[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ANALGESIC STUDIES. β-ETHYL AND β-ISOPROPYLAMINE DERIVATIVES OF PYRIDINE AND THIAZOLE[1]

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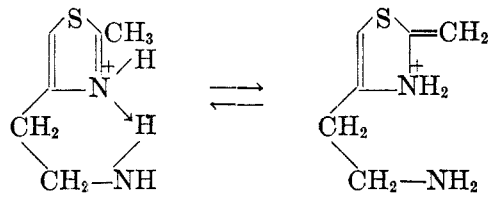
In comparing the three isomeric β-pyridylethylamines, Niemann and Hays (1) observed that the 2-isomer exhibited histamine-type activity, while the 3- and 4-isomers had an epinephrine-like effect. They explained the absence of histamine action in these two amines on the basis of the postulate that the ion of only the 2-isomer could exist in a form in which both the heterocyclic and the aliphatic nitrogen atoms participated in a chelated ring. Since β-arylethylamine derivatives show, in general, a less prolonged physiological effect than branched-chain amines of corresponding structure, we decided to synthesize several β-pyridylisopropylamines in order to explore the effect of branching on the activity of such compounds. As the work progressed it became desirable to include examples of the isosteric β-thiazolylethylamine series for further comparison.

In the course of testing β-(2-methyl-4-thiazolyl)ethylamine (I) Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School, observed that this compound exhibited considerable analgesia in rats. We considered it possible that the methyl group in the reactive 2-position may tautomerize, and that the ionized amine then reacts to some extent as represented by I (b). This form would have less tendency to exhibit chelation than β-(4-thiazolyl)ethylamine,[2] and the tautomerizable methyl group could thus be held responsible for a decrease of histamine activity in this compound.



I(a) I(b)

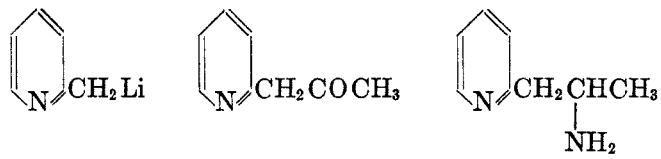
In order to support this assumption, β-(2-pyridyl)isopropylamine and β-(6-methyl-2-pyridyl)isopropylamine were tested. The former showed an appreciable histamine-like action, while the latter was practically devoid of this effect and was found to have an analgesic action in cats. It should be observed that β-(2-aryl-4-thiazolyl)ethylamines have been shown to possess a high degree

[1] Several experiments reported in this article were performed by G. E. U. in the Research Laboratories of Smith, Kline, and French Laboratories.

[2] This can be corroborated by an inspection of Stuart models of the two tautomers. After conclusion of most of this work we learned of the article by Erlenmeyer and Müller (2) who mentioned β-(4-thiazolyl)ethylamine "was qualitatively similar to histamine in its type of activity."

of "physiological activity" (3); β-(2-benzyl-4-thiazolyl)ethylamine described in this article had no analgesic properties.

β-(2-Pyridyl)isopropylamine (IV) was prepared by the Leuckart reaction from 2-pyridylacetone (III) which, in turn, was obtained by interaction of 2-picolyllithium (II) and acetonitrile with subsequent hydrolysis of the resulting ketimine. While the synthesis of 2-pyridylacetone and its 6-methyl homolog produced acceptable yields, certain other homologs could not be obtained in a very satisfactory manner by this route. 2-Methyl-5-ethylpyridine furnished 22% of (5-ethyl-2-pyridyl)acetone, and 2-*n*-amylpyridine only 10% of 3-(2-pyridyl)heptanone-2. However, the conversion of these ketones to the corresponding primary amines was readily accomplished.

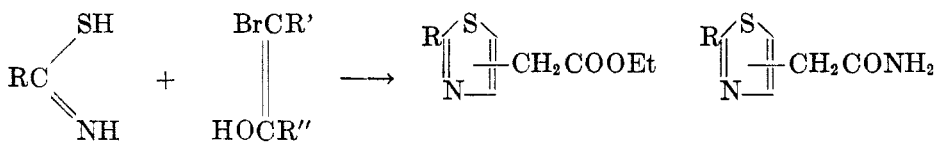


II III IV

Metal exchange of γ-picoline with phenyllithium seemed to take a normal course but treatment of the lithium derivative with acetonitrile or with acetyl chloride and subsequent hydrolysis, failed to give a ketonic product. 2,4-Lutidine also furnished a non-ketonic compound under the same conditions.

Several attempts to prepare β-(3-pyridyl)isopropylamine were unsuccessful. Contrary to expectation (4), pure 1-nicotinyl-1-isonitrosoethane (5) absorbed only two moles of hydrogen under the conditions of the Rosenmund and Karg reduction, which has been applied by the authors of this reaction to the reduction of isonitroso ketones to primary amines.

The synthesis of most of the β-thiazolylethylamines (X) followed, on the whole, the pattern set by Price and Pickel (6) in their preparation of β-(4-methyl-5-thiazolyl)ethylamine. The necessary bromo keto esters (V) were condensed with thioamides (VI), the resulting ethyl thiazolylacetates (VII) were converted to the nitriles (IX) through the amides (VIII), and the acetonitrile derivatives were hydrogenated to the amines (X). In the reactions leading to thiazoles unsubstituted in position-2, formamide and phosphorus pentasulfide could be used (7) but they proceeded more uniformly when this mixture was replaced by thioformamide.



VI V VII VIII

R′ or R″ may be —CH_2COOEt

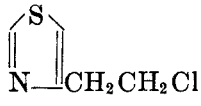
IX X

The dehydration of the amides to the nitriles went best under the influence of phosphorus oxychloride. Difficulties encountered in the dehydration of thiazole-4-acetamide were overcome by modifying the standard procedure. The hydrogenation of the nitriles was accomplished in the presence of Raney nickel catalyst, if necessary at elevated pressures. However, the catalytic hydrogenation of thiazole-4-acetonitrile did not go satisfactorily for us even though various conditions and catalysts were tried. On the other hand, Erlenmeyer and Müller (2) did not mention any difficulty in this reduction in their report of the synthesis of β-(4-thiazolyl)ethylamine. We had begun an alternative synthesis (XI–XIV) but did not complete it after reading the paper of the Swiss authors.

