[CONTRIBUTION FROM PURDUE UNIVERSITY]

The Preparation of Sulfanilamide Derivatives Containing a Urea or Thiourea Grouping

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Very few derivatives of sulfanilamide containing a urea or thiourea grouping have been prepared. Northey[1a] lists ten which have the urea or thiourea grouping in the N^4 position, but none in which either of these groupings occupies the N^1 position.[2,3,4]

It was thought desirable to investigate more thoroughly these types of derivatives and to test their bacteriostatic activities in the hope that some of them might prove useful in chemotherapy. Two series of derivatives were prepared: one with the urea or thiourea grouping in the N^4 position and one with one of these in the N^1 position.

Table I lists those of the first type, N-alkyl- and N-aryl-N′-sulfonamidophenylureas and thioureas. These compounds were all prepared by the same general method, by the reaction of sulfanilamide with the appropriate isocyanate or isothiocyanate.

$$p\text{-}H_2NO_2SC_6H_4NH_2 + RN{=}C{=}O \longrightarrow p\text{-}H_2NO_2SC_6H_4NHCONHR, \text{ and}$$

$$p\text{-}H_2NO_2SC_6H_4NH_2 + RN{=}C{=}S \longrightarrow p\text{-}H_2NO_2SC_6H_4NHCSNHR$$

The details for these preparations are given in the experimental procedures. The lower members of the series, in which R varies from methyl to *n*-amyl, are readily recrystallized from alcohol or water. The *n*-amyl derivative has definite wax-like properties.

Table II lists N-alkyl and N-aryl N′-*p*-acetylsulfanilamidoureas and thioureas which comprise the N^1 substituted derivatives. The first two members of this series, acetylsulfanilamidourea and acetylsulfanilamidothiourea were prepared from *p*-acetylaminobenzenesulfonyl chloride and semicarbazide and thiosemicarbazide, respectively, in pyridine solution.

$$p\text{-}AcHNC_6H_4SO_2Cl + H_2NNHCONH_2 \longrightarrow p\text{-}AcHNC_6H_4SO_2NHHNCONH_2, \text{ and}$$

$$p\text{-}AcHNC_6H_4SO_2Cl + H_2NNHCSNH_2 \longrightarrow p\text{-}AcHNC_6H_4SO_2HNNHCSNH_2$$

The other members of the series were prepared by the reaction of acetylsulfanilylhydrazine with isocyanates and isothiocyanates in dioxane and ethanol solution, respectively.

$$p\text{-}AcHNC_6H_4SO_2HNNH_2 + RN{=}C{=}S \longrightarrow p\text{-}AcHNC_6H_4SO_2HNNHCSNHR$$

This series represents an entirely new type of derivative. These compounds are extremely insoluble in most common solvents but dissolve readily in dilute alkali.

In the course of the work one or two other types of derivatives were prepared. These are listed in Table III. The sulfanilylhydrazines also represent a new type of derivative. One derivative was prepared by the reaction of sulfathiazole with methyl isothiocyanate to give N-(N-thiazolyl)-*p*-sulfonamidophenyl-N′-methylthiourea.

The pharmalogical data for these compounds will be reported later.

Experimental

N-Methyl-N′-*p*-sulfonamidophenylthiourea.—Twenty grams of sulfanilamide, 80 ml. of absolute ethanol and 8.5 g. of methyl isothiocyanate were mixed in a small flask and refluxed on the steam-bath for twenty-two hours. The flask was then cooled in an ice-bath. The white crystalline precipitate was filtered and washed, with three small portions of ethanol, and dried in a vacuum desiccator. The yield was 23 g. (81%). The product was recrystallized from 95% ethanol using 500 ml. of solvent for 5 g. of sample. Gleaming plates were obtained (m. p. 205–206°).

