was distilled once under a water-pump vacuum and then a second time at 0.25 mm. and the *n*-octadecylbenzene collected at 155–160°. The yield of *n*-octadecylbenzene was 24.2 g. or 73%. The boiling point of this compound has been reported as 249° at 15 mm.[8] and 225–250° at 14 mm.[9]

The product was further identified by conversion to its *p*-sulfonamide derivative, m.p. 100–101°, by chlorosulfonation followed by treatment with ammonia. The melting point is in agreement with values found in the literature.[6,9]

(8) F. Krafft, *Ber.*, **19**, 2982 (1886); V. A. Hetling and V. S. Shchekin, *J. Gen. Chem., U.S.S.R.*, **13**, 717 (1943); *C. A.*, **39**, 693 (1945).

(9) F. Seidel and O. Engelfreid, *Ber.*, **69**, 2567 (1936).

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Some Derivatives of *p*-Aminosalicylic Acid[1]

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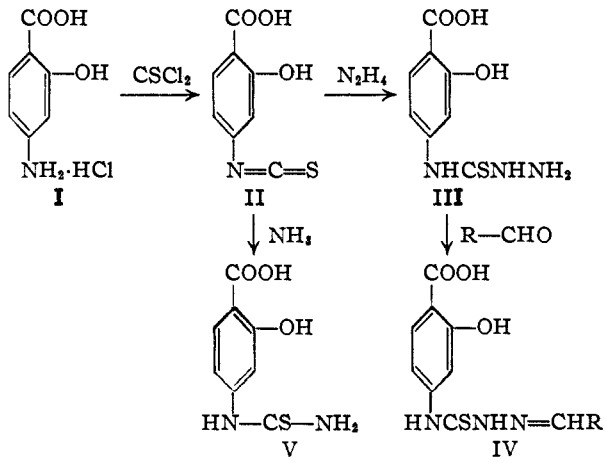
Since Lehmann's[3] announcement of the tuberculostatic activity of *p*-aminosalicylic acid (PAS) and Domagk's[4] discovery of the use of the aromatic aldehyde thiosemicarbazones for the same purpose both have enjoyed widespread clinical use. It was our purpose to combine chemically the PAS-fragment with aromatic thiosemicarbazones into one molecule. This necessitated that the N^4-position of the thiosemicarbazone be substituted and such substitution had previously been reported to inactivate biologically the molecule.[5] However, it was hoped that N^4-substitution with the PAS-fragment would enable these compounds to retain their activity or increase it by acting synergistically if *in vivo* cleavage resulted.

The thiosemicarbazones (IV) were produced by the following series of reactions



The aldehydes used for the condensations were benzaldehyde, *p*-nitrobenzaldehyde, nicotinaldehyde, cinnamaldehyde and 5-nitro-2-furaldehyde.

During the course of the investigation these additional derivatives of PAS were also prepared: *p*-thioureidosalicylic acid (V), by treating II with aqueous ammonia; 4-(4-phenyl-2-thiazolyl)-aminosalicylic acid, from V with phenacyl bromide; 2-(4-carboxy-3-hydroxyanilino)-1,3,4-thiadiazole, by treating III with formic acid.

Acknowledgment.—The authors wish to thank Dr. J. D. Thayer of the Venereal Disease Experiment Laboratory, United States Public Health Service, School of Public Health, University of North Carolina for testing these compounds (*in vitro* and *in vivo*) to determine their tuberculostatic activity. His findings will be published at a later date.

Experimental

***p*-Isothiocyanosalicylic Acid (II).**—*p*-Aminosalicylic acid (30.6 g.) was suspended in 350 ml. of water and 67 ml. of concentrated hydrochloric acid added with mechanical stirring. To this suspension another 350-ml. portion of water was added and finally 27 g. of thiophosgene in one portion. After 3 hours of stirring the orange color of the thiophosgene was dissipated indicating completion of the reaction. The solid product was filtered, the filter cake washed many times with water and dried over phosphorus pentoxide. This produced 32 g. (82.4%) of white solid that was recrystallized from benzene and melted from 186–187° (followed by resolidification). The pure product was slightly unstable to light.

Anal. Calcd. for $C_8H_5NO_3S$: N, 7.2; S, 16.4; neut. equiv., 195. Found: N, 7.2; S, 16.3; neut. equiv., 200.

***p*-Thioureidosalicylic Acid (V).**—*p*-Isothiocyanosalicylic acid (5.5 g.) was dissolved in 100 ml. of aqueous ammonia (28%) and the solution stirred overnight. This solution was then heated to boiling, treated with Norite, filtered and acidified with concentrated hydrochloric acid producing 5 g. (83.6%) of white solid. When recrystallized from aqueous ethanol white cubes were obtained that melted at 179–180°.

