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# Sulfanilamide Compounds. VI. $N^4$-Acyl-$N^1$-heterocyclic Sulfanilamides and $N^1$-heterocyclic Sulfanilamides

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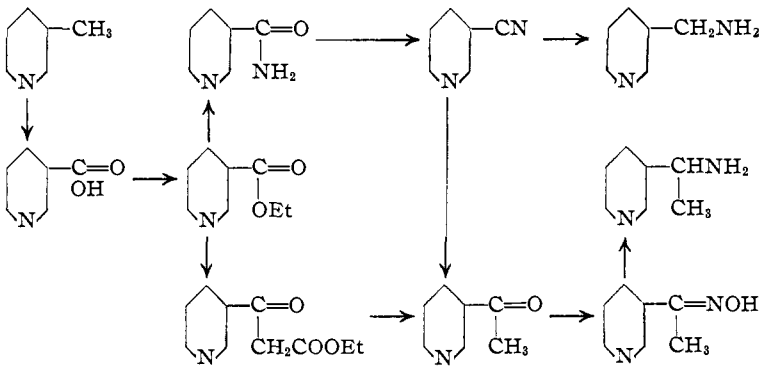
With the ultimate aim of studying the relationships between structure and antibacterial action, we have prepared a series of $N^4$-acyl-sulfanilyl- and sulfanilyl derivatives of 2-, 3- and 4-aminopyridine, 2-, 3- and 4-(pyridyl)-methylamine, and [1-(2-, 3- and 4-pyridyl)-ethyl]-amine. More particularly, we have wished to study the effects of position isomerism, introduction of a methylene group between the heterocyclic ring and amino nitrogen, and the substitution of one of these methylene hydrogens by a lower alkyl group. At this time we are reporting only the preparation and some of the properties of these derivatives; detailed biologic data, now being collected, and the interpretation will be published elsewhere at a later date.

2-Aminopyridine was obtained through a commercial source[1]; 3-aminopyridine was prepared by the degradation of nicotinamide according to Pollak,[2] and 4-aminopyridine by the decomposition of 4-pyridyl-pyridinium dichloride.[3]

The syntheses of the isomeric (pyridyl)-methylamines,[4] and [1(pyridyl)-ethyl]-amines[5] were carried out as indicated in the following scheme




Picolinic acid hydrochloride[6] was prepared by oxidation of 2-picoline; nicotinic acid was obtained as the commercial product,[7] and iso-nicotinic acid[8] by the oxidation of 4-picoline.[9] The pyridine monocarboxylic acid esters were prepared by esterifying the corresponding acids with absolute alcohol and sulfuric acid as described by Camps.[10] Ammonolysis of the esters with strong ammonia water at room temperature gave the corresponding amides[10] which, upon dehydration with phosphoric anhydride, were converted into the respective cyano-pyridines.[11] With moderate pressures of hydrogen and Raney nickel[12] these cyano-pyridines were reduced to the (pyridyl)-methylamines, identified in the cases of the 2- and 3- isomers, as the *p*-nitrobenzoates[4]; the benzoyl derivative of 4-(pyridyl)-methylamine was obtained as an oil instead of the 108° melting solid reported by Graf *et al.*[4] By combined modification of the method of Strong and McElvain[13] and Hurd and Webb[14] the pyridine monocarboxylic acid esters were condensed with ethyl acetate in the presence of anhydrous sodium ethoxide[15] and the condensation products hydrolyzed with aqueous hydrochloric acid to yield methyl-2-pyridyl-,[16] methyl-3-pyridyl-,[17] and methyl-4-pyridyl ketone.[18] Methyl 2- and 3-pyridyl ketones were also prepared through the action of methylmagnesium iodide on 2- and 3-cyano-pyridines according to LaForge's[5] procedure for the 3-isomer. The method was considerably inferior to that of decomposition of the pyridoylacetic es-

(1) B. L. Lemke, New York, N. Y.
(2) Pollak, *Monatsh.*, **16**, 45 (1895).
(3) Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).
(4) Graf, Parathoner and Tatzel, *J. prakt. Chem.*, [2], **146**, 88 (1936) have described the preparation of these amines by reduction of the corresponding cyanopyridines with chromous acetate, but the method appears less desirable than that described later in this report.
(5) LaForge, THIS JOURNAL, **50**, 2477 (1928), prepared one member, [1-(3-pyridyl)-ethyl]-amine, of this group by reduction of methyl-3-pyridyl ketoxime with zinc dust and acetic acid.
(6) Singer and McElvain, *ibid.*, **57**, 1136 (1935).
(7) Gane Chemical Works, Inc., New York, N. Y.
(8) Behrmann and Hofmann, *Ber.*, **17**, 2698 (1884).
(9) 4-Picoline was obtained by decomposition of its oxalate which was isolated from crude "gamma-picoline" by modifying the method of Lidstone, *J. Chem. Soc.*, 241 (1940).
(10) Camps, *Arch. Pharm.*, **240**, 345 (1902).
(11) Camps, *ibid.*, **240**, 366 (1902).
(12) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).
(13) Strong and McElvain, *ibid.*, **55**, 818 (1933).
(14) Hurd and Webb, *ibid.*, **49**, 551 (1927).
(15) Magnani and McElvain, *ibid.*, **60**, 817 (1938); Kroeker and McElvain, *ibid.*, **56**, 1172 (1934).
(16) Pinner, *Ber.*, **34**, 4240 (1901).
(17) Engler, *ibid.*, **22**, 597 (1889).
(18) Pinner, *ibid.*, **34**, 4250 (1901).

