TABLE I

Product	B. p. or m. p., °C.	Yield, %
α-Acetylphenylacetonitrile	89–90[a]	68 (45)[h]
Propionylacetonitrile	109–110 (20)[b]	40
α-Propionylphenylacetonitrile	71–72.5[c]	60
n-Butyrylacetonitrile	103–105 (11)[d]	33
α-Benzoylphenylacetonitrile	89–90[e]	61[i] (50)[i,j]
Ethyl cyanoacetate	106–107 (22)[f]	40 (20)[i,j]
Ethyl α-cyanophenylacetate	152–154 (11)[g]	69[i,j]

[a] This melting point and that (112–113°) of the oxime agree with those reported in ref. 10, 11. [b] The boiling point reported by Henry [*Bull. classe sci. Acad. roy. Belg.*, [4] **2**, 62 (1900)] and by Van Reymenant [*ibid.*, [4] **2**, 743 (1900)] is 164–165°. Our product was characterized by alcoholysis to ethyl propionylacetate which was identified by its copper salt, m. p. 143–144° (Dupont, *Compt. rend.*, **148**, 1524 (1909). [c] The melting point reported by Bodroux (ref. 9) is 73° and that by Walther and Schickler (ref. 10) is 58°. [d] Agrees with boiling point reported in ref. 14. [e] This boiling point and the melting point (160–161.5°) of the oxime agree essentially with those reported in ref. 10. [f] Agrees with boiling point reported in literature (see ref. 15). [g] Nelson and Cretcher (ref. 8) report 145° at 7 mm. and 165° at 19 mm. [h] Yield with 0.3 mole each of reactants. [i] Only 0.38 mole of ester used. [j] Only 0.33 mole of sodium amide used.

triles. Thus, sodium amide has produced considerably better yields than sodium ethoxide[10] in the propionylation or benzoylation of phenylacetonitrile; however, sodium ethoxide[11] as well as sodium amide produces good yields in the acetylation of this nitrile. Sodium ethoxide has been employed in the isobutyrylation[12] or benzoylation[13] of acetonitrile but apparently not in the propionylation or *n*-butyrylation of this nitrile for which sodium amide has been fairly satisfactory.[14] Sodium ethoxide[15] as well as sodium amide produces good yields in the carbethoxylation of phenylacetonitrile but only the latter base has produced even a fairly satisfactory yield in the carbethoxylation of acetonitrile. In general, sodium amide effects these reactions in less time than sodium ethoxide.

(10) Walther and Schickler, *J. prakt. Chem.*, **55**, 305 (1897).
(11) "Organic Syntheses," Coll. Vol. II, 487 (1943).
(12) Kroeker and McElvain, THIS JOURNAL, **56**, 1172 (1934).
(13) Dorsch and McElvain, *ibid.*, **54**, 2962 (1932).
(14) Sodium triphenylmethide also, has been employed in the *n*-butyrylation of acetonitrile; Abramovitch and Hauser, *ibid.*, **64**, 2720 (1942).
(15) Wallingford, Jones and Homeyer, *ibid.*, **64**, 576 (1942).

Experimental

Sodium amide (0.6 mole) was prepared in liquid ammonia as previously described.[7] The reaction flask was placed on a steam-bath and absolute ether was added at such a rate as to maintain 300 cc. of liquid in the flask. After evaporation of the ammonia the ether began to boil, and 0.3 mole of phenylacetonitrile or acetonitrile in 50 cc. of absolute ether was added with stirring. The mixture was boiled for one-half hour. Longer heating appeared to be undesirable, since preliminary experiments with acetonitrile and diethyl carbonate indicated that the maximum concentration of nitrile anion is attained within fifteen to thirty minutes.

The ethyl ester (0.6 mole) to be condensed, dissolved in 50 cc. of absolute ether, was added, and the mixture was boiled under reflux and stirred for two hours; then it was poured on 100 g. of ice and acidified with concentrated hydrochloric acid. The ethereal phase was separated and the water layer was extracted with two 100-cc. portions of ether. The combined extracts were dried over Drierite, the solvent was distilled, and the residue was recrystallized, or distilled *in vacuo;* the data are given in Table I.

When 0.3 mole of caprylonitrile was treated with two equivalents each of sodium amide and diethyl carbonate as described above, none of the condensation product was obtained,[16] but the aqueous acid phase deposited on standing caprylamide, m. p. 105–105.5°,[17] in 30% yield.

