bonate although giving a satisfactory *p*H gave no product. Ethyl sulfate in place of methyl sulfate gave a 50% yield of pyrimethamine.

EXPERIMENTAL

In a 3-l. 3-necked flask fitted with a reflux condenser and a crescent-type stirrer was placed 210.5 g. of crude α-propionyl *p*-chlorophenylacetonitrile (calc'd as 1 mole but actually 85–90% material). To this was added 300 cc. ≈ 3 equivalents of methyl sulfate (commercial material but free of acid), 327.5 g. of sodium bicarbonate (3.9 equivalents), 720 cc. of dioxane, and 80 cc. of water. The flask was heated on a steam-bath and stirred vigorously. The reaction-temperature was 82.5° 22 minutes after the start and rose gradually to 87° an hour and a half later. The reaction was allowed to go 45 minutes further (probably unnecessary). The reaction mixture then was diluted with 800 cc. of benzene and 800 cc. of water and was cooled. The benzene layer was washed with water until approximately neutral. The aqueous layer and first wash neutralized 38 cc. of conc'd hydrochloric acid and therefore contained *ca.* 0.45 mole of bicarbonate—about half of the calculated excess. The benzene layer then was extracted with *N* alkali, washed with water, and evaporated to dryness *in vacuo.*

To the above oil was added a filtered solution of 1.1 moles of guanidine (from guanidine hydrochloride and sodium ethoxide) in 600 cc. of abs. ethanol. The solution was refluxed for four hours[10] and allowed to cool. The solid product weighed 134 g. and was pyrimethamine of good quality.

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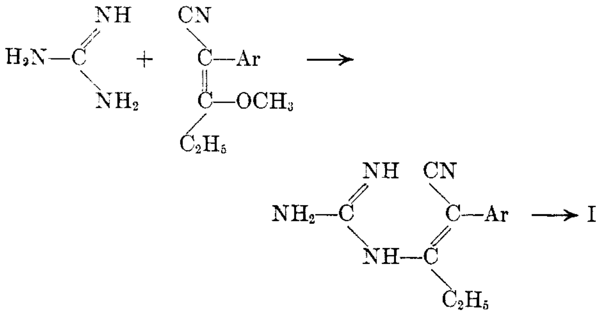
[10] In the above and all of the other preparations of pyrimethamine it was observed that 10–20 minutes after the start of the reaction the flask became filled with a crystalline mush. On continued refluxing this material redissolved and was replaced by a much more compact solid which was the pyrimethamine. It is tempting to speculate as to the first solid being uncyclized addition product the probable course of the reaction being:[3]



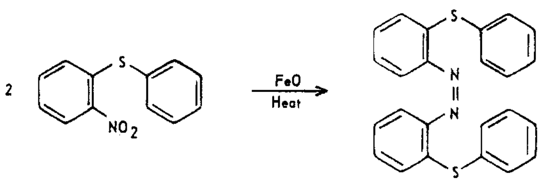
$$H_2N-C(=NH)-NH_2 + NC-C(Ar)=C(OCH_3)-C_2H_5 \longrightarrow NH_2-C(=NH)-NH-C(C_2H_5)=C(Ar)-CN \longrightarrow I$$

Reactions of 2-Nitrodiphenyl Sulfide and Related Sulfones in Attempted Ring Closure

DONALD L. VIVIAN AND HENRY C. WATERMAN

Received April 20, 1956

The synthesis of phenothiazine was attempted by subjecting 2-nitrodiphenyl sulfide to the action of ferrous oxide (from ferrous oxalate) at 275–285°. This method is analogous to that used by Waterman and Vivian[1] for the preparation of phenazine by ring closure of 2-nitrodiphenylamine through the nitro group. From the reaction there was obtained a compound melting at 188–189°, in the form of small, matted orange needles. While its analysis agreed with the theory for phenothiazine (m.p. 184–185°), a pronounced depression of the melting point of a mixture of the two showed it not to be the desired compound. Consideration of other structures having the same empirical formula suggested 2,2′-bis(phenylmercapto)azobenzene, and titration with $TiCl_3$ supported this view. Hence the reaction appears to have been:



When the 2-nitrodiphenyl sulfide was converted to the corresponding sulfone, and this substance was subjected to the same reaction conditions, the resulting product was not an azo compound, but was the known 2-aminodiphenyl sulfone, as shown by the analysis and melting point.

In like fashion, both 4-chloro-2-nitrodiphenyl sulfone and 5-chloro-2-nitrodiphenyl sulfone gave the corresponding amino compounds when subjected to high-temperature reduction by ferrous oxalate dihydrate.

EXPERIMENTAL

2,2′-bis(Phenylmercapto)azobenzene. A mixture of 0.6 g. of 2-nitrodiphenyl sulfide,[2] 0.8 g. of ferrous oxalate dihydrate, and 8 g. of granulated lead was heated in an oil-bath at 270–280° for 25 minutes. Vacuum sublimation from an oil-bath at 250°, pressure about 2 mm., gave 0.4 g. of an orange-red product melting at 182–184° to a dark red liquid, without decomposition. Recrystallized twice from absolute alcohol, the compound formed small, matted orange needles, m.p. 188–189°.[3]

Anal.[4] Calc'd for $C_{24}H_{18}N_2S_2$: C, 72.4; H, 4.55; N, 7.05; S, 16.0. Found: C, 72.4; H, 4.90; N, 7.19; S, 15.8.

This compound gave an immediate deep green color with concentrated sulfuric acid, while phenothiazine gave a dull red. A mixture melting point determination gave 157–179°, proving that the compound was not phenothiazine.