TABLE I

| Substituted sulfanilamide | Method of prepn. | Formula | M. p., °C. (uncorr.) | N, % Calcd. | Found |
|---|---|---|---|---|---|
| $N^4$-Acetyl-$N^1$-2-pyridyl- | I and II | $C_{13}H_{13}N_3O_3S$[a] | 224–226 | 14.43 | 14.35 |
| $N^4$-*n*-Caproyl-$N^1$-2-pyridyl- | | $C_{17}H_{21}N_3O_3S$[b] | 200–201 | 12.10 | 12.25 |
| $N^4$-Acetyl-$N^1$-(2-pyridyl)-methyl- | I | $C_{14}H_{15}N_3O_3S$[c] | 124–125 | 13.76 | 13.64 |
| $N^4$-*n*-Caproyl-$N^1$-(2-pyridyl)-methyl- | I | $C_{18}H_{23}N_3O_3S$[c] | 129.5–130.5 | 11.62 | 11.58 |
| $N^4$-Acetyl-$N^1$-[1-(2-pyridyl)-ethyl]- | I | $C_{15}H_{17}N_3O_3S$[d] | 142–142.5 | 13.17 | 13.06 |
| $N^4$-*n*-Caproyl-$N^1$-[1-(2-pyridyl)-ethyl]- | I | $C_{19}H_{25}N_3O_3S$[c] | 143.5–144 | 11.20 | 11.23 |
| $N^4$-Acetyl-$N^1$-3-pyridyl- | I | $C_{13}H_{13}N_3O_3S$[e] | 280 | 14.43 | 14.35 |
| $N^4$-*n*-Caproyl-$N^1$-3-pyridyl- | I | $C_{17}H_{21}N_3O_3S$[c] | 174–175 | 12.10 | 11.95 |
| $N^4$-Acetyl-$N^1$-(3-pyridyl)-methyl- | I | $C_{14}H_{15}N_3O_3S$[c] | 181–181.5 | 13.76 | 13.57 |
| $N^4$-*n*-Caproyl-$N^1$-(3-pyridyl)-methyl- | I | $C_{18}H_{23}N_3O_3S$[c] | 97.5–99.5 | 11.62 | 11.44 |
| $N^4$-Acetyl-$N^1$-[1-(3-pyridyl)-ethyl]- | I | $C_{15}H_{17}N_3O_3S$[c] | 249 | 13.17 | 13.54 |
| $N^4$-*n*-Caproyl-$N^1$-[1-(3-pyridyl)-ethyl]- | I | $C_{19}H_{25}N_3O_3S$[c] | 168.5 | 11.20 | 11.98 |
| $N^4$-Acetyl-$N^1$-4-pyridyl- | II | $C_{13}H_{13}N_3O_3S$[f] | 256–257 | 14.43 | 14.65 |
| $N^4$-*n*-Caproyl-$N^1$-4-pyridyl- | II | $C_{17}H_{21}N_3O_3S$[f] | 222–223 | 12.10 | 11.90 |
| $N^4$-Acetyl-$N^1$-(4-pyridyl)-methyl- | I | $C_{14}H_{15}N_3O_3S$[d] | 196–200 | 13.76 | 13.54 |
| $N^4$-*n*-Caproyl-$N^1$-(4-pyridyl)-methyl- | I | $C_{18}H_{23}N_3O_3S$[c] | 131 | 11.62 | 11.31 |
| $N^4$-Acetyl-$N^1$-[1-(4-pyridyl)-ethyl]- | I | $C_{15}H_{17}N_3O_3S$[d] | 205 | 13.17 | 13.20 |
| $N^4$-*n*-Caproyl-$N^1$-[1-(4-pyridyl)-ethyl]- | I | $C_{19}H_{25}N_3O_3S$[d] | 159–160 | 11.20 | 11.41 |
| $N^1$-2-Pyridyl- | A | $C_{11}H_{11}N_3O_2S$[a] | 189 | 16.86 | 16.94 |
| $N^1$-(2-Pyridyl)-methyl- | A | $C_{12}H_{13}N_3O_2S$[d] | 130.8–131 | 15.97 | 16.24 |
| $N^1$-[1-(2-Pyridyl)-ethyl]- | A | $C_{13}H_{15}N_3O_2S$[d] | 135–136 | 15.16 | 15.01 |
| $N^1$-3-Pyridyl- | A and B | $C_{11}H_{11}N_3O_2S$[c] | 256–257 | 16.86 | 17.55 |
| $N^1$-(3-Pyridyl)-methyl- | A | $C_{12}H_{13}N_3O_2S$[d] | 133–133.5 | 15.97 | 16.14 |
| $N^1$-[1-(3-Pyridyl)-ethyl]- | A | $C_{13}H_{15}N_3O_2S$[c] | 164.5–165.5 | 15.16 | 15.45 |
| $N^1$-4-Pyridyl- | B | $C_{11}H_{11}N_3O_2S$[g] | 235–236 | 16.86 | 17.06 |
| $N^1$-(4-Pyridyl)-methyl- | A | $C_{12}H_{13}N_3O_2S$[d] | 183–183.5 | 15.97 | 16.20 |
| $N^1$-[1-(4-Pyridyl)-ethyl]- | A | $C_{13}H_{15}N_3O_2S$[c] | 194–195 | 15.16 | 15.15 |

