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.

Experimental

The sulfonation of the arylureas and the acetylarylureas presents no difficulties. The resulting sulfonyl chloride derivatives of the arylureas are, however, difficult to purify and no analytical data are listed for them. On the other hand, the acetylarylureasulfonyl chlorides are not difficult to purify and are produced in good yields. The chlorides are converted into the amides by treatment with ammonia or diethylamine. The removal of the acetyl group from the acetylarylureasulfonamides is effected by treating them with boiling hydrochloric acid solution. Mechanical stirring is used in all the reactions carried out, and the temperatures recorded are those for the reaction mixtures.

Acetylation of the Arylureas.—The arylureas are acetylated according to the method of Walther and Wolodowski.[5] To 70 g. of the urea, dissolved or suspended in 200 cc. of pyridine, is added slowly 60 g. of acetyl chloride. During the addition, the reaction mixture is stirred and cooled to 10° below zero. The reaction mixture is then warmed to 30° for one-half hour, poured into cold dilute hydrochloric acid solution, filtered, and washed. Without further purification, the acetylated product is dried and sulfonated. The yields are from 80–90%.[6]

Sulfonation of the Arylureas and the Acetylarylureas.—The procedure is that given in "Organic Syntheses,"[7] except that the temperature during sulfonation of the arylurea is maintained between 0–10°. Higher temperatures tend to darken the reaction product and lower the yields. To 170 cc. of chlorosulfonic acid is added with stirring 70 g. of the arylurea and after the addition the reaction mixture is heated to 50° for one to two hours. The sulfonyl chlorides are filtered, washed and dried before conversion into the amides. Calculated upon air dried aliquots, the yields are 60–70%.

The procedure for the sulfonation of the acetylarylureas is the same as indicated above for the arylureas. The temperature at which the sulfonation is carried out is 10–15° and the amount of the acetylarylureas employed is 90 g. The yields of the crude acetylarylureasulfonyl chlorides are 75–85%. They are crystallized from hot benzene or toluene.

Amide Derivatives.—Fifty grams of the sulfonyl chloride derivatives of the arylureas or the acetylarylureas is treated with 150 cc. of 28% ammonia or 150 cc. of 30% diethylamine. The mixtures are stirred and warmed on a water-bath for one-half hour and then set aside to cool. In some cases the diethylamides remain as oils which are made to solidify by trituration with alcohol. The unsubstituted amides crystallize from hot water or diluted alcohol, while the diethylamides crystallize from a mixture of ethyl acetate and benzene.

Removal of the acetyl group from the acetylarylureasulfonamides is accomplished by treatment with boiling 5 *N* hydrochloric acid solution. The time of hydrolysis, for 40 g. of the various acetyl compounds, using twice the calculated amount of acid and stirring, varies from one-half to two hours. When pure samples of these resulting amides are mixed with the corresponding ones prepared by direct sulfonation and subsequent amidation of the arylureas, no depression in melting points is observed.

The melting points and analytical data are given in tabular review.

TABLE I

p-ACETYLARYLUREASULFONYL CHLORIDES, $CH_3CONHCONH\text{-}Ar\text{-}SO_2Cl$

-Ar-	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
Phenyl	192–193	$C_9H_9O_4N_2SCl$	10.12	10.32
o-Tolyl	197–199	$C_{10}H_{11}O_4N_2SCl$	9.63	9.53
m-Tolyl	199–201	$C_{10}H_{11}O_4N_2SCl$	9.63	9.58

p-ACETYLARYLUREASULFONAMIDES, $CH_3CONHCONH\text{-}Ar\text{-}SO_2NH_2$

Phenyl	246–247	$C_9H_{11}O_4N_3S$	16.33	16.05
o-Tolyl	231–233	$C_{10}H_{13}O_4N_3S$	15.49	15.25
m-Tolyl	226–227	$C_{10}H_{13}O_4N_3S$	15.49	15.30

p-ARYLUREASULFONAMIDES, $NH_2CONH\text{-}Ar\text{-}SO_2NH_2$

Phenyl	206–207	$C_7H_9O_3N_3S$	19.52	19.47
o-Tolyl	223–225	$C_8H_{11}O_3N_3S$	18.33	17.99
m-Tolyl	209–210	$C_8H_{11}O_3N_3S$	18.33	18.05

DIETHYL *p*-ARYLUREASULFONAMIDES, $NH_2CONH\text{-}Ar\text{-}SO_2N(C_2H_5)_2$

Phenyl	148–149	$C_{11}H_{17}O_3N_3S$	15.49	15.47
o-Tolyl	165–167	$C_{12}H_{19}O_3N_3S$	14.72	14.53
m-Tolyl	147–148	$C_{12}H_{19}O_3N_3S$	14.72	14.61

Summary

The preparation and properties of a series of sulfonamide derivatives of some of the arylureas. as well as the intermediate derivatives, are described.

The parent substance, *p*-acetylphenylureasulfonamide (N^4-carbamylsulfanilamide), shows no activity in experimental streptococcal infection in mice.

SWARTHMORE, PA. RECEIVED JANUARY 15, 1940

(5) Walther and Wolodowski, *J. prakt. Chem.*, [2] **59**, 272 (1899).

(6) The acetyl *m*-tolylurea is not found recorded in the literature. It crystallizes from alcohol and melts at 127°. Calcd.: N, 14.58. Found: N, 14.41.

(7) *Org. Syntheses*, Coll., Vol. I, p. 7.