Summary

1. The acylation and carbethoxylation of certain nitriles with certain esters have been effected in the presence of sodium amide.

2. The two courses of reaction of nitriles with sodium amide are discussed.

(16) Since Ziegler and Ohlinger (ref. 4) have reported that higher aliphatic nitriles may be alkylated by adding sodium amide to a mixture of the nitrile and alkyl halide at the boiling point of ether, an attempt was made to carbethoxylate caprylonitrile in this manner; however, the nitrile was recovered. Since little diethyl carbonate was recovered, it appeared that the sodium amide reacted with this ester rather than with the nitrile.
(17) Hofmann, *Ber.*, **17**, 1408 (1884).

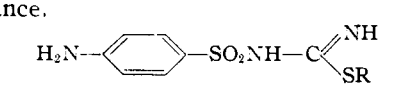
DURHAM, NORTH CAROLINA RECEIVED OCTOBER 13, 1945

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

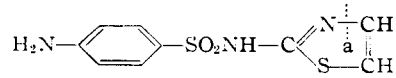
Sulfathiourea[1]

BY FELIX BERGMANN

The synthesis of sulfanilyl-isothioureas of the general formula I was initiated by the idea that these compounds are derived from sulfathiazole, II, by opening the thiazole ring along line a.[2,3,4] If it is assumed that sulfa drugs act by adsorption at an essential enzymatic system of the living cell, then the isothiourea derivatives I could replace II because of their structural resemblance.

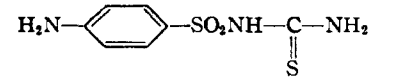


I

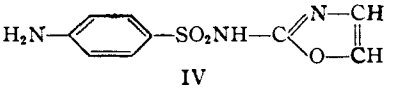


II

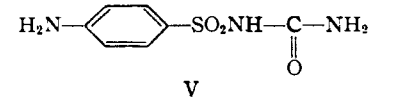
(1) This name is proposed as abbreviation of the more accurate designation of the compound as "sulfanilyl-thiourea."
(2) Cox, *J. Org. Chem.*, **7**, 307 (1942).
(3) Hungarian Patent 127,731; *C. A.*, **36**, 2270 (1942).
(4) Winnek, *et al.*, THIS JOURNAL, **64**, 1682 (1942); *C. A.*, **36**, 5791 (1942). This paper, like many others cited in this publication, was available to the author only from the *C. A.*



III



IV



V

Like the alkyl-isothioureas, the compounds I split off mercaptans under the influence of alkali and are completely resistant toward mineral acids, with which they form more or less stable salts. From Table I it can be seen that the hydrochlorides of I (R = alkyl) usually dissociate spontaneously during recrystallization, whereas I (R = benzyl) forms a completely stable salt, from which the base can be liberated only by treatment with ammonia. The allyl derivative shows an intermediate behavior. In contrast with this behavior, acid hydrolysis converts the corresponding isourea derivatives[5,4] into sulfanilyl-urea (V), and benzene[6]- or toluene[6a]-sulfonyl-isothioureas into mercaptans and the corresponding sulfonamides.

TABLE I

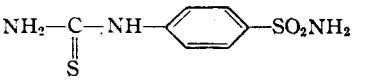
MELTING POINTS OF SULFANILYL-ISOTHIOUREAS

R =	Free base, °C.	Hydrochloride, °C.	Behavior of hydrochloride
CH_3	184[a]	226	Dissociates spontaneously. Obtained from ethanolic HCl
C_2H_5	165[b]	180	
n-C_3H_7	130	175	
n-C_4H_9	115	175–180	
n-C_5H_{11}	125	175	
Allyl	174	185	Hydrochloride from aq. HCl (10%)
Benzyl	145	216	Stable; free base with aq. NH_3
β-Phenethyl	141	188	Dissociates spont.

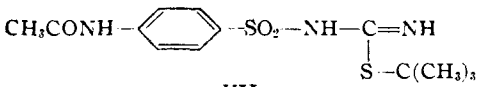
[a] Reference 2. [b] Winnek, *et al.* (footnote 4) report a m. p. of 154°.