N-Phenyl-N′-*p*-sulfonamidophenylurea.—Ten grams of sulfanilamide was dissolved in 100 ml. of dioxane which had been purified by recrystallization. The flask containing the dioxane solution was equipped with a reflux condenser which was fitted with a dropping funnel. A solution of 7.8 g. of phenyl isocyanate, in 50 ml. of dioxane, was then added at a fairly rapid rate to the sulfanilamide solution. The mixture turned orange. It was heated on the steam-bath for twelve hours. At the end of this period the precipitate was filtered, washed well with dioxane and dried in a vacuum desiccator. The yield was 16 g. (90%). The crude product was decolorized and recrystallized twice from ethanol. The purified crystals melted at 231–233°.

Acetylsulfanilylhydrazine.—This was prepared from hydrazine hydrate and *p*-acetylaminobenzenesulfonyl chloride according to the method of Stell,[5] who reported a melting point of 178°. The product obtained by us melted at 183–184° but showed the correct composition.

Sulfanilylhydrazine.—This was prepared from acetylsulfanilylhydrazine by hydrolysis with concentrated hydrochloric acid according to the method of Stell.[5] The product was recrystallized from water and melted at 131° dec.

***p*-Acetylsulfanilamidourea.**—Fifty ml. of dry redistilled pyridine was placed in a small three-necked flask equipped with a thermometer and stirrer. To this was added 5 g. of semicarbazide hydrochloride which partially dissolved to give a yellow solution. Ten grams of *p*-acetaminobenzenesulfonyl chloride was then added over a period of about fifteen minutes. The temperature was kept below 30° by cooling the flask with an ice-bath. When all the chloride had been added the mixture was heated on the steam-bath for an hour. The solution was cooled and 2 g. of sodium hydroxide, dissolved in 150 ml. of water, was added. On further cooling a crystalline precipitate formed. This was filtered, washed with cold water, and dried. White crystals (7 g.) were obtained (45%). They were recrystallized with difficulty from boiling water. Fine white plates were obtained (m. p. 227°, dec.).

N-*p*-Acetylsulfanilamido-N′-butylthiourea.—Ten grams of acetylsulfanilylhydrazine was placed in a small flask

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[1] Abstract of a thesis submitted to the faculty of Purdue University by Jay S. Roth in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1944.

(1a) E. H. Northey, *Chem. Rev.*, **27**, 173 (1940).

(2) P. S. Winnek, *et al.*, THIS JOURNAL, **64**, 1682 (1942).

(3) J. Walker, *J. Chem. Soc.*, 1304 (1940).

(4) G. M. Dyson, British Patent, 517,682, Feb. 6, 1940.

(5) C. Stell, *J. prakt. Chem.*, **112**, 1117 (1926).

TABLE I

N-ALKYL AND N-ARYL N′-*p*-SULFONAMIDOPHENYLUREAS AND THIOUREAS

Compounds	Soly.	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	
		Ureas				
N-Phenyl-N′-*p*-sulfonamidophenyl-	Ethanol	231–233	$C_{13}H_{13}O_3N_3S_2$	14.45	13.10	13.20
N-*p*-Nitrophenyl-N′-*p*-sulfonamidophenyl-[a]	Acetone + H_2O	258–259	$C_{13}H_{12}O_5SN_4$	16.66	16.69	16.74
N-*p*-Chlorophenyl-N′-*p*-sulfonamidophenyl-	Acetone + H_2O	239–240	$C_{13}H_{12}O_3SN_3Cl$	12.9	12.72	12.80
		Thioureas				
N-Methyl-N′-*p*-sulfonamidophenyl-	Sl. ethanol	205–206	$C_8H_{11}O_2N_3S_2$	18.99	18.90	19.02
N-Ethyl-N′-*p*-sulfonamidophenyl-	Hot H_2O	201–202	$C_9H_{13}O_2N_3S_2$	16.22	16.25	16.15
N-Propyl-N′-*p*-sulfonamidophenyl-	Ethanol	182–183	$C_{10}H_{15}O_2N_3S_2$	15.4	15.34	15.40
N-Butyl-N′-*p*-sulfonamidophenyl-[b]	Ethanol	170–171	$C_{11}H_{17}O_2N_3S_2$	14.62	14.70	14.73
N-Allyl-N′-*p*-sulfonamidophenyl-[c]	Ethanol	189–190	$C_{10}H_{13}O_2N_3S_2$	17.32	17.25	17.35
N-Amyl-N′-*p*-sulfonamidophenyl-	Ethanol + hot H_2O	157–158	$C_{12}H_{19}O_2N_3S_2$	13.95	13.72	13.78
N-Phenyl-N′-*p*-sulfonamidophenyl-	Acetone + H_2O	190–191	$C_{13}H_{13}O_2N_3S_2$	13.68	13.43	13.45
N-*p*-Sulfonamidophenyl-N′-*o*-tolyl-	Acetone + H_2O	215–216	$C_{14}H_{15}O_2N_3S_2$	13.10	12.77	12.87
N-*α*-Naphthyl-N′-*p*-sulfamidophenyl-	Acetone + H_2O	193–194	$C_{17}H_{15}O_2N_3S_2$	11.80	11.73	11.69