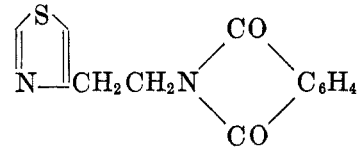
β-Chloropropionyl chloride (XI) was converted to 1-bromo-4-chlorobutanone-2 (XII) *via* the diazo ketone, and the bromo ketone was condensed with thioformamide to yield β-(4-thiazolyl)ethyl chloride (XIII). The phthalimido compound XIV prepared next was hard to hydrolyze, and this approach was interrupted at this point.

$ClCH_2CH_2COCl$ XI

$ClCH_2CH_2COCH_2Br$ XII



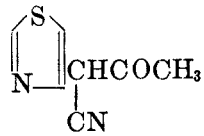
XIII



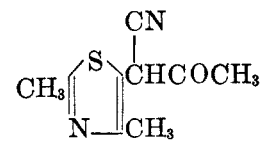
XIV

The effect of N-alkylation of the primary amino group in an analgesically active ethylamine derivative was tested in the case of β-(2-methyl-4-thiazolyl)-benzylethylamine. This secondary amine did not exhibit any of the analgesic activity observed in the primary amine (I) from which it was prepared through the benzal derivative.

For a contemplated synthesis of β-thiazolylisopropylamines the corresponding thiazolyl acetone derivatives were needed as intermediates. Their preparation from thiazolyl acetonitrile derivatives and methylmagnesium halides proved unsuitable because of excessive formation of tars. Condensation of the acetonitriles with ethyl acetate was successful in two cases, but the cyano ketones thus obtained (XV) and (XVI) yielded only the corresponding thiazolyl acetonitrile derivatives on acid cleavage.



XV



XVI

EXPERIMENTAL[3]

2-Pyridylacetone. This ketone was prepared from α-picolyllithium and acetonitrile by a method developed independently by us but which was essentially that described by Ruigh (8). The yield was around 35%. See the details for the preparation of 6-methyl-2-pyridylacetone.

β-(2-Pyridyl)isopropylamine. A solution of 69 g. (0.51 mole) of 2-pyridylacetone in 52 g. of 85% formic acid was added dropwise to 112.5 g. (2.5 moles) of formamide in an apparatus set for downward distillation, and with the reaction flask in an oil-bath heated to 160–180°. After the addition was completed, heating was continued for five hours, water and other low-boiling materials were removed under reduced pressure up to 84° (8 mm.), and the remaining liquid was cooled and treated with two 100-cc. portions of concentrated hydrochloric acid. Some ammonium chloride precipitated; the mixture was heated on a steam-bath for one hour, cooled, made strongly alkaline, and distilled with steam. Two liters of clear distillate was collected, made strongly alkaline by addition of solid sodium hydroxide, and the precipitated oil was separated. The aqueous layer was extracted several times with ether and benzene, the extracts were combined with the oil, and dried over potassium hydroxide. Fractionation of the dried solution yielded 42 cc. (about 60%) of a colorless oil, b.p. (12 mm.) 96.5–97°. The boiling point reported in the literature (9) is 103–104° (13 mm.).

No crystalline hydrochlorides or sulfates of the base could be obtained.

6-Methyl-2-pyridylacetone. To a suspension of 13 g. of lithium in 400 cc. of dry ether, stirred mechanically under an atmosphere of nitrogen, was added a solution of 147 g. of dry bromobenzene in 200 cc. of ether over a period of two hours. After the spontaneous refluxing had subsided, stirring and boiling was maintained for another three hours. A solution of 100 g. of pure 2,6-lutidine in 100 cc. of ether was dropped in without external heating. The mixture turned orange-red and boiled. It was refluxed for two hours, and allowed to stand under nitrogen overnight. A solution of 39 g. of dry acetonitrile in 100 cc. of ether was added slowly to the stirred and slightly warmed mixture. Mild refluxing and a lightening of the color were observed. After another four to five hours' boiling, the mixture was poured onto 500 g. of crushed ice, and neutralized and hydrolyzed with a mixture of 350 g. of ice and 350 cc. of 35% hydrochloric acid with external cooling and stirring. The ether layer was separated, the acid solution washed with ether, cooled, and made alkaline with an ice-cold solution of 200 g. of sodium hydroxide in 300 cc. of water. The alkaline mixture was extracted with six portions of ether, the ether extract was dried over sodium sulfate, filtered, and evaporated. The residue was fractionated, yielding as the main portion a yellow oil weighing 71 g., b.p. 96–98° (0.5 mm.), 114–115° (9.5–10 mm.), 119–120° (16 mm.). From the foreruns, another 8 g. of the ketone was obtained.

The *picrate* crystallized from ethanol as yellow needles, m.p. 136–137.5°.

Anal. Calc'd for $C_{15}H_{14}N_4O_8$: C, 47.62; H, 3.73; N, 14.81.
Found: C, 47.98; H, 3.61; N, 14.77.

The *semicarbazone* was prepared from the ketone and a neutral semicarbazide solution in aqueous alcohol. After removal of the alcohol, colorless needles separated which, after two recrystallizations from dilute ethanol, appeared as shining crystals, m.p. 144–144.5°.

Anal. Calc'd for $C_{10}H_{14}N_4O$: N, 27.17. Found: N, 26.79.

β-(6-Methyl-2-pyridyl)isopropylamine. The Leuckart reaction was performed on the whole as described for the lower homolog. A solution of 28 g. of 6-methyl-2-pyridylacetone in 20.8 g. of 88% formic acid, and 44.8 g. of formamide were used. The crude amine was extracted from the reaction mixture without previous steam distillation. The fraction of b.p. 72° (0.5 mm.), 78–82° (1–1.5 mm.), 94° (4.5 mm.), 95° (5 mm.), 112–113° (14–15 mm.), weighed 13.7 g. and consisted of a colorless oil of strong amine odor.

The *dihydrochloride* was prepared in acetone-ether solution, recrystallized from

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[3] All melting points are corrected. Microanalyses by Miss Lillian Siliano and Mrs. Gertrude Carney of Smith, Kline, and French Laboratories.

methanol, and washed with acetone. The colorless crystals melted at 213.5–215° and were slightly hygroscopic.

Anal. Calc'd for $C_9H_{14}N_2 \cdot 2HCl$: Cl, 31.78. Found: Cl, 31.67.