The general method for the synthesis of the homologous series I is not applicable to the preparation of its first member (R = H), which substance most probably exists in the tautomeric form III as sulfathiourea. III bears the same structural relationship to sulfa-thiazole (II) as sulfanilylurea (V) to sulfa-oxazole (IV). As (IV) is inactive,[7] while (V) shows a certain bacteriostatic activity,[8] one might reasonably expect III to have an activity similar to sulfathiazole. Furthermore, Bell and Roblin[8] ascribe the transitory character of the activity of sulfanilylurea to the fact that the living cell may well apply its urea decomposing mechanism to this drug. Thiourea on the other hand, is known to pass the body unchanged.[9]

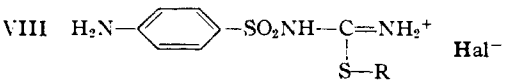
Sulfathiourea, as far as we are aware, is mentioned once in the literature[10] and its melting point is given as 202°. As we have found the substance III to melt at 182°, it is not impossible that there has been confusion with its isomer, N-(*p*-sulfonamidophenyl)-thiourea (VI), which has been prepared by Walker[11] from sulfanilamide and potassium thiocyanate and possesses a m. p. of 209°.

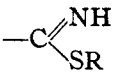
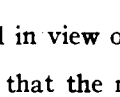


VI

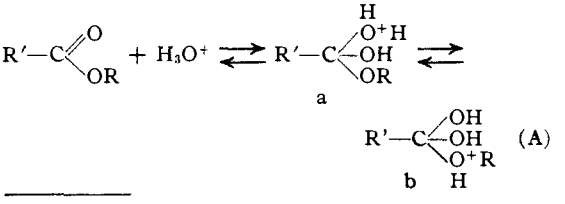


VII



In view of the formal analogy of the right part of formula I,  with a carbalkoxy group  and in view of the observation by Day and Ingold[12] that the normal acid hydrolysis of esters, which is an "acyl-oxygen fission," can be replaced by the alternative "alkyl-oxygen fission," if the alkyl group R has the tendency to form a carbonium ion R^+, we assumed that, *e. g.*, the *t*-butyl derivative of I would undergo acid hydrolysis to III. Indeed, when the acetyl derivative VII was heated with ethanolic hydrochloric acid, sulfathiourea III was obtained, although in low yield.

This analogy, however, is purely formal, as no alkyl group R appears to permit *normal* "ester-hydrolysis" of the compounds I. This fact appears still stranger, if we recall that the sulfanilyl-isoureas do undergo hydrolysis (with acids, into V). We wish to offer the following attempt at an explanation: According to Watson,[13] ester hydrolysis by acids requires addition of the oxonium ion to the ester group (scheme A), forming a mixture of two isomeric ions a and b. Ion b is then

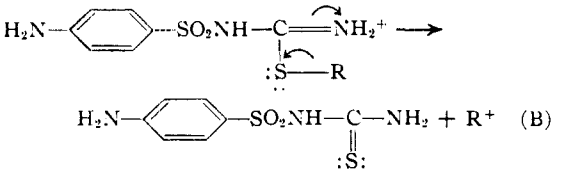


(A)

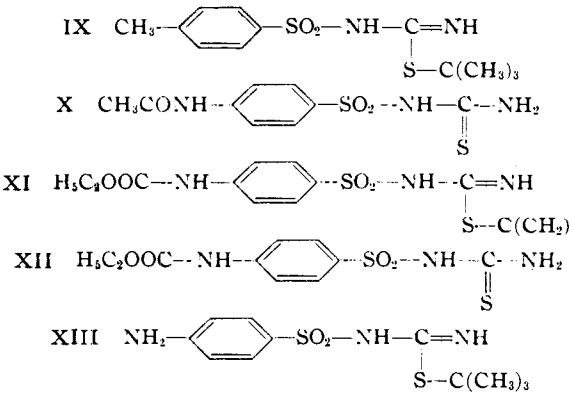
(5) Cox, THIS JOURNAL, **64**, 2225 (1942).
(6) Cox and Raymond, *ibid.*, **63**, 300 (1941).
(6a) See Experimental of this paper.
(7) Anderson, *et al.*, *ibid.*, **64**, 2902 (1942).
(8) Bell and Roblin, *ibid.*, **64**, 2905 (1942).
(9) Medes, *Biochem. J.*, **31**, 1330 (1937).
(10) Mayer, *C. A.*, **36**, 5199 (1942).
(11) Walker, *J. Chem. Soc.*, 1304 (1940).
(12) Day and Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941); see also Balfe, *et al.*, *J. Chem. Soc.*, 556, 605 (1942).
(13) Watson, "Modern Theories of Organic Chemistry," Oxford Press, New York, N. Y., 1943, p. 130.

able to split off the alkoxonium ion ROH_2^+ in place of the oxonium ion, leaving a free carboxyl. According to this mechanism, the necessary condition for acyl-oxygen fission is the addition of a proton to the oxygen of the —O—R group.