[a] Calcd.: C, 46.40; H, 3.59. Found: C, 46.27, 46.43; H, 3.55, 3.64. [b] Calcd.: C, 45.95; H, 5.96. Found: C, 45.75, 45.83; H, 6.04, 6.10. [c] Calcd.: C, 44.4; H, 4.82. Found: C, 44.7, 45.0; H, 4.96, 5.12.

TABLE II

N-ALKYL OR N-ARYL N′-*p*-ACETYLSULFANILAMIDOUREAS AND THIOUREAS

Compounds	Soly.	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	
Acetylsulfanilylhydrazine[a]	s. hot H_2O	183 d.	$C_8H_{11}O_3N_3S$	18.32	18.1	
		Thioureas				
p-Acetylsulfanilamido-[b]	Hot H_2O	193–194 d.	$C_9H_{12}O_3N_4S_2$	19.5	19.9	20.2
N-*p*-Acetylsulfanilamido-N′-methyl-	Dil. NaOH	228 d.	$C_{10}H_{14}O_3N_4S_2$	16.77	16.72	16.65
N-*p*-Acetylsulfanilamido-N′-ethyl-[c]	Dil. NaOH	214 d.	$C_{11}H_{16}O_3N_4S_2$	17.71	16.90	17.10
N-*p*-Acetylsulfanilamido-N′-propyl-	Dil. NaOH	210 d.	$C_{12}H_{18}O_3N_4S_2$	16.98	16.77	16.73
N-*p*-Acetylsulfanilamido-N′-amyl-[d]	Dil. NaOH	204 d.	$C_{14}H_{22}O_3N_4S_2$	15.64	15.52	15.60
N-*p*-Acetylsulfanilamido-N′-butyl-	Dil. NaOH	212–213 d.	$C_{13}H_{20}O_3N_4S_2$	16.3	16.20	16.14
N-*p*-Acetylsulfanilamido-N′-allyl-	Dil. NaOH	212.5–214 d.	$C_{12}H_{16}O_3N_4S_2$	17.1	17.00	16.94
N-*p*-Acetylsulfanilamido-N′-phenyl-[e]	Dil. NaOH	216–217 d.	$C_{15}H_{16}O_3N_4S_2$	15.4	15.38	15.32
N-*p*-Acetylsulfanilamido-N-*p*-methoxyphenyl-	Dil. NaOH	209–210 d.	$C_{16}H_{18}O_4N_4S_2$	14.2	14.20	14.16
N-*p*-Acetylsulfanilamido-N′-*α*-naphthyl-	Dil. NaOH	232–233 d.	$C_{19}H_{18}O_3N_4S_2$	13.53	13.45	13.39
		Ureas				
p-Acetylsulfanilamido-[f]	Hot H_2O	227 d.	$C_9H_{12}O_4N_4S$	20.59	19.4	
N-*p*-Acetylsulfanilamido-N′-*p*-bromophenyl-	Dil. NaOH	215–216 d.	$C_{15}H_{15}O_4N_4SBr$	12.97	13.07	13.18
N-*p*-Acetylsulfanilamido-N′-*o*-tolyl-	Dil. NaOH	206.5–207.5 d.	$C_{16}H_{18}O_4N_4S$	15.47	15.42	15.53
N-*p*-Acetylsulfanilamido-N′-*p*-nitrophenyl-[g]	Dil. NaOH	214.5–215.5 d.	$C_{15}H_{15}O_6N_5S$	17.81	17.75	17.69