3-(2-Pyridyl)-2-heptanone. Phenyllithium, prepared from 7 g. of lithium dust and 80 g. of bromobenzene in 450 cc. of dry ether, was treated with 75 g. of 2-*n*-amylpyridine[4] and then with acetonitrile as described in the preparation of 6-methyl-2-pyridylacetone. Besides much unchanged starting material (34 g.) and high-boiling fractions, 17 g. of a yellow oil, b.p. 138–142° (4 mm.) was obtained. It yielded a *semicarbazone* which crystallized as colorless crystals from dilute alcohol, m.p. 126–126.5°.

Anal. Calc'd for $C_{13}H_{20}N_4O$: N, 22.57. Found: N, 22.35, 22.44.

1-Amino-2-methyl-3-(2-pyridyl)hexane. The Leuckart reaction with 17 g. of 3-(2-pyridyl)heptanone-2, 12.5 g. of formic acid, and 27 g. of formamide yielded 9 g. of an almost colorless oil, b.p. 129–130° (2.5 mm.), 152–154° (4–5 mm.) which turned pale brown on standing and was not obtained in a completely pure state. The hydrochloride, picrate, sulfate, and phenylurea could not be crystallized.

Anal. Calc'd for $C_{12}H_{20}N_2O$: Neut. equiv., 192.3. Found: 201.3, 200.0.

(5-Ethyl-2-pyridyl)acetone. One hundred grams of 2-methyl-5-ethylpyridine[5] was allowed to react with phenyllithium prepared from 14.7 g. of lithium dust and 185 g. of bromobenzene, and then treated with 70 g. (100% excess) of acetonitrile. The mixture was worked up as usual, and the oily reaction product fractionated. A considerable amount of unchanged starting material was recovered; the ketonic fraction (36 g.) boiled at 90–130° (1.5 mm.), mostly at 112–113°. Two refractionations yielded 22 g. of pale yellow oil, b.p. 95° (0.3 mm.). It was converted to the *picrate*, and the long yellow needles of the salt were recrystallized from acetone-ethanol to the constant melting point 108–109.5°.

Anal. Calc'd for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.38, 14.45.

β-(5-Ethyl-2-pyridyl)isopropylamine. This compound was prepared by the Leuckart reaction using 44 g. of (5-ethyl-2-pyridyl)acetone, 32.4 g. of formic acid, and 70 g. of formamide. The yield of the amine, b.p. 100° (1.5 mm.), was 12 g. The colorless oily base did not give a solid hydrochloride. The *picrate* crystallized from acetone or ethanol as long yellow needles, m.p. 222–224° (dec.).

Anal. Calc'd for $C_{16}H_{19}N_5O_7$: N, 17.81. Found: N, 18.08, 17.91.

Ethyl γ-bromoacetoacetate. The directions of Conrad (10) were modified in the following manner.

To an ice-cold solution of 600 g. of ethyl acetoacetate in 750 cc. of dry ether, 741 g. of bromine was added dropwise in the course of 90 minutes with vigorous shaking and good cooling. Hydrogen bromide was evolved during the addition. After standing at room temperature for 24 hours, the mixture was decomposed with 600 g. of ice, washed with a sodium carbonate solution saturated with sodium chloride, to alkaline reaction, and finally with saturated sodium chloride solution. The ether layer was dried over calcium chloride with shaking for one day, the solvent removed under reduced pressure on a water-bath, and the cooled residual oil stabilized immediately by addition of 2–3 g. of barium carbonate. The reddish lachrymatory oil may be kept in a dark bottle for several days. The yield in several runs varied from 510 to 825 g. Attempts to distill the crude brominated ester under greatly diminished pressure resulted in considerable decomposition with evolution of hydrogen bromide. Moreover, the colorless distillate did not furnish appreciably better yields in thiazole ring closures than the crude material.

The red bicarbonate-alkaline extract of the crude reaction mixture contained small amounts of a highly lachrymatory oil, probably ethyl α-bromoacetoacetate, which could be liberated by acidifying the solution.

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[4] Purchased from Reilly Tar and Chemical Corporation and redistilled, b.p. 208–209° (753 mm.).

[5] Kindly supplied by Dr. Robert Frank, University of Illinois.

Ethyl 4-thiazolylacetate. (a) A mixture of 400 g. of crude ethyl γ-bromoacetoacetate, 400 g. of dry benzene, 80 g. of formamide, and 80 g. of (practical grade) phosphorus pentasulfide was shaken vigorously for one to two and one-half hours until it became warm spontaneously. The flask was immersed in cold water with continued shaking, and the temperature was not permitted to rise above 50°. The exothermic condensation lasted about 90 minutes, and the yellow phosphorus pentasulfide turned to a reddish tar. The mixture was then allowed to stand for 18 to 24 hours, and decomposed with 1075 cc. of 0.75 *N* hydrochloric acid. The large quantity of brown resins was filtered, the two layers in the filtrate were separated, and the acid solution was washed several times with ether. It was then cleared with Darco, made alkaline with solid sodium carbonate, and extracted with ten portions of ether. The combined ether extracts were washed with saturated sodium chloride solution, dried over sodium sulfate for at least one day, and filtered through Darco in order to remove some tar which settled out slowly. The solvent was removed, and the oily residue fractionated. The colorless ester boiled at 111° (2 mm.), 116° (6 mm.), 138–140° (30 mm.), or 160° (71 mm.) and smelled slightly of pyridine. The best yield obtained in eight analogous condensations was 60 g., but the average was 35 g.

If the temperature was allowed to rise above 50° during the condensation it became hard to control the reaction. In one instance cooling was delayed too long, and the solvent boiled out explosively. In another, the reaction was so slow to start that the flask was warmed on a steam-bath; although it was set in an ice-bath as soon as the reaction began, the reaction could not be controlled.

The *picrate* of the ester crystallized from ethanol or methanol; the pale yellow needles melted at 109–110°. A recent article (11) records this melting point at 112°.

Anal. Calc'd for $C_{13}H_{12}N_4O_9S$: N, 14.00. Found: N, 14.16.

(b) Our second method, used independently, is so similar to that recently described by Jones, Robinson, and Strachan (11) that we wish to forego a detailed description. The thioformamide used was kindly supplied by Dr. C. C. Christman, then of Merck & Company, Elkton, Virginia. The yields in several runs were essentially those obtained by the British authors.

4-Thiazolylacetamide. A mixture of 198 g. of ethyl 4-thiazolylacetate and 600 cc. of 20% ammonium hydroxide was shaken overnight, the clear solution evaporated under reduced pressure or under an air-jet, and the semi-solid residue treated with some dioxane. The crystalline amide was filtered and recrystallized from dioxane. By working up the mother liquors, additional quantities of the amide were obtained, a total of 132.5 g. (74%). In another run, 55 g. of the ester yielded 48 g. (98%) of the amide. The colorless plates melted at 123–123.5°.