[a] Crossley, Northey and Hultquist, THIS JOURNAL, **62**, 372 (1940). [b] Kolloff and Hunter, *ibid.*, **62**, 1646 (1940). [c] From dilute alcohol. [d] From water. [e] Winterbottom, THIS JOURNAL, **62**, 160 (1940). [f] From alcohol. [g] Ewins and Phillips, British Patent 516,288; *cf.* Northey, *Chem. Rev.*, **27**, 106 (1940).

ters. The ketones were readily converted into their respective ketoximes[17,19,20] by treatment with hydroxylamine. Catalytic reduction of these oximes with Raney nickel yielded the corresponding [1-(2-, 3- and 4-pyridyl)-ethyl]-amines.

The $N^4$-acyl-$N^1$-heterocyclic sulfanilamides were prepared by the action of the recrystallized $N^4$-acyl-sulfanilyl chloride on the heterocyclic amine in (I) an acetone–pyridine medium[21] or in (II) dioxane.[22] The $N^1$-heterocyclic sulfanilamides were prepared by hydrolysis of the corresponding $N^4$-acyl-derivatives with either (A) alcoholic hydrochloric acid[21] or (B) aqueous sodium hydroxide.[22]

## Experimental

**4-Picoline Oxalate.**—Two hundred cubic centimeters of "gamma-picoline"[23] contained in a 1-liter beaker was heated to 80–85° on a hot-plate. During the course of five to ten minutes, 220 g. of anhydrous oxalic acid (Eastman Kodak Co. "Practical") was added with good stirring. To the resulting viscous mass, 400 cc. of boiling absolute alcohol (commercial grade) was slowly stirred in and the whole heated briefly on the hot-plate until solution was complete. The solution was allowed to cool spontaneously and stand overnight. The crystalline sludge was then collected, pressed as free as possible from mother liquor and crystallized from 700 cc. of absolute alcohol.[24] The massive, white crystals were collected, washed with a little absolute alcohol and dried in air; yield, 60–70 g., m. p. 139–140°.[25]

**4-Picoline.**—One hundred cubic centimeters of 60% sodium hydroxide was added slowly to a solution of 100 g. of 4-picoline oxalate in 200 cc. of water contained in a 1-liter Erlenmeyer flask. After cooling, the supernatant liquid was decanted and exhaustively extracted with ether. The extract was dried over anhydrous magnesium sulfate, the ether distilled from a steam-bath and the picoline distilled at atmospheric pressure; yield, 30–33 g., b. p. 141–142°.

### (Pyridyl)-methylamines

**(2-Pyridyl)-methylamine.**—Ten grams of Raney nickel was added to a solution of 19.1 g. (0.184 mole) of 2-cyanopyridine in a mixture of 100 cc. of 95% alcohol and 25 cc. of concentrated ammonium hydroxide contained in an

(19) Pinner, *Ber.*, **34**, 4241 (1901).
(20) Pinner, *ibid.*, **34**, 4251 (1901).
(21) Winterbottom, THIS JOURNAL, **62**, 160 (1940).
(22) Crossley, Northey and Hultquist, *ibid.*, **62**, 372 (1940).
(23) Reilly Tar and Chemical Corporation, Indianapolis, Ind.
(24) The hot solution should not be chilled in an ice-chamber, but should be allowed to cool spontaneously without disturbing.
(25) The melting and boiling points reported are not corrected.

appropriate reaction vessel. The mixture was hydrogenated at approximately four atmospheres of hydrogen and at room temperature. After filtering off and washing the catalyst with alcohol, the combined filtrates were distilled; the alcohol and ammonia being removed at atmospheric pressure. (2-Pyridyl)-methylamine distilled at 90–93° at 3 mm.[26]; yield, 7.6 g. (38.2%).

