and maintained at this temperature for two hours. The reaction mixture was cooled and treated directly with an excess of cold 28% ammonia solution, adding the ammonia in divided portions with continuous stirring. The stirring was continued for approximately one hour and the precipitate collected and washed several times with water followed by recrystallization from 50% alcohol; yield 40 to 50%. The melting point was identical with that of the product from (1) and gave the same mixed melting point.

**$N^1$-Acetyl-$N^4$-nicotinylsulfanilamide.**—To 25 cc. of acetic anhydride was added gradually 2.8 g. (0.01 mole) of $N^4$-nicotinylsulfanilamide. The mixture was refluxed for one hour and cooled in an ice-bath. The precipitate was collected and washed with water, then dissolved in sodium hydroxide ($p$H 8), decolorized with activated charcoal and precipitated by the addition of dilute hydrochloric acid to $p$H of 5. The precipitate was filtered, washed and dried; yield approximately 50%.

**$N^1$,$N^4$-Dinicotinylsulfanilamide.**—To 5.5 g. (0.02 mole) of $N^4$-nicotinylsulfanilamide and 5.7 g. (0.04 mole) of nicotinyl chloride was added 20 cc. of anhydrous pyridine and the product refluxed for one hour. Several volumes of water were added to the cooled reaction product and the solution acidified with dilute hydrochloric acid to a $p$H of 5. The precipitate was collected and washed with several portions of water, redissolved with sodium hydroxide to a $p$H of 8, filtered and reprecipitated by the addition of dilute hydrochloric acid to a $p$H of 5. The product was again washed and dried; yield approximately 40%. The product melts sharply at 222°, resolidifies on heating and melts again at 248°. Titration with sodium hydroxide of the form melting at 248° gives the same equivalent weight as before melting.

## Summary

1. The $N^4$-nicotinylsulfanilamide and $N^1$,$N^4$-dinicotinylsulfanilamide are described.

2. The melting points of $N^1$ and $N^4$-nicotinylsulfanilamide are the same.

3. The preliminary pharmacologic investigation indicates that the $N^4$-nicotinylsulfanilamide is effective in the treatment of experimental hemolytic streptococcus infections and also certain types of pneumococcus infections. The toxicity of the $N^4$-nicotinylsulfanilamide is lower than either sulfanilamide or sulfapyridine.

SAN FRANCISCO, CALIF. RECEIVED JANUARY 2, 1940

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

# α-Furfurylpropylamine and Di-α-furfuryl Tertiary Amines

BY J. E. ZANETTI AND J. T. BASHOUR

α-Furfurylpropylamine has now been synthesized by the same general method as previously used with other secondary α-furfuryl amines.[1] It is a colorless oil with a faint fishy odor boiling at 80–81° under 20 mm. pressure, $d^{25}_{25}$ 0.947, $n^{20}D$ 1.4679. Its hydrochloride melts at 138–140°.

*Anal.* Calcd. for $C_8H_{13}ON$: N, 10.1. Found: N, 10.2.

Very little has been done in the field of tertiary α-furfuryl amines and only one tertiary amine containing two furfuryl groups has been reported, namely, the tri-α-furfurylamine synthesized by Zanetti and Beckmann.[2] Von Braun and Kohler[3] synthesized several tertiary furfurylamines which, however, contained only one α-furfuryl group and Von Braun and Braunsdorf[4] made an analog of novocaine containing one α-furfuryl group on the tertiary nitrogen.

In our synthesis of secondary α-furfurylamines,[5] tertiary amines were suspected in the small amount of high boiling residue accompanying each preparation. However, in the synthesis of these amines, unfavorable yields are obtained unless the purified secondary amines be made to react with furfuryl bromide.

These tertiary amines are either high boiling liquids or solids and are miscible with most organic solvents. Their properties and the analyses are given in Table I. They are colorless when pure but turn yellow on standing. They have only faint ammoniacal odors. With hydrochloric acid in ether solution they form stable hydrochlorides. As in the case of the secondary furfurylamines, excess of hydrochloric acid must not be used as dark decomposition products will readily form.

## Experimental Part

In a flask provided with an air condenser the furfuryl bromide in ether solution is allowed to stand for one to three hours over crushed potassium hydroxide and then the secondary amine is added with agitation. With intermittent shak-

(1) Zanetti and Bashour, THIS JOURNAL, **61**, 3133 (1939).
(2) Zanetti and Beckmann, *ibid.*, **50**, 2081 (1928).
(3) Von Braun and Kohler, *Ber.*, **51**, 86 (1918).
(4) Von Braun and Braunsdorf, *Ber.*, **54**, 2081 (1921).
(5) Zanetti and Bashour, THIS JOURNAL, **61**, 3133 (1939).