Anal. Calc'd for $C_5H_6N_2OS$: N, 19.70. Found: N, 19.83.

4-Thiazolylacetonitrile. Fifty grams of finely powdered 4-thiazolylacetamide was added in several portions to 300 cc. of phosphorus oxychloride contained in a 1-liter flask cooled in water. The mixture now contained large lumps of material and was shaken mechanically for 72 hours. The fine pale brown powder was filtered, washed with some phosphorus oxychloride, and placed in a flask containing 500 g. of fresh phosphorus oxychloride. This mixture was boiled under reflux for two hours until all the solid had gone into solution. This could be facilitated by crushing larger lumps with a glass rod, or by adding some sodium chloride which, by mechanical action, broke up the lumps. The yield of the nitrile was not affected by the addition of sodium chloride. The dark clear solution thus obtained, and the phosphorus oxychloride filtrate from the original treatment of the amide, were worked up separately in a similar manner.

Excess phosphorus oxychloride was removed under reduced pressure, the brown viscous residue decomposed carefully with chipped ice, and the solution filtered from tar through a layer of Darco. At this point, the two acid solutions were combined, and made distinctly alkaline with sodium bicarbonate. Much sodium phosphate, and some tar precipitated. After filtration, the precipitate was washed well with ether and discarded. The filtrate was extracted exhaustively with ether, the ether extract dried over sodium sulfate, the solvent

removed on a steam-bath, and the oily residue fractionated. The colorless distillate boiled at 97–98° (2 mm.) or 110° (5 mm.), $n_D^{25.6}$ 1.5391. The yield was 81%. This contrasts with the 40–50% obtained by Erlenmeyer and Müller (2) by dehydration with phosphorus pentoxide.

Anal. Calc'd for $C_5H_4N_2S$: C, 48.37; H, 3.25.

Found: C, 48.26; H, 3.75.

The *picrate* crystallized from ethanol as yellow needles, m.p. 107.5–108.5°.

Anal. Calc'd for $C_{11}H_7N_5O_7S$: N, 19.83. Found: N, 19.86.

α-(4-Thiazolyl)-α-cyanoacetone. To 7.2 g. of sodium dust dispersed in 200 cc. of hot xylene by rapid stirring under an atmosphere of nitrogen, 40 cc. (about 1.5 moles) of absolute ethanol was dropped slowly without further external heating. After the spontaneous boiling had subsided, the mixture was stirred for another twenty minutes, cooled to 40°, and a mixture of 30 g. of 4-thiazolylacetonitrile, 32 g. of ethyl acetate freshly distilled over phosphorus pentoxide, and 500 cc. of absolute ether was added dropwise. Occasional cooling was necessary to keep the temperature at 30–40°. The color of the mixture changed to orange-yellow, and the sodium salt of the cyano ketone precipitated out. After stirring rapidly for another 90 minutes, 100 cc. of dry ether was added to complete the precipitation of the sodium salt. The salt was filtered, washed with ether, dissolved in 200 cc. of water, and the solution extracted with ether. It was then acidified slowly with acetic acid, and made ammoniacal. The precipitated oil was extracted with six portions of ether, the extracts were dried over sodium sulfate, the solvent was evaporated, and the dark oil was distilled. It boiled at 140° (1–2 mm.), and the colorless distillate solidified in the receiver to crystals weighing 23.7 g. (59%). Recrystallization from dilute methanol yielded prisms or needles, m.p. 65.5–67.5°.

Anal. Calc'd for $C_7H_6N_2OS$: N, 16.93. Found: N, 16.86.

Hydrolysis of α-(4-thiazolyl)-α-cyanoacetone. A suspension of three grams of the cyano ketone in 21 cc. of 15% sulfuric acid was boiled under reflux for 7.5 hours; the material steam-distilled into the condenser, and then dissolved slowly as hydrolysis proceeded. The cooled solution was made alkaline with sodium carbonate and extracted five times with ether. The residual oil from the dried ether solution was converted to a picrate which melted at 103–105°; a mixture melting point with 4-thiazolylacetonitrile picrate (m.p. 107–108°) was 106–107°. The oily reaction product gave no semicarbazone.

1-Bromo-4-chlorobutanone-2. Eighty grams of β-chloropropionyl chloride was dropped into a stirred solution of diazomethane (from 215 g. of nitrosomethylurea) in 3 l. of methylene chloride at −5° over a period of forty minutes. After the vigorous evolution of nitrogen had slowed down, the solution was allowed to stand at room temperature overnight. It was then cooled to 0°, stirred rapidly, and 90 cc. of 48% hydrobromic acid added gradually. Stirring was continued for several hours, anhydrous sodium carbonate was then added to neutralize excess hydrogen bromide, the methylene chloride layer was separated, dried over calcium chloride, and the solvent distilled, the last portions being removed under reduced pressure. The vacuum distillation of the solvent was interrupted as soon as the bromo ketone turned dark; the lachrymatory oil weighed 80 g. and was not purified further.

β-(4-Thiazolyl)ethyl chloride.[6] Commercial thioformamide was diluted with twice its volume of water, and extracted into several portions of ether. The solvent was distilled under reduced pressure, and the pale brown oil used immediately.

Eighty grams of crude 1-bromo-4-chlorobutanone-2 was dissolved in 100 cc. of absolute ethanol, the stirred solution cooled to − 5°, and 54 g. of thioformamide, dissolved in 54 cc. of ethanol, dropped in over a period of one hour, the temperature being kept below 0°. Careful cooling was necessary especially towards the end of the period when the temperature tended to rise considerably. After standing at 4° for two days the solution was concentrated under diminished pressure, the dark tarry residue was diluted with 100 cc. of 0.1 *N* hydrochloric acid, and filtered through filter pulp and charcoal. The slightly turbid filtrate

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[6] Prepared with the assistance of Mr. R. E. Ferebee.

was made alkaline with sodium bicarbonate, and extracted with six 100-cc. portions of ether. The yellow ether solution was dried over potassium carbonate, and the solvent distilled in a vacuum. The residual oil was converted to the picrate in ethanol solution. The crude picrate weighed 79.5 g. (49%, based on the bromo ketone). It was recrystallized by dissolving it in a small volume of hot acetone, adding an excess of absolute ethanol, and boiling off the acetone. The picrate was very sparingly soluble in ethanol and crystallized on cooling. The yellow needles melted at 134°.