In an analogous fashion, 3-cyano-pyridine gave (3-pyridyl)-methylamine, b. p. 95–98°[27]; yield, 60.1%; *p*-nitrobenzoate, m. p. 190–191°.

Similarly, 4-cyano-pyridine gave (4-pyridyl)-methylamine, b. p. (5 mm.) 115.5–117°; b. p. (3–4 mm.) 110–112°; yield, 60.3%.

### Methyl Pyridyl Ketones

**Methyl 4-Pyridyl Ketone.**—To 26.0 g. (0.382 mole) of anhydrous sodium ethoxide contained in a 1-liter three-necked, round-bottomed flask equipped with a water-cooled condenser, mercury-sealed, mechanical stirrer and a 250 cc. separatory funnel was added a mixture of 37.7 g. (0.25 mole) of ethyl iso-nicotinate and 41.7 g. (0.47 mole) of ethyl acetate with stirring. The mixture became quite warm, assumed a reddish-orange color and the ethoxide slowly dissolved. After stirring for an hour, the mixture was gently refluxed for ten hours, and allowed to stand overnight. The mass was dissolved in 250 cc. of water and the unreacted esters removed by extraction with ether. Dissolved ether was removed from the aqueous solution by warming, after which the cooled solution was neutralized with concentrated hydrochloric acid (20 cc.). The dark oil which appeared was directly dissolved by the addition of a further 80 cc. of concentrated hydrochloric acid. Evolution of carbon dioxide began spontaneously, and the hydrolysis was completed by vigorously refluxing the clear solution for two and one-half hours. The cold acid solution was made alkaline with solid potassium carbonate, exhaustively extracted with ether and the extract dried with anhydrous potassium carbonate. The ether was removed on a steam-bath and the residual oil distilled at atmospheric pressure. The ketone, a pale yellow oil, boiled at 211–212°; yield, 24.0 g. (79.5%).

Under the same conditions, ethyl nicotinate gave methyl 3-pyridyl ketone, b. p. 217–218°; yield, 81.0%,[28] and ethyl picolinate gave methyl-2-pyridyl ketone, b. p. 187–190°; yield, 50.4%.[28]

**[1-(Pyridyl)-ethyl]-amines.**—These amines were prepared by the catalytic reduction of the methyl pyridyl ketoximes according to the procedure described for the (pyridyl)-methylamines. Methyl 2-pyridyl ketoxime was reduced to [1-(2-pyridyl)-ethyl]-amine, b. p. 194–196°; yield, 65.1%. Analysis of the singly-distilled product gave the following: *Anal.* Calcd. for $C_7H_{10}N_2$: N, 22.95. Found: N, 22.02. Methyl 3-pyridyl ketoxime gave [1-(3-pyridyl)-ethyl]-amine,[5] b. p. 216–219°; yield, 53.3% and methyl 4-pyridyl ketoxime yielded [1-(4-pyridyl)-ethyl]-amine, b. p. 221–223°; yield, 65.6%; picrate, m. p. 159–160°.

## Summary

A series of $N^4$-acyl-sulfanilyl- and sulfanilyl derivatives of the three mono amino pyridines, 2-, 3- and 4-(pyridyl)-methylamines and [1-(2-, 3- and 4-pyridyl)-ethyl]-amines have been prepared and are undergoing biologic assessment. Details have been given for the preparation of 4-picoline through its oxalate. A convenient method has been described for the preparation of 2-, 3- and 4-(pyridyl)-methylamines and for [1-(3-pyridyl)-ethyl]-amine. Brief description has been given of two new heterocyclic amines, believed to be [1-(2-pyridyl)-ethyl]- and [1-(4-pyridyl)-ethyl]-amines.

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(26) The amine obtained from another run boiled at 75–76° at 2–3 mm.; however, the *p*-nitrobenzoate of the product of each run melted at 137–138° which is in close agreement with the melting point (136°) reported by Graf, *et al.*[4]

(27) Later runs yielded a product of higher boiling point, *i. e.*, 115–116° but here, too, the melting point of the *p*-nitrobenzoate was unchanged.

(28) Using the method of LaForge,[5] the best yield of this compound we were able to obtain was 35.5%; while for the methyl-2-pyridyl ketone, the yield was only 22%.