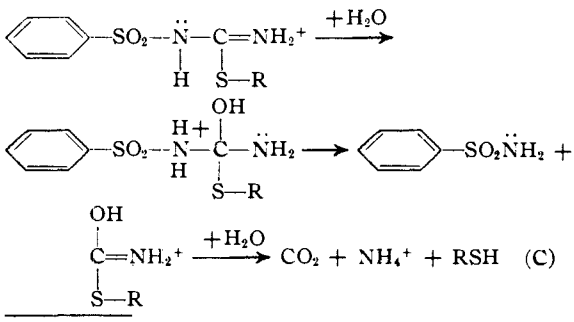
While the iso-urea derivatives behave toward acids like esters, the iso-thiourea compounds I form stable salts (VIII). This can be ascribed to the lower tendency of the sulfur atom to add protons.[14,15] In VIII, the positively charged nitrogen exerts an attraction on electrons; if R can exist as positive ion, it follows this electron-attracting influence and, thus, causes the reaction



The observation of Cox,[6] that benzenesulfonyl-isothioureas are being hydrolyzed (de-alkylated)



by acids, which we have confirmed for *p*-toluene-sulfonyl-S-methyl-isothiourea, can be brought into accord with our hypothesis. In this reaction, the sulfonamide is obtained as final product and not the urea derivative, as is the case with the benzenesulfonyl-O-alkyl-isoureas,[5] and it appears possible that in Cox' reaction the mercaptans are not primary fission products, but that it proceeds by the following mechanism (scheme C)



(14) Compare, *e. g.*, Zellhoefer, Copley and Marvel, THIS JOURNAL, **60**, 1337 (1938); Copley, Marvel and Ginsberg, *ibid.*, **61**, 3161 1939).

(15) Applications of these considerations to the hydrolysis of thio-esters are now under investigation.

Electron release from R would impede this splitting reaction. Indeed, the *p*-toluenesulfonyl-S-*t*-butyl-isothiourea (IX) is stable toward boiling acids. It becomes thus clear that the N^4-acetamino group in VII, as in all acetyl derivatives of I, makes a reaction according to scheme C impossible: In the resonance structure of VII, the N^1-nitrogen atom cannot function as proton acceptor, and therefore scheme B applies.

Conversely, the difference in behavior between VII and IX represents chemical indication of resonance in the sulfanilamides, which is supported by manifold physical evidence.[16]

Alkyl-sulfur fission in VII can be accomplished without de-acylation at room temperature by the use of concentrated hydriodic acid, which causes quantitative conversion into N^4-acetyl-sulfathiourea (X). The same observation was made on the N^4-carbethoxy derivative XI, which is converted by hydriodic acid into XII.

These experiments show that the removal of the *t*-butyl group in VII and XI precedes de-acylation, and on the theoretical side, that the resonance of the sulfanilamide system in these N^4-acyl compounds is not impaired in acid medium, as it is the case for the free amino-compounds.[16c] For this reason, it can be foreseen that sulfanilyl-S-*t*-butyl-isothiourea (XIII) will be unable to undergo "sulfur-alkyl fission" in acid solution. Experiments to synthesize XIII are now under way.

Experimental Part

(WITH S. ISRAELASHVILI AND Z. WEINBERG)

General Procedure.—The appropriate sulfonyl chloride (0.1 mole) and alkyl-isothiourea salt (0.1 mole) were suspended in acetone (100 cc.) and anhydrous sodium carbonate (0.1 mole) was added in portions. The mixture was stirred at room temperature for two hours and subsequently refluxed for the same period of time. After filtration from the inorganic precipitate, the solvent was distilled off and the residue recrystallized.

Deacetylation was carried out by refluxing with 5% ethanolic hydrochloric acid. From this solution, if necessary after concentration *in vacuo*, the crude hydrochlorides of I were obtained. In the case that these substances tended to dissociate during recrystallization, analytically pure samples could usually be obtained by recrystallization from concentrated ethanolic hydrochloric acid.

N^4-Acetylsulfanilyl-S-*t*-butyl-isothiourea is obtained in 80% yield, m. p. 203° (from acetic acid); rectangular prismatic plates (VII).