Anal. Calc'd for $C_{11}H_9ClN_4O_7S$: C, 35.07; H, 2.41; N, 14.87.
Found: C, 35.52; H, 2.69; N, 14.53.

The base was liberated by dissolving the picrate in 75 cc. of an 8% lithium hydroxide (12) solution and extracting exhaustively into ether. The ether extract was placed over anhydrous potassium carbonate which both dried the solution and precipitated some potassium picrate. The solution was cleared with Darco, filtered, and the ether distilled, the last 100 cc. being removed in a vacuum. The oily β-(4-thiazolyl)ethyl chloride (20 g.) was immediately condensed with potassium phthalimide.

2-(4-Thiazolyl)-N-phthalimidoethane. Condensation of 20 g. of the oily 2-(4-thiazolyl)-ethyl chloride just described with 40 g. of potassium phthalimide in 200 cc. of decalin at 180–190° with stirring for nine hours, filtration from insoluble material, and removal of the decalin *in vacuo* resulted in a dark residue weighing 2.5 g. which crystallized from ethanol. Recrystallization from dilute ethanol furnished colorless needles, m.p. 99–100° (after slight sintering).

Anal. Calc'd for $C_{13}H_{10}N_2O_2S$: N, 10.85. Found: N, 10.70.

Ethyl (2-methyl-4-thiazolyl)acetate was prepared from thioacetamide and ethyl γ-bromoacetoacetate by the method of Steude (13) without isolation of its hydrobromide. The colorless ester boiled at 138–140° (20 mm.) or 165° (31 mm.). The yields, in several batches, varied from 23 to 41%.

The *hydrochloride* of the ester crystallized slowly from acetone. Recrystallized from methanol-ether, the colorless prisms melted at 184–186° (decomp.).

Anal. Calc'd for $C_8H_{11}NO_2S \cdot HCl$: N, 6.32. Found: N, 6.54.

2-Methyl-4-thiazolylacetamide. Fifty-seven grams of ethyl 2-methyl-4-thiazolylacetate was shaken with 165 cc. of 20% ammonium hydroxide overnight, the dark clear solution filtered rapidly with some charcoal, and the amide allowed to crystallize from the filtrate. The long, colorless octagonal plates were washed with a little ammonium hydroxide. They were practically pure; recrystallization from dioxane led to the m.p. 139–140°. By concentrating and purifying the mother liquors, a total yield of 42 g. was obtained.

Anal. Calc'd for $C_6H_8N_2OS$: N, 17.94. Found: N, 18.29, 18.38.

2-Methyl-4-thiazolylacetonitrile. A mixture of 38 g. of 2-methyl-4-thiazolylacetamide and 250 cc. of freshly distilled phosphorus oxychloride was refluxed gently for 90 minutes. The solid amide melted to a brown oil which gradually went into solution; after a few minutes, crystals separated out but went back into solution in the course of the heating. Excess phosphorus oxychloride was removed at 60° and 35 mm. pressure, the residue was decomposed with crushed ice, and the cooled solution was made strongly alkaline with sodium carbonate. The mixture was extracted with three portions of ether, the ether layer was washed with water and filtered with the aid of Darco. The clear, almost colorless solution was dried over sodium sulfate, the solvent was removed on a steam-bath, and the oily nitrile distilled at 143° (26 mm.) or 104–105° (3 mm.) as a colorless oil, n_D^{25} 1.5252. The yield was 92%.

The *picrate* crystallized from ethanol as hard yellow prisms, m.p. 104–106°.

Anal. Calc'd for $C_{12}H_9N_5O_7S$: N, 19.07. Found: N, 19.63.

β-(2-Methyl-4-thiazolyl)ethylamine. A solution of 44 g. of 2-methyl-4-thiazolylacetonitrile in 440 cc. of saturated ethanolic ammonia was mixed with 20 g. of Raney nickel catalyst, and hydrogenated at an initial pressure of 75 atmospheres. Absorption began at 110°, and was completed at 120–130° overnight. The catalyst was filtered with the aid of Darco, the filtrate concentrated in a vacuum at 90°, and the dark oil fractionated. At 82–83° (2–3

mm.), or 78° (1 mm.), 19 g. of a colorless oil distilled, n_D^{25} 1.5350. Its *picrate* crystallized as long yellow needles from ethanol, m.p. 209–211° (decomp.).

Anal. Calc'd for $C_{12}H_{13}N_5O_7S$: N, 18.86. Found: N, 19.05.

Besides the primary amine, a viscous greenish fraction of b.p. 150–210° (2 mm.) was also obtained. It was converted to the picrate, and the salt recrystallized from much ethanol. The broad golden-yellow needles melted at 148–149.5° and appeared to be di-β-(2-methyl-4-thiazolyl)ethylamine picrate.

Anal. Calc'd for $C_{18}H_{20}N_6O_7S_2$: N, 16.93. Found: N, 16.99.

The base was liberated from the pure picrate, dried over potassium hydroxide, and the almost colorless oil converted to the hydrochloride in acetone-ether solution. After recrystallization from methanol-acetone the colorless, water-soluble crystals melted at 205–207°; yield, 1 g.

Anal. Calc'd for $C_{12}H_{17}N_3S_2 \cdot 3HCl$: N, 11.15. Found: 10.89.

In another batch, hydrogenation of the nitrile proceeded rapidly under ordinary pressure at 25°. The yield of primary amine was 75%. However, in several other runs, high pressures had to be employed.

β-(2-Methyl-4-thiazolyl)ethylbenzalimine. A solution of 19 g. of β-(2-methyl-4-thiazolyl)-ethylamine in 20 cc. of absolute ethanol was dropped into an ice-cold solution of 14 g. of freshly distilled benzaldehyde in 28 cc. of absolute ethanol. After standing at room temperature for 48 hours the pale yellow solution was concentrated at 15 mm. and 70°, and the oily residue fractionated. Besides 9 g. of unchanged primary amine, a fraction boiling at 163° (2 mm.) was obtained in a yield of 28.5 g. The colorless oil was redistilled and exhibited b.p. 152–154° (1 mm.), n_D^{26} 1.5885.

The *dipicrate* crystallized as fine yellow needles from a small volume of ethanol; m.p. 129–130°.