Evidence of its azo structure was given by its behavior on titration in aqueous alcohol by $TiCl_3$,[5] which was that of a typical azo compound, resulting in a colorless solution.

Anal. Calc'd for $C_{24}H_{18}N_2S_2$: $TiCl_3$ required for 31.2 mg. sample, 36.5 mg.; Found: 32 mg. (some small part of the compound was not in solution).

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[2] Tarbell, Todd, Paulson, Lindstrom, and Wystrach, *J. Am. Chem. Soc.*, **70**, 1384 (1948).

[3] All melting points are corrected.

[4] Analyses by the Microanalytical Laboratory of the National Institutes of Health, under the direction of Dr. W. C. Alford.

[5] Titration by $TiCl_3$ courtesy of Dr. Kenneth A. Freeman, Chief, Color Certification Branch, Food & Drug Administration.

2-Aminodiphenyl sulfone. A mixture of 2.0 g. of 2-nitrodiphenyl sulfone,[6] 5.0 g. of ferrous oxalate dihydrate, and 50 g. of granulated lead was heated for 15 minutes in a bath at 285–290°. Vacuum sublimation gave 0.53 g. of a sparkling yellow compound melting at 118–119°. Two recrystallizations from 50% alcohol gave pure white prisms or rhomboids, m.p. 122–124°. The recorded m.p. of 2-aminodiphenyl sulfone is 122°.[7]

Anal. Calc'd for $C_{12}H_{11}NO_2S$: C, 61.8; H, 4.74; N, 6.07; S, 13.7. Found: C, 61.7; H, 4.75; N, 6.11; S, 13.4.

2-Amino-4-chlorodiphenyl sulfone. A mixture of 2.0 g. of 4-chloro-2-nitrodiphenyl sulfone,[8] 2.6 g. of ferrous oxalate dihydrate, and 20 g. of granulated lead was heated for 8 minutes in an oil-bath at 264–270°. Vacuum distillation of the product gave 0.9 g. of light orange material. This, on two recrystallizations from 50% ethanol, formed short white prisms or rods, melting at 120–121°. Analysis agreed with values for aminochlorodiphenyl sulfone:

Anal. Calc'd for $C_{12}H_{10}ClNO_2S$: C, 53.9; H, 3.74. Found: C, 53.5; H, 3.94.

2-Amino-5-chlorodiphenyl sulfone. A mixture of 2.0 g. of 5-chloro-2-nitrodiphenyl sulfone,[9] 2.6 g. of ferrous oxalate dihydrate, and 20 g. of granulated lead was heated in an oil-bath at about 270° for eight minutes. Vacuum distillation of the product gave 0.8 g. of an orange-colored solid, which on two recrystallizations from 50% ethanol formed small white rods, melting at 111–112°. Analysis agreed with values for aminochlorodiphenyl sulfone:

Anal. Calc'd for $C_{12}H_{10}ClNO_2S$: C, 53.9; H, 3.74. Found: C, 53.6; H, 3.68.

This 2-amino-5-chlorodiphenyl sulfone was photosensitive, darkening appreciably on long exposure to visible light. The 2-amino-4-chlorodiphenyl sulfone shared this property to a lesser degree, but the unhalogenated 2-aminodiphenyl sulfone was not light-sensitive, and remained pure white.

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(6) Levi and Smiles, *J. Chem. Soc.*, 1488 (1932).
(7) Ullmann and Pasdermadjian, *Ber.*, **34**, 1153 (1901).
(8) Loudon and Shulman, *J. Chem. Soc.*, 1618 (1938).
(9) Loudon, *J. Chem. Soc.*, 904 (1939).

The Relative Stabilities of *Cis* and *Trans* Isomers. II. The Decalin and Hydrindan Ring Systems[1]

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Received April 30, 1956

The relative stabilities of *cis* and *trans* isomers in fused ring systems of the decalin and hydrindan types are of theoretical and practical interest, and they have recently been the subject of an appreciable amount of work and discussion.[3–8] In spite of this widespread interest, no general rationalization of the relative stabilities of the *cis* and *trans* isomers of these ring systems under various circumstances has been advanced. It would be useful to be able to predict which isomer would be the more stable in different situations, but this can hardly be done at present. For instance, *trans*-decalin is by any criterion more stable than its *cis* isomer,[9] while with 9-methyldecalin the *cis* isomer predominates at equilibrium.[3] When the *cis* and *trans* structures were assigned respectively to the *normal* and *allo* series in steroids, the unsubstituted decalins were used as models, and the assignments are known to be correct.[10] Yet, had the more closely analogous 9-methyldecalins been used as models, the reverse and incorrect conclusions would have been reached. Turning to the hydrindans, certain curiosities are again to be found. It is reported that *trans* hydrindan and its 2-keto derivative have lower heats of combustion than the corresponding *cis* compounds,[11,12] while 1-keto-hydrindan and 4-keto-hydrindan both furnish *cis* isomers upon equilibration.[13]

Actually the confusion evident in the examples mentioned is more apparent than real. Much of the difficulty results from the fact that proper differentiation between heat contents and free energies has not been made in the past. Generally these quantities are lumped together as "stabilities." As long as the relative heat contents and free energies have the same sign, as they do in the vast majority of cases, no difficulties are encountered in qualitative discussion. However, in the systems at present under consideration there is good evidence for the fact that even an approximate parallelism between these properties does not exist.

Ordinarily we are most interested in the correspondence between the free energy and the *cis* and *trans* relationships of compounds, the goal being to predict which isomer will have the lower free energy or conversely, to assign the structures from the free energies. Frequently the free energy

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