Anal. Calcd. for $C_8H_8N_2O_3S$: N, 13.2; S, 15.1. Found: N, 13.2; S, 14.8.

4-(4-Phenyl-2-thiazolyl)-aminosalicylic Acid.—*p*-Thioureidosalicylic acid (4 g.) and phenacyl bromide (4 g.) were dissolved in an excess of absolute ethanol and heated on a steam-bath for 14 hours. The excess ethanol was removed under diminished pressure leaving a green-grey residue. This was washed with several portions of petroleum ether (60–90°) to remove any excess phenacyl bromide leaving 5 g. (85%) of the crude product. Recrystallization from aqueous ethanol (Norite) produced an off-white solid that melted from 217–218°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3S$: N, 9.0; S, 10.3. Found: N, 9.0; S, 10.4.

4-(4-Carboxy-3-hydroxyphenyl)-thiosemicarbazide (III).—It was found in this particular preparation that the method of Pulvermacher[6] for making thiosemicarbazides from isothiocyanates produced a low yield of impure product. The method found most desirable was to suspend *p*-isothiocyanosalicylic acid (7.9 g.) in 250 ml. of water, stir mechanically and add hydrazine hydrate (4.8 g.). This was refluxed for 4 hours producing a clear liquid. Norite was added to the boiling liquid, the solution filtered, the hot filtrate stirred and acidified with 10% hydrochloric acid. After cooling slowly, 7.7 g. (84%) of fine white solid was recovered that melted from 198–199° with gas evolution. This could be recrystallized from a very large excess of water without, however, any alteration of the melting point.

Anal. Calcd. for $C_8H_9N_3O_3S$: N, 18.5; S, 14.1. Found: N, 18.6; S, 13.9.

General Method of Preparing the Thiosemicarbazones (IV).—Some 4-(4-carboxy-3-hydroxyphenyl)-thiosemicarbazide (3–7 g.) was suspended in 150 ml. of distilled water and 15 ml. of acetic acid added along with the aldehyde in slight excess. Usually immediate reaction took place as evidenced by the formation of a yellow solid. This mixture was heated to reflux (in the case of 5-nitrofurfuraldehyde decomposition took place at temperatures above 65°) for several hours, the flask cooled and the reaction

(1) Taken from a thesis submitted to the Graduate School of the University of North Carolina by R. B. Seligman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Deceased.

(3) J. Lehmann, *Lancet*, **250**, 15 (1946).

(4) G. Domagk, *et al.*, *Naturwissenschaften*, **33**, 315 (1946).

(5) E. Hoggarth, A. R. Martin, N. E. Storey and E. H. P. Young, *Brit. J. Pharmacol.*, **4**, 248 (1950).

(6) G. Pulvermacher, *Ber.*, **27**, 615 (1894).

TABLE I

THIOSEMICARBAZONES

Condensing aldehyde	Recrys. solvent	M.p.,[d] °C. (uncor.)	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Benzaldehyde	Aqueous ethanol	193–194.5	80	13.4	13.5	..	...
p-Nitrobenzaldehyde	Aqueous acetone[a]	203–204	85	15.6	15.6	..	...
Nicotinaldehyde	None[b]	237–238	86	17.7	17.9	10.1	9.9
Cinnamaldehyde	Aqueous acetone	194.5–195.3	88	12.3	12.4	9.4	9.3
5-Nitro-2-furaldehyde diacetate	Aqueous acetone[c]	205.5	55	16.0	15.7		

[a] After dissolving in base and reprecipitating with concd. hydrochloric acid. [b] Purified by continuous extraction with absolute ethanol. [c] First triturating with water at 65°. [d] All decomposed with gas evolution.

product filtered. Purification of these thiosemicarbazones proved very difficult. See Table I for complete details.

2-(4-Carboxy-3-hydroxyanilino)-1,3,4-thiadiazole.—A mixture of 4-(4-carboxy-3-hydroxyphenyl)-thiosemicarbazide (1.5 g.) and an excess of 85% formic acid was refluxed for 48 hours. The mixture was filtered while hot, the filtrate cooled and cold water added to aid in precipitating the crude product. The white solid produced weighed one gram (64%) and, after recrystallization (aqueous formic acid), melted from 241–242° (dec.).

Anal. Calcd. for $C_9H_7N_3O_3S$: N, 17.7; S, 13.5. Found: N, 17.7; S, 13.9.