Anal. Calcd. for $C_{13}H_{19}O_3N_3S_2$. N, 12.8. Found: N, 13.1.

Nine and two-tenths grams of this product was refluxed for two hours with 5% hydrochloric acid in ethanol (100 cc.) and the solvent was evaporated *in vacuo*. The residual oil crystallized only with great difficulty on trituration with a mixture of ethanolic hydrochloric acid and acetic acid. *Sulfanilyl-thiourea* (III) forms big plates, from water, m. p. 182°: yield 10–15%. *Anal.* Calcd. for $C_7H_9O_2N_3S_2$: C, 36.4; H, 3.9; N, 18.2. Found: C, 36.1; H, 3.7; N, 17.9. When the above acetyl derivative (10 g.) was shaken with hydriodic acid (1.7; 100 cc.)

(16) (a) Halverstadt and Kumler, THIS JOURNAL, **63**, 624 (1941); (b) Kumler and Daniels, *ibid.*, **65**, 2190 (1943); (c) Kumler and Strait, *ibid.*, **65**, 2349 (1943).

TABLE II

SULFANILYL ISOTHIOUREAS NH_2—C$_6$H$_4$—$SO_2NHC(=NH)$—SR

R =	M. p., °C.	Recryst. from	Formula	Nitrogen, % Calcd.	Found
Methyl[a]	226 (dec.)	Acetic acid	$C_8H_{11}O_2N_3S_2 \cdot HCl$	14.9	14.5
n-Propyl	130	Ethanol	$C_{10}H_{15}O_2N_3S_2$	15.4	15.3
n-Butyl	115	50% Ethanol	$C_{11}H_{17}O_2N_3S_2$	14.6	14.6
n-Amyl	125	Ethanol	$C_{12}H_{19}O_2N_3S_2$	14.0	14.3
Allyl[b]	174	Water	$C_{10}H_{13}O_2N_3S_2$	15.5	15.3
Benzyl[c]	145	Butyl acetate	$C_{14}H_{15}O_2N_3S_2$	13.1	13.0[d]
β-Phenethyl	141	Ethanol	$C_{15}H_{17}O_2N_3S_2$	12.5	12.3

[a] The compound reported is the hydrochloride (see Table I). To prove its purity, carbon–hydrogen analysis was made. Calcd.: C, 34.2; H, 4.3. Found: C, 34.1; H, 4.6. [b] The hydrochloride was obtained from 10% aqueous hydrochloric acid, m. p. 185°. *Anal.* Calcd. for $C_{10}H_{13}O_2N_3S_2 \cdot HCl$: N, 13.7. Found: N, 13.6. [c] The stable hydrochloride was recrystallized from butanol, m. p. 216°. *Anal.* Calcd. for $C_{14}H_{15}O_2N_3S_2 \cdot HCl$: C, 47.1; H, 4.5; N, 11.8. Found: C, 47.5; H, 5.0; N, 11.8. [d] Calcd.: C, 52.3; H, 4.7. Found: C, 52.1; H, 4.9.

TABLE III

N^4-ACETYLSULFANILYL ISOTHIOUREAS

CH_3CONH—C$_6$H$_4$—SO_2NH—C(=NH)—SR

R =	M. p., °C.	Recryst. from	Formula	Nitrogen, % Calcd.	Found
n-Propyl	175	Butanol	$C_{12}H_{17}O_3N_3S_2$	13.3	13.3
n-Butyl	155	Butyl acetate	$C_{13}H_{19}O_3N_3S_2$	12.8	12.6
n-Amyl	141	50% ethanol	$C_{14}H_{21}O_3N_3S_2$	12.2	12.2
Allyl	165	Butanol	$C_{12}H_{15}O_3N_3S_2$	13.4	13.1
Benzyl	170	Butanol	$C_{16}H_{17}O_3N_3S_2$	11.6	11.3
β-Phenethyl	163	Butanol	$C_{17}H_{19}O_3N_3S_2$	11.1	11.3

for two hours, it went slowly into solution. When poured onto ice, the solution deposited a resinous mass, which crystallized upon trituration with ethanol. Acetylsulfanilyl-thiourea (**X**, from ethanol short needles, m. p. 202°. The yield was quantitative. *Anal.* Calcd. for $C_9H_{11}O_3N_3S_2$: C, 39.6; H, 4.0; N, 15.2. Found: C, 39.7; H, 4.0; N, 15.6.