Anal. Calc'd for $C_{25}H_{20}N_8O_{14}S$: N, 16.31. Found: N, 16.94.

β-(2-Methyl-4-thiazolyl)ethylbenzylamine. A solution of 28.5 g. of freshly distilled β-(2-methyl-4-thiazolyl)ethylbenzalimine in 400 cc. of absolute ethanol was hydrogenated in the presence of 10 g. of Raney nickel catalyst at 90° and 75 atmospheres of hydrogen for one day. After filtering the catalyst, the almost colorless solution was concentrated at 20 mm. pressure, and the oily residue fractionated. After a small forerun, 22.2 g. (77.4%) of a colorless oil boiled at 154–155° (1–2 mm.); n_D^{27} 1.5668. It was converted to its *dihydrochloride* in acetone solution, and the salt recrystallized from methanol-ether. The colorless leaflets melted at 186–189° (evacuated tube) after sintering at 183°.

Anal. Calc'd for $C_{13}H_{16}N_2S \cdot 2HCl$: Cl, 23.23. Found: Cl, 23.02, 23.01.

The *picrate* crystallized from ethanol. The yellow needles melted at 165.5—167.5°.

Anal. Calc'd for $C_{13}H_{16}N_2S \cdot C_6H_3N_3O_7$: N, 15.18. Found: N, 14.86, 14.90.

Ethyl (2,4-dimethyl-5-thiazolyl)acetate. A solution of 65 g. of thioacetamide in 260 cc. of absolute ethanol was cooled to −3°, and 140 g. of ethyl β-bromolevulinate, dissolved in 140 cc. of absolute ethanol, dropped in over a period of one hour with occasional shaking. After four hours at −3°, the mixture was kept at 4° overnight, and at 25° for 36 hours. The solvent was distilled at 40° and 20 mm., the pale yellow residue dissolved in 500 cc. of 0.1 *N* hydrochloric acid, and extracted with ether. The acid solution was made alkaline with sodium bicarbonate and extracted with four portions of ether. The ether extract was dried over sodium sulfate, filtered, the solvent distilled, and the pale yellow oil fractionated. The colorless fraction boiling at 150° (18 mm.) weighed 91 g. (78%) and showed n_D^{24} 1.5115. It turned yellow on standing.

The *picrate* crystallized from ethanol as yellow blades, m.p. 109.5–111°.

Anal. Calc'd for $C_{15}H_{16}N_4O_9S$: N, 13.08. Found: N, 13.11.

2,4-Dimethylthiazole-5-acetic acid. A solution of 20 g. of the ester and 6.5 g. of potassium hydroxide in 100 g. of methanol was refluxed for three hours, the solvent removed under reduced pressure, the yellow residue dissolved in water and neutralized to *p*H 6.5. The acid crystallized after a few minutes. After completing the crystallization overnight, the ma-

terial was filtered, dried in the air, recrystallized from a little ethanol, and washed with ethyl acetate and finally with ether. The yield of colorless crystals melting at 183–184° was 18 g.

Anal. Calc'd for $C_7H_9NO_2S$: N, 8.18. Found: N, 8.37.

2,4-Dimethyl-5-thiazolylacetamide. This amide was prepared from the ester with ammonium hydroxide in the usual manner. It crystallized from the reaction mixture in almost pure form in a yield of 82%. Recrystallization from a little ethanol rendered colorless felted needles, m.p. 174–175.5°.

Anal. Calc'd for $C_7H_{10}N_2OS$: N, 16.45. Found: N, 16.69.

2,4-Dimethyl-5-thiazolylacetonitrile. Forty-two grams of 2,4-dimethyl-5-thiazolylacetamide was mixed slowly with 420 cc. of phosphorus oxychloride, and the mixture heated to boiling. The amide turned oily and went into solution, but a crystalline precipitate appeared soon which, in turn, went into solution in the course of the reaction. After 75 minutes, the excess phosphorus oxychloride was distilled under reduced pressure, the dark viscous residue was decomposed with 500 g. of ice, the brown solution was filtered with Darco, and made alkaline with sodium carbonate. The nitrile precipitated as a brown oil which crystallized soon; the yield, augmented by some additional material obtained by extraction of the alkaline mother liquors with benzene, was 64%. Purification by distillation at 123° (2.5 mm.) yielded a colorless distillate which solidified in the receiver. It was recrystallized from dilute ethanol, the resulting colorless prisms melting at 87–88°.

Anal. Calc'd for $C_7H_8N_2S$: N, 18.41. Found: N, 18.38.

The *picrate* crystallized from ethanol as shining yellow leaflets, m.p. 122.5–124°.

Anal. Calc'd for $C_{13}H_{11}N_5O_7S$: N, 18.37. Found: N, 18.46.

β-(2,4-Dimethyl-5-thiazolyl)ethylamine. A solution of 23 g. of 2,4-dimethyl-5-thiazolylacetonitrile in 460 cc. of absolute ethanol was hydrogenated in the presence of 12 g. of Raney nickel catalyst under atmospheric pressure. Almost all the required hydrogen was absorbed within a few hours. The catalyst was filtered with Darco, the pale yellow filtrate concentrated in a vacuum, and the residue distilled. Nine grams of colorless distillate, b.p. 84° (2 mm.), n_D^{26} 1.5358 was collected.

The *dipicrate* crystallized from ethanol and melted at 189–190°.

Anal. Calc'd for $C_{19}H_{18}N_8O_{14}S$: N, 18.24. Found: N, 18.97, 18.95.

α-(2,4-Dimethyl-5-thiazolyl)-α-cyanoacetone. A mechanically stirred suspension of 22.4 g. of sodium methoxide in 500 cc. of absolute ether was treated, under an atmosphere of dry nitrogen, with a mixture of 56 g. of 2,4-dimethylthiazolyl-5-acetonitrile and 35 g. of dry ethyl acetate in 700 cc. of ether. When, after the dropwise addition of 50 cc. of this mixture, and refluxing for fifteen minutes, no reaction was observed, 10 cc. of absolute ethanol was added. The color changed immediately to a reddish purple. The remainder of the reagents was now added over a period of 45 minutes while the sodium enolate separated as a pale tan powder. Refluxing was continued for another five and one-half hours, and 5 g. of ethyl acetate and 5 cc. of absolute ethanol were added in portions. The slurry became somewhat thicker; the precipitate was filtered, and washed with benzene and ether. By evaporation of the filtrate, 13 g. of unaltered 2,4-dimethyl-5-thiazolylacetonitrile was recovered.