[a] Calcd.: C, 41.8; H, 4.8. Found: C, 39.4; H, 5.46. [b] Calcd.: C, 37.5; H, 4.17. Found: C, 37.2, 37.3; H, 4.76, 4.41. [c] Calcd.: C, 41.75; H, 5.06. Found: C, 41.65; H, 5.17. [d] Calcd.: C, 46.90; H, 6.19. Found: C, 46.83; H, 6.27. [e] Calcd.: C, 49.5; H, 4.39. Found: C, 49.7; H, 4.79. [f] Calcd.: C, 39.69; H, 4.44. Found: C, 39.4; H, 5.66. [g] Calcd.: C, 45.78; H, 3.84. Found: C, 45.9; H, 3.98.

TABLE III

MISCELLANEOUS DERIVATIVES

Name	Soly.	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	
Sulfanilylhydrazine	s. hot H_2O	131	$C_6H_9O_2N_3S$	19.91	19.78	19.70
N-*p*-Acetylsulfanilyl-N′-phenylhydrazine	s. ethanol	157–159 d.	$C_{14}H_{15}O_3N_3S$	13.77	13.56	13.70
N-*p*-Acetylsulfanilyl-N′-3-nitrophenylhydrazine[a]	s. acetone H_2O	180–181 d.	$C_{14}H_{14}O_5N_4S$	16.00	15.90	15.79
N-(N-Thiazolyl)-*p*-sulfonamidophenyl-N′-methylthiourea	s. hot H_2O	190–193	$C_{11}H_{12}O_2N_4S_3$	17.04	16.93	16.85

[a] Calcd.: C, 47.98; H, 4.03. Found: C, 48.10; H, 4.17.

with a ground glass joint and to this was added 150 ml. of absolute ethanol and 5 g. of butyl isothiocyanate. The mixture was refluxed on the steam-bath for twenty-four hours. At the end of this time the reaction mixture was cooled in an ice-bath and the white crystalline precipitate filtered. washed well with boiling ethanol, and dried in a vacuum desiccator. The yield of fine white crystals was 11.2 g. (70%, m. p. 212–3° dec.).

N-*p*-Acetylsulfanilamido-N′-*p*-nitrophenylurea.—Eight grams of acetylsulfanilylhydrazine and 150 ml. of purified dioxane were placed in a small flask with a ground glass joint. Then 5.5 g. of *p*-nitrophenyl isocyanate was added.

A reaction took place immediately with the formation of a heavy pale-yellow precipitate and the evolution of heat. The mixture was heated on a steam-bath for one hour with shaking. The precipitate was filtered, washed with dioxane and ether, and dried in a vacuum desiccator. The yield was 13.6 g. (10%) of pale-yellow crystals melting at 214.5-215.5° dec.

N-*p*-Acetylsulfanilyl-N′-phenylhydrazine.—Four and five-tenths grams of phenylhydrazine was placed in a beaker containing 5 g. of sodium carbonate dissolved in 100 ml. of cold water. To this was added slowly with stirring 10 g. of *p*-acetylaminobenzenesulfonyl chloride. The mixture was removed from the ice-bath after all the chloride had been added and stirred for an additional thirty minutes. The tan precipitate was removed by filtration, washed with water, and dried in a vacuum desiccator. It weighed 11 g. (76% yield). Three recrystallizations from an alcohol-water mixture, using Norit, gave a white crystalline product melting at 157-9° dec.