TABLE I

| Amine, di-α-furfuryl- | | Methyl | Ethyl | Propyl | Butyl | Amyl | Phenyl[a] |
|---|---|---|---|---|---|---|---|
| Boiling point | °C. | 100–102 | 109–110 | 115–117 | 126–128 | 137–139 | 163–167 |
| | Mm. | 5 | 5 | 5 | 5 | 5 | 5 |
| Sp. gr., 25/25 | | 1.074 | 1.055 | 1.034 | 1.019 | 1.005 | ..... |
| $n^{20}D$ | | 1.5086 | 1.5059 | 1.4978 | 1.4976 | 1.4950 | ..... |
| Hydrochloride m. p., °C. | | 153–154 | 149–151 | 147–148 | 105–106 | 103–105 | 137–141[b] |
| Formula | | $C_{11}H_{13}O_2N$ | $C_{12}H_{15}O_2N$ | $C_{13}H_{17}O_2N$ | $C_{14}H_{19}O_2N$ | $C_{15}H_{21}O_2N$ | $C_{16}H_{15}O_2N$ |
| Nitrogen, % | Calcd. | 7.3 | 6.8 | 6.4 | 6.0 | 5.7 | 5.5 |
| | Found | 7.3 | 7.1 | 6.5 | 6.2 | 5.9 | 5.7 |
| Carbon, % | Calcd. | ... | ... | ... | 72.1 | ... | 75.9 |
| | Found | ... | ... | ... | 72.1 | ... | 76.4 |
| Hydrogen, % | Calcd. | ... | ... | ... | 8.2 | ... | 5.9 |
| | Found | ... | ... | ... | 8.3 | ... | 6.1 |

[a] Melting point 31–32°; recrystallized from six times the quantity of petroleum ether or methyl alcohol in the ice-bath.
[b] By immersion in preheated baths.

ing the solution rapidly clouds and reaches the boiling point within several minutes to an hour (difurfurylphenylamine developed a dark red color but did not boil). At times excessive heat evolution must be reduced by use of an ice-bath. After twelve hours, the ether is removed and the mixture carried through fractional distillation at reduced pressure in an atmosphere of nitrogen, until successive fractions showed no difference in refractive index. Yields were uniformly about 80% of the theoretical.

The authors are indebted to Mr. Saul Gottlieb for the microanalysis of these compounds.

## Summary

1. Six tertiary di-α-furfurylamines were synthesized by the action of furfuryl bromide on secondary α-furfurylamines and their properties reported.

Further work on these amines is being continued in these Laboratories.

COLUMBIA UNIVERSITY
NEW YORK, N. Y. RECEIVED NOVEMBER 23, 1939

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF SWARTHMORE COLLEGE]

# Sulfonamide Derivatives of Arylureas

BY EDWARD H. COX

The para sulfonamide derivative of phenylurea is in reality a derivative of sulfanilamide. This relationship has prompted the work of preparing some of the arylureasulfonamides with the anticipation that they might possess therapeutic activity comparable to that of sulfanilamide.

The parent substance in the series, *p*-phenylureasulfonamide is then $N^4$-carbamylsulfanilamide. This compound has been prepared recently by Kolloff[1] and given the name *p*-uraminobenzenesulfonamide. The reaction for its preparation is an application of that reported by Buck and Ferry[2] and involves the action of nitrourea on sulfanilamide in alcohol. The therapeutic activity of the compound was not reported.

In the present work it has been found that the arylureas or their acetyl derivatives can be sulfonated by means of chlorosulfonic acid. The resulting sulfonyl chlorides can then be transformed into the amides or substituted amides. The yields are consistently high throughout the series of reactions.

Some of the $N^4$-acyl derivatives of sulfanilamide show as high a therapeutic activity[3] as sulfanilamide itself and this is believed to be due to deacylation in the organism with the resultant freeing of the sulfanilamide. In the present case the carbamyl group apparently is not removed *in vivo* and therefore the arylureasulfonamides show no activity in experimental streptococcal infection in mice.[4]

Since it is proposed to continue the work on this series with certain modifications, the author considered it of interest to record the preparation and properties of these arylurea derivatives.

(1) Kolloff, THIS JOURNAL, **60**, 950 (1938).
(2) Buck and Ferry, *ibid.*, **58**, 854 (1936).
(3) Miller, Rock and Moore, *ibid.*, **61**, 1198 (1939); Adams, Long and Johanson, *ibid.*, **61**, 2342 (1939).
(4) The author wishes to thank Dr. Perrin H. Long of The Johns Hopkins Medical School for carrying out the biological tests.