water, and dried over anhydrous sodium sulfate. The ether was evaporated under reduced pressure leaving the residue as a yellow, oily liquid. The liquid contained a small amount of pyridine which was distilled off at 50° under vacuum. The residue was then fractionated at 165°, 5 mm. pressure, yield 21 g. (77%).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.16; H, 7.25. Found: C, 67.01, 67.08; H, 7.12, 7.08.

The β-butyryl-α,α′-benzylideneglycerol crystallized to a solid mass after being placed in a refrigerator at 5° for one hour. The mass was dissolved in ethyl ether to which an equal volume of petroleum ether was added. After a short period at 5° the crystals which separated were washed with cold petroleum ether (0°) into a suction funnel, which had been previously cooled with solid carbon dioxide. The crystals were long, colorless prisms very soluble in ether and alcohol and insoluble in petroleum ether and water, m. p. 16–18° (uncor.).

The m. p. (16–18°) is consistent with the melting points of other esterified acetals prepared by other investigators. Stimmel and King[7] prepared the beta-capryl (m. p. 32.5°), beta-lauryl (m. p. 44.6°), beta-myristyl (m. p. 62°), beta-palmityl (m. p. 63.8°) and beta-stearyl (m. p. 69°) esters of α,α′-benzylideneglycerol and found that as the length of the carbon chain of the fatty acid in the beta position increased, the melting point progressively increased. Bergmann and Carter,[4] however, found that the β-acetyl-α,α′-benzylideneglycerol melted at 99–100°. This esterified acetal was also prepared by the author and the melting point reported by Bergmann and Carter was verified. The melting point of the acetyl derivative is out of line with all the analogous compounds so far prepared in the series. It is interesting to note that the mixed triglycerides containing one mole of acetic acid also exhibit relatively high melting points compared to higher members of the series.

Preparation of beta-Monobutyrin.—This beta monoglyceride was prepared from 10 g. of β-butyryl-α,α′-benzylideneglycerol by the method of Bergmann and Carter.[4] One-half gram of palladium black, as reported by Stimmel and King,[7] was found to be sufficient for the hydrogenation; yield, 5.75 g. (88%).

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.49; H, 9.26. Found: C, 51.44, 51.38; H, 9.15, 9.20.

The beta-monobutyrin was a colorless liquid soluble in alcohol and ether, b. p. 140–141° (4 mm.), sap. eq. 162.10 (theory 162.18). For further identification the *beta* monobutyrin was used to prepare β-butyryl-α,α′-distearin, m. p. 51.5° (McElroy and King,[8] 51°).

Summary

Catalytic detritylation by reduction of the esterified α,α′-dityrityl ether of glycerol has been verified in the preparation of beta monopalmitin in good yield. Thus, an additional method for preparing beta monoesters of the fatty acids is available, as suggested by Verkade.

A new intermediate β-butyryl-α,α′-benzylideneglycerol, m. p. 16–18°, has been prepared and the melting point found to be consistent with other esterified acetals of the aliphatic series.

beta-Monobutyrin, a new beta monoester, has been prepared and the structure verified by making a triglyceride of known constitution.

(7) Stimmel and King, THIS JOURNAL, **56**, 1724 (1934).

(8) McElroy and King, *ibid.*, **56**, 1191 (1934).

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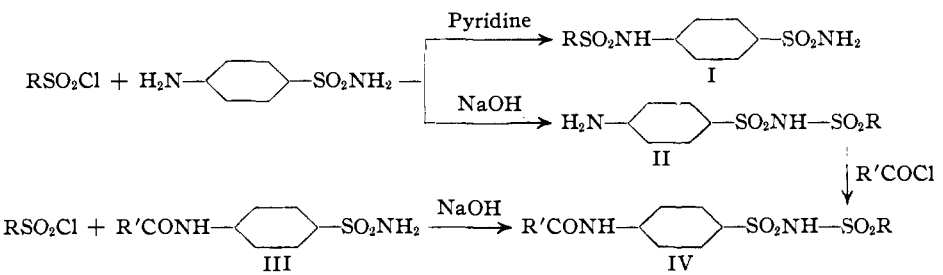
Substituted Sulfanilamides. II. N^1- and N^4-Sulfonyl Derivatives

BY JAMES M. SPRAGUE, LANE F. MCBURNEY AND L. W. KISSINGER

Certain N^4-acyl derivatives of sulfanilamide have shown good protective action against experimental streptococcal infections in mice.[1] For comparison with these acylsulfanilamides a number of sulfonyl derivatives have been prepared. N^1-*p*-Aminobenzenesulfonylsulfanilamide (disulfanilamide) and N^4-*p*-aminobenzenesulfonylsulfanilamide have been reported[2,3] recently.

The N^4-sulfonyl derivatives I were prepared by treating sulfanilamide in pyridine solution with a sulfonyl chloride.



(1) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939).

(2) Crossley, Northey and Hultquist, *ibid.*, **60**, 2222 (1938).

(3) Rosenthal, *et al.*, *Pub. Health Reports*, **52**, 662 (1937); **53**, 5340 (1938); Bauer, THIS JOURNAL, **61**, 613 (1939).

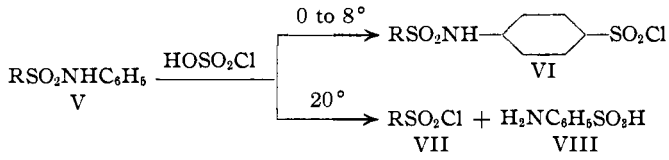
TABLE I

SULFONYL SULFANILAMIDES

( ) Sulfanilamide	M. p., °C. (uncor.)	Yield, % (purif.)	Formula	Nitrogen, % Calcd.	Found
N^4-Methanesulfonyl-	180–181	68	$C_7H_{10}O_4N_2S_2$	11.19	11.17
N^4-Ethanesulfonyl-	175–176	68	$C_8H_{12}O_4N_2S_2$	10.60	10.58
N^4-1-Butanesulfonyl-	160–161	70	$C_{10}H_{16}O_4N_2S_2$	9.58	9.40
N^4-1-Pentanesulfonyl-	156–156.5	73	$C_{11}H_{18}O_4N_2S_2$	9.14	9.10
N^4-1-Hexanesulfonyl-	153–153.5	53	$C_{12}H_{20}O_4N_2S_2$	8.74	8.68
N^4-1-Dodecanesulfonyl-	157–158	56	$C_{18}H_{32}O_4N_2S_2$	6.92	6.88
N^4-Phenylmethanesulfonyl-	226–227	41	$C_{13}H_{14}O_4N_2S_2$	8.58	8.42
N^4-Benzenesulfonyl-	147–148	70	$C_{12}H_{12}O_4N_2S_2$	8.97	8.94
N^1-1-Butanesulfonyl-	205–206	31	$C_{10}H_{16}O_4N_2S_2$	9.58	9.52
N^1-1-Pentanesulfonyl-	179–180	27	$C_{11}H_{18}O_4N_2S_2$	9.14	9.06
N^1-Phenylmethanesulfonyl-	226–227	25	$C_{13}H_{14}O_4N_2S_2$	8.58	8.40
N^1-1-Pentanesulfonyl-N^4-acetyl-	202.5–203.5	..	$C_{13}H_{20}O_5N_2S_2$	8.04	7.99
N^1-1-Pentanesulfonyl-N^