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The Synthesis of Heterocyclic Compounds from Aryl Azides. III. Some Six-membered Rings and Some Azidobiaryls

BY PETER A. S. SMITH, BERNARD BEAU BROWN, RICHARD K. PUTNEY AND RONALD F. REINISCH

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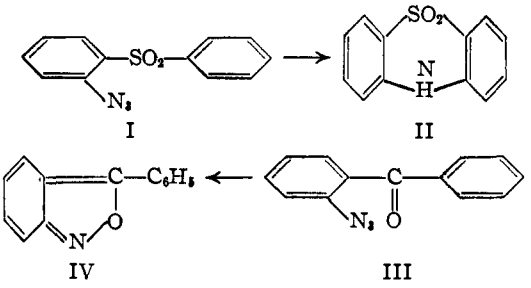
The formation of the pyrrole nucleus component of fused-ring systems has been reported by the pyrolysis and photolysis of aryl azides[1,2] of the *o*-azidobiaryl type. We now report the extension of this method to some compounds in which the two aryl groups are separated by one other atom. In addition, α-(*o*-azidophenyl)-furan and *o,o'*-diazidobiphenyl have been investigated.

o-Aminodiphenyl ether and *o*-aminodiphenyl sulfide both yielded azides by diazotization and treatment with sodium azide. *o*-Azidodiphenyl ether lost nitrogen when heated in inert solvents, but the product was largely an intractable tar, from which was obtained only a small amount of an impure picrate, resembling that reported from the expected phenoxazine. *o*-Azidodiphenyl sulfide, very sensitive to sunlight but otherwise stable, lost nitrogen between 140 and 180° to give 32% of phenothiazine. *o*-Azidodiphenylamine could not be prepared directly, because diazotized *o*-aminodiphenylamine cyclizes spontaneously to form 1-phenylbenzotriazole; however, *o*-amino-N-acetyldiphenylamine yielded an azide in the usual way. Although it lost nitrogen when heated, the product was intractable, and could not be made to yield any phenazine or its dihydro derivative.

o-Azidodiphenylsulfone (I) and *o*-azidobenzophenone (III) both lost nitrogen when heated in decalin solution. The sulfone gave a fair yield of phenothiazine dioxide (II) by cyclization to the adjacent benzene ring, accompanied by some *o*-aminodiphenyl sulfone arising from reduction by the solvent. The ketone underwent cyclization to the carbonyl oxygen atom instead, giving 3-phenylanthranil (IV). This is analogous to the cyclization of *o*-azido nitro compounds to the oxygen of the nitro group, giving furoxans, even when a benzene ring is also available.[1]



The behavior of *o*-azidobenzophenone conforms to that predicted for it by Meisenheimer, Senn and Zimmermann.[3] They postulated that the conversion of 4-phenyl-5,6-benzotriazine-3-oxide, formed by the diazotization of *anti*-*o*-aminobenzophenone oxime, to phenylanthranil (IV) proceeded by initial isomerization to the azide III, which at the temperatures used lost nitrogen and cyclized. Since at higher temperatures phenylanthranil isomerizes to acridone, the behavior of *o*-azidobenzophenone and *o*-azidodiphenylsulfone should not be considered fundamentally different; the different types of product obtained at moderate temperatures appear to be a reflection of what need only be a small difference in stability of the parallel oxacyclic intermediates.

A series of reactions intended to lead to a furanoindole was initiated by the coupling of *o*-nitrobenzenediazonium chloride to furan. The *o*-nitrophenylfuran so obtained is tentatively assumed to be the α-isomer by analogy with the corresponding reaction with thiophene.[2] Reduction produced an amine which appeared to be a single substance, but an attempt to deaminate it to the known α-phenylfuran gave only tar. No pure compound could be obtained when the azide was sought, and the attempted preparation of an azo dye with β-naphthol gave a dye of a different composition. Diazotization thus appeared to be accompanied by additional changes, perhaps involving nitrosation of the furan nucleus.

o,o'-Diazidobiphenyl was prepared from the dinitro compound by way of the unisolated diamine, in the hope of preparing 4,5-pyrrolocarbazole from it. The stable azide indeed lost gas near 180°, but

(1) P. A. S. Smith and B. B. Brown, THIS JOURNAL, 73, 2435 (1951).
(2) P. A. S. Smith and J. H. Boyer, *ibid.*, 73, 2626 (1951).
(3) J. Meisenheimer, O. Senn and P. Zimmermann, *Ber.*, 60, 1736 (1927).