordinary conditions. If it is an aminoester, however, it should yield an alkaline solution which, in the case of acetylephedrine and acetyl-Ψ-ephedrine, would be expected to be susceptible to quantitative titration with standard acid. It seemed possible also that the relationship between acetylephedrine and acetyl-Ψ-ephedrine on the one hand and the corresponding salts on the other might be that which exists between an N-acyl-β-aminoalcohol and the salt of the isomeric O-acyl-β-aminoalcohol. Although stable esters

(1) Nagai, *J. Pharm. Soc. Japan*, No. 127, 832 (1892). The author is indebted to Dr. J. G. Yoshioka for the translation of a portion of this publication which does not appear to be indexed in the Western literature, although reference to it and acetyl-*l*-ephedrine is made in a review by Chen and Kao, *J. Am. Pharm. Assoc.*, **15**, 625 (1926).

(2) Schmidt and Calliess, *Arch. Pharm.*, **250**, 154 (1912); see also Calliess, *Deut. Apoth. Z.*, **25**, 677 (1910).

(3) Schmidt, *ibid.*, **252**, 111 (1914).

(4) Mitchell, *J. Chem. Soc.*, 1153 (1940).