The precipitate was treated with 400 cc. of water, and 15.5 g. of colorless insoluble material removed. This material could be dissolved in hot dilute mineral acids, and crystallized when the solution was made ammoniacal. It was not studied further.

The clear alkaline filtrate of the insoluble material was acidified to *p*H 6.5, the precipitated cyano ketone was filtered, and washed with a little water. The almost colorless crystals weighed 34.5 g., and no appreciable additional amount could be obtained from the filtrate by evaporation at *p*H 6–7. Recrystallization from ethanol-water yielded colorless needles which sintered very slightly at 114°, and seemed to re-solidify at 120°. On heating to 200°, they darkened, and decomposed completely at 204–205°.

Anal. Calc'd for $C_9H_{10}N_2OS$: N, 14.42. Found: N, 14.44.

Hydrolysis of the cyano ketone with 15% sulfuric acid led to almost complete recovery of 2,4-dimethylthiazole-5-acetonitrile, and only very small amounts of an oily non-ketonic by-product were collected.

2-Benzyl-4-thiazolylacetic acid. The crude ethyl γ-bromoacetoacetate from 800 g. of ethyl acetoacetate was added to a well agitated ice-cold suspension of 300 g. of phenylthioacetamide in 1 liter of ethanol over a period of 90 minutes. When about one-half of the bromo ester had been added, the mass solidified but became more liquid and lumpy as the reaction proceeded. The mixture stood in ice for two hours, and at 25° for 48 hours; it liquefied during this latter period. The solvent was distilled under reduced pressure, the brown oily residue treated with 0.1 *N* hydrochloric acid, the aqueous solution was separated, washed with ether, and made alkaline with sodium carbonate. The oily ethyl 2-benzyl-4-thiazolylacetate was extracted into three portions of ether, the ether solution dried, filtered, and the solvent distilled. The crude ethyl ester (10 g.) was converted to the amide as described below.

The *picrate* of the ethyl ester crystallized from ethanol as yellow leaflets, melting at 109–110° after slight sintering.

Anal. Calc'd for $C_{20}H_{18}N_4O_9S$: N, 11.43. Found: N, 11.48.

The aqueous alkaline mother liquor of the ethyl ester was acidified slightly with acetic acid, and 2-benzyl-4-thiazolylacetic acid precipitated as colorless felted needles. It was recrystallized from dilute ethanol and melted at 126.5–128°. The yield was 31 g.

Anal. Calc'd for $C_{12}H_{11}NO_2S$: N, 6.01. Found: N, 5.87.

The acid was suspended in 200 cc. of ether and methylated with 0.5 g. of diazomethane. All but 0.5 g. of the acid went into solution in a rapid reaction. The ether solution was washed with sodium carbonate solution and water, dried, the solvent distilled, and the residual crude oily methyl 2-benzyl-4-thiazolylacetate converted to the amide.

In a second experiment, no free 2-benzyl-4-thiazolylacetic acid but only the ethyl ester was obtained. The yield was 81 g.

2-Benzyl-4-thiazolylacetamide. Nineteen grams of crude methyl (or ethyl) 2-benzyl-4-thiazolylacetate was shaken with 150 cc. of 20% ammonium hydroxide overnight, the solidified practically pure amide filtered, and washed with 50 cc. of water. The yield was 17 g. It was recrystallized from a little ethanol and appeared as colorless flat glittering leaflets, m.p. 132–133°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.06. Found: N, 12.01, 11.75.

2-Benzyl-4-thiazolylacetonitrile. The amide was refluxed with a tenfold volume of phosphorus oxychloride for twenty minutes, and the mixture worked up as usual. The solid nitrile was fairly insoluble in dilute acids, but complete precipitation occurred after the acid solution had been made alkaline. It was purified by solution in ether, filtration from some insoluble by-product, and fractionation; the pale yellow oil boiled at 203–205° (3–4 mm.); the yield was 76%. Recrystallization from dilute ethanol with the aid of Darco furnished colorless needles, m.p. 43–44°.

Anal. Calc'd for $C_{12}H_{10}N_2S$: N, 13.07. Found: N, 12.97.

β-(2-Benzyl-4-thiazolyl)ethylamine. A solution of 14 g. of 2-benzyl-4-thiazolylacetonitrile in 200 cc. of saturated absolute ethanolic ammonia was hydrogenated with the aid of 7 g. of Raney nickel catalyst under atmospheric pressure. The reduction was complete within a few hours, and the mixture worked up in the customary manner. Fractionation of the oily amine yielded 7.5 g. of a colorless distillate, b.p. 162–165° (2 mm.) which attracted carbon dioxide from the air with the formation of a solid addition compound.

The *dipicrate* crystallized from ethanol as felted yellow needles, m.p. 143.5–144.5°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2C_6H_2N_3O_7$: N, 16.56. Found: N, 16.47.

The base was recovered from the pure picrate and converted to the *dihydrochloride* in acetone-ether solution. After recrystallization from ethanol-ether, the colorless crystals melted at 167–170°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2HCl$: N, 9.62. Found: N, 9.16, 9.36.

Thiobenzamide. The method of Gabriel and Heyman (14) was modified as follows. A

solution of 200 g. of benzonitrile in 800 cc. of ethanol was saturated with ammonia in the cold, and then hydrogen sulfide was passed in at a moderate rate for 60 hours. The mixture was poured into 4 l. of water, the precipitated thioamide filtered, washed with water, and dried in the air. It melted at 108–111° without recrystallization. The yield was practically quantitative.

2-Phenyl-4-methyl-5-thiazolylacetic acid. A solution of 65 g. of thiobenzamide in 450 cc. of boiling absolute ethanol was treated with the crude ethyl β-bromolevulinate prepared from 100.8 g. of ethyl levulinate, over a period of ten minutes. Only a moderate exothermic reaction occurred, the solution first turning red and then again lighter. After refluxing for 24 hours, dilute hydrochloric acid was added, some insoluble hydrobromide filtered, the filtrate concentrated to remove excess ethanol, and extracted with ether. The ether solution was washed with dilute hydrochloric acid, and the combined acid solutions were allowed to stand. They deposited crystals of ethyl 2-phenyl-4-methyl-5-thiazolylacetate hydrobromide, which after combination with the insoluble precipitate previously filtered, weighed 43.5 g. The salt was recrystallized from ethanol-ether. The colorless crystals were sparingly soluble in water with partial hydrolysis and melted at 170–172° after sintering at 167°.