N-(N-Thiazolyl)-*p*-sulfonamidophenyl-N′-methylthiourea.—Seventeen and seven-tenths grams of sulfathiazole was placed in a small flask with a ground glass joint. To this was added 150 ml. of absolute ethanol and 5 g. of methyl isothiocyanate. The mixture was refluxed on the steam-bath for twenty-two hours. At the end of this time there was a slight residue in the flask. The reaction mixture was cooled in an ice-bath and the crystalline precipitate filtered, washed with ethanol, and dried. The yield was 17 g. (75%). The product was thoroughly ground up and treated with dilute hydrochloric acid to remove any unreacted sulfathiazole. It was then recrystallized from boiling water using Norit. White needles melting at 190-193° were obtained.

Summary

1. Twelve sulfanilamide derivatives containing a substituted urea or thiourea grouping in the N^4 position and fourteen containing a urea or thiourea grouping in the N′ position were prepared and described.

2. The preparation of acetylsulfanilylhydrazine and N-*p*-acetylsulfanilyl-N′-3-nitrophenylhydrazine is described.

3. Methyl isothiocyanate was found to react with sulfathiazole to give N-(N-thiazolyl)-*p*-sulfonamidophenyl-N′-methylthiourea.

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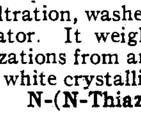
[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO]

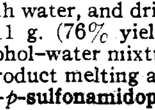
Factors Influencing the Course and Mechanism of Grignard Reactions. XVI. An Isomer of Isophorone—$\Delta^{3,4}$-3,5,5-Trimethylcyclohexenone

BY M. S. KHARASCH AND P. O. TAWNEY

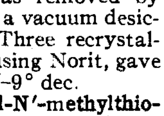
In a previous paper[1] it was shown that methylmagnesium bromide, in the presence of a small amount of ferric chloride, converts isophorone into an isomeric substance for which the structures (II) and (III) were considered.



Isophorone (I)



Enol (II)



Keto (III)

The following facts favor the enol structure (II): (a) The compound is easily reconverted into isophorone, especially in the presence of acid. (b) The new compound yields a semicarbazone which is identical with that of isophorone, since the two do not depress each other's melting points. The following facts favor the keto structure (III): (a) The molar refraction of the new compound checks with that calculated for a compound with structure (III). (b) Cyclohexylidineacetic acid and cyclohexenylacetic acid are easily converted into one another as are cyclohexylidine acetone and cyclohexenylacetone.[2] By analogy, similar behavior might be expected of the two ketones (I) and (III).

At the time the aforementioned paper was published, the available data were insufficient to warrant a decision between structures (II) and (III). Structure (III) was favored, inasmuch as no stable enol of a cyclic ketone (saturated or unsaturated) has ever been isolated. The absorption spectra of the two compounds in question have, however, since been determined. They indicate conclusively that the new isomer has the keto structure (III). That is to say, when methylmagnesium bromide reacts upon isophorone in the presence of small amounts of ferric chloride, it shifts the double bond from the α-β to the β-γ position.

The ultraviolet absorption curves for isophorone I and $\Delta^{3,4}$-3,5,5-trimethylcyclohexenone (III) are given in Fig. 1. These curves (as well as the infrared absorption curves in Fig. 2) were obtained through the courtesy of the Stamford Research Laboratories of the American Cyanamide Company, to whom sincere thanks are here expressed. These investigators have also kindly provided an analysis of their findings, from which some of the following statements are taken.

The ultraviolet absorption curve for isophorone exhibits an intense broad absorption band with maxima near 2845, 2975, 3070 and 3700 mm.$^{-1}$. The band at 4450 mm.$^{-1}$ indicates the presence of conjugated unsaturation; the absorption near 3700 mm.$^{-1}$ may possibly represent approximately 0.5% of a substance such as compound (II) with two conjugated double bonds in the ring. Cooke and Macbeth[3] have examined the ultraviolet absorption spectra of a number of unsaturated aldehydes and ketones. The curve they obtained for piperitone (IV) in hexane very closely approximates that of isophorone (I) in

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(1) Kharasch and Tawney, THIS JOURNAL, **63**, 2308 (1941).

(2) Linstead, *J. Chem. Soc.*, 1603 (1930).

(3) Cooke and Macbeth, *J. Chem. Soc.*, 1408 (1938).