N^4-Carbethoxysulfanilyl-S-*t*-butyl-isothiourea (XI) was prepared from N^4-carbethoxy-sulfanilyl chloride[17] in 64% yield. From butanol, prismatic plates, m. p. 206–207° *Anal.* Calcd. for $C_{14}H_{21}O_4N_3S_2$: C, 46.8; H, 5.9; N, 11.7. Found: C, 46.6; H, 5.9; N, 11.6.

When this compound (10 g.) was shaken with hydriodic acid (50 cc.) at room temperature, it went quickly into solution, and after thirty minutes a thick, pasty mass was obtained. It was successively triturated with water and ethanol. Carbethoxysulfathiourea (XII) is dimorphic: from butanol or acetic acid, it crystallizes in yellow pointed prisms, m. p. 140°, from ethanol in prismatic columns, m. p. 178° (dec.). After standing for several days, the lower-melting form shows a higher melting point, reaching eventually the value of 178°. The yield was 95%. *Anal.* Calcd. for $C_{10}H_{13}O_4N_3S_2$: C, 39.6; H, 4.3; N, 13.9. Found: C, 39.4; H, 4.6; N, 13.6.

From N^4-carbethoxysulfanilyl-thiourea (XII), sulfathiourea can be obtained by alkaline hydrolysis: 10 g. of XII were heated on the water-bath with a solution of sodium hydroxide (5 g.) in water (20 cc.). Then the solution was acidified with ethanolic hydrochloric acid and diluted with absolute ethanol, until no more sodium chloride precipitated. After filtration and evaporation *in vacuo*, a semicrystalline mass remained, which was dissolved in a minimum of boiling water and filtered. Three grams (40%) of sulfathiourea (III) were thus obtained, m. p. 178°.

p-Toluenesulfonyl-S-*t*-butyl-isothiourea (IX).—Condensation of *p*-toluenesulfonyl chloride with *t*-butyl-isothiourea hydrochloride, according to the usual procedure, gave the compound IX in 40% yield; from toluene as stout prisms; the melting point was 109–110°. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2S_2$: C, 50.4; H, 6.3. Found: C, 50.8; H, 6.3.

The substance was recovered unchanged after shaking with hydriodic acid for twelve hours and after refluxing with 10% ethanolic hydrochloric acid for two hours.

p-Toluenesulfonyl-S-methyl-isothiourea was obtained analogously. The yield was 30%. From ethanol, clusters of prisms, m. p. 119–120°. *Anal.* Calcd. for $C_9H_{12}O_2N_2S_2$: C, 44.3; H, 4.9; N, 11.5. Found: C, 44.4; H, 5.1; N, 11.8.

When this product (1 g.) was shaken with hydriodic acid (5 cc.), it passed immediately into solution and crystallized unchanged after about ten minutes.

When *p*-toluenesulfonyl-S-methyl-isothiourea (1.5 g.) was refluxed for one hour with 10% ethanolic hydrochloric acid (15 cc.), a crystalline precipitate appeared soon, which was easily soluble in water and was identified as ammonium chloride. The filtrate was evaporated to dryness and treated with aqueous ammonia. The solid was recrystallized from benzene and formed clusters of leaflets, m. p. 135°. It was identified as *p*-toluenesulfonamide. *Anal.* Calcd. for $C_7H_9O_2NS$: C, 49.1; H, 5.3; N, 8.2. Found: C, 48.9; H, 5.6; N, 8.5.

Summary

Sulfathiourea (III) cannot be synthesized by a method analogous to the preparation of sulfanilylurea, because sulfanilyl-S-alkyl-isothioureas are not dealkylated by acids. N^4-Acetylsulfanilyl-S-*t*-butyl-isothiourea (VII), however, is converted into III (or its acetyl derivative) by an "alkyl-sulfur fission." The fact that no *normal* "acyl-sulfur fission" occurs with the sulfanilyl-isothioureas, is explained by failure of the sulfide sulfur atom to combine with a proton, a condition apparently not necessary for "alkyl-sulfur fission."

p-Toluenesulfonyl-S-*t*-butyl-isothiourea (IX) is not appreciably attacked by boiling acids, showing that, through resonance, the N^4-acetamino group participates in the "alkyl-sulfur fission" of VII.

REHOVOTH, PALESTINE RECEIVED MARCH 15, 1945

(17) Adams, Long and Johanson, THIS JOURNAL, **61**, 2342 (1939).