Anal. Calc'd for $C_{14}H_{15}NO_2S \cdot HBr$: N, 4.09. Found: N, 4.22.

When the acid mother liquors of the hydrobromide were neutralized with sodium carbonate, and buffered with a little acetic acid, 2 g. of ammonium 2-phenyl-4-methyl-5-thiazolylacetate precipitated. Two recrystallizations from absolute ethanol yielded fine colorless needles, m.p. 228–229°.

Anal. Calc'd for $C_{12}H_{14}N_2OS$: N, 11.91. Found: 11.71.

2-Phenyl-4-methyl-5-thiazolylacetamide. (a) The amide was prepared from ethyl 2-phenyl-4-methyl-5-thiazolylacetate hydrobromide according to the general directions given in a similar case by Price and Pickel (6). It was precipitated from the reaction mixture in a yield of 56% and was recrystallized from dioxane and finally from dilute ethanol. The colorless needles melted at 168–169°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.06. Found: 12.00.

(b) One gram of ammonium 2-phenyl-4-methyl-5-thiazolylacetate was warmed gently with 10 cc. of thionyl chloride for a few minutes, and the red solution allowed to stand overnight. The excess thionyl chloride was distilled under reduced pressure, and 20 cc. of 20% ammonium hydroxide added to the cooled residue. After a vigorous reaction the tarry residue solidified. The amide, obtained in almost quantitative yield, was washed with water and recrystallized once from dilute ethanol. It melted at 167–168°.

2-Phenyl-4-methyl-5-thiazolylacetonitrile. The amide just described was dehydrated with ten times its weight of phosphorus oxychloride, and the mixture worked up as in the analogous cases. The nitrile was very little soluble in dilute acids but was best extracted into ether from an alkaline solution. The ether extract had to be filtered from a small but voluminous tarry precipitate before being washed, and dried over sodium sulfate. The nitrile was purified by distillation; it boiled at 194–196° (6 mm.) and solidified in the receiver. It was finally recrystallized from slightly dilute ethanol, the colorless needles melting at 104.5–106°. The yield was nearly quantitative.

Anal. Calc'd for $C_{12}H_{10}N_2S$: N, 13.07. Found: 13.07.

β-(2-Phenyl-4-methyl-5-thiazolyl)ethylamine. After several trials, the following conditions seemed to give the best results.

A solution of 6 g. of 2-phenyl-4-methyl-5-thiazolylacetonitrile in 400 cc. of absolute ethanol containing 8 g. of potassium hydroxide was hydrogenated with 10 g. of Raney nickel catalyst under ordinary pressure. About 75% of the calculated amount of hydrogen was absorbed in two days, the catalyst filtered, the solvent removed under reduced pressure, and the residue taken up in dilute hydrochloric acid. The acid solution was washed with ether to remove traces of unreduced nitrile, made alkaline, and the amine extracted with three portions of ether. The oily amine from the ether extract boiled at 155–170° (4 mm.).

The *dipicrate* crystallized from ethanol. After several recrystallizations from much

ethanol the orange prisms sintered at 210°, blackened and decomposed at 220–230°, and melted at 238–239° with complete decomposition.

Anal. Calc'd for $C_{24}H_{20}N_8O_{14}S$: N, 16.57. Found: N, 17.05.

The base was regenerated from the picrate by means of lithium hydroxide solution, and converted to its *dihydrochloride* in ethanol-acetone. Recrystallization from the same solvent mixture furnished colorless crystals, m.p. 218–220°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2HCl$: Cl, 24.35; N, 9.62.
Found: Cl, 23.93; N, 9.61.

2-Benzylthiazole. To a boiling solution of 50 g. of phenylthioacetamide in dry benzene, 47 g. of freshly distilled chloroacetaldehyde hydrate was added dropwise with shaking and heating. The reaction was not vigorous; the mixture separated into two layers, the lower one darkening soon. It was refluxed for two and one-half hours with occasional shaking, cooled, diluted with water, made strongly acidic, and the resulting thick emulsion broken up by filtration through Darco. The benzene layer was separated, the acid solution made alkaline with sodium hydroxide and extracted four times with ether. During the first extraction, another bad emulsion occurred which had to be removed as the one above. During the drying of the combined ether extracts with potassium hydroxide, a brown flocculent tar appeared which was filtered before distilling off the ether. The remaining dark oil was fractionated. A colorless oil weighing 35 g. (60.4%) distilled at 106–107° (3 mm.) or 104° (2 mm.) and showed n_D^{20} 1.5919. It was not readily soluble in one equivalent of acid, and darkened on standing.

The *picrate* crystallized from ethanol as yellow needles, m.p. 162–162.5° (decomp.), after some sintering at 157.5°.

Anal. Calc'd for $C_{16}H_{12}N_4O_7S$: N, 13.86. Found: N, 13.99.

2-Benzylthiazoline. A mixture of 3.5 g. of β-bromoethylammonium bromide and 2.5 g. of phenylthioacetamide was heated to 130°; it melted with slight darkening and evolution of gas. The temperature was raised to 190–200° for one hour, the mass was cooled, dissolved in 20 cc. of water, the solution cleared with Darco, made alkaline and extracted twice with ether. The ether extract was washed with water, dried over potassium hydroxide, and the oily residue from this extract distilled. It weighed 1.3 g. and boiled at 125–126° (3–4 mm.) or 135–136° (7 mm.). The colorless oil turned dark on standing.

The *picrate* crystallized from ethanol as long yellow needles, m.p. 141–142°. It was readily soluble in water.

Anal. Calc'd for $C_{16}H_{14}N_4O_7S$: N, 13.83. Found: N, 14.04.

SUMMARY

A number of β-pyridylisopropylamine derivatives, and β-thiazolylethylamines have been prepared. The amines in the pyridine series were obtained by converting α-picoline and some of its derivatives to the corresponding α-pyridyl acetones, and subjecting the ketones to the Leuckart reaction. The thiazolylethylamines were formed by condensing bromo keto esters with thioamides, and converting the resulting alkyl thiazolyl acetates through the amides and nitriles to the amines. Syntheses leading toward β-(4-thiazolyl)ethylamine, and the preparation of two thiazolyl α-cyano ketones are reported.

Several of the primary amines showed analgesic activity. A hypothesis distinguishing them from similar compounds which exhibit histamine-type effects has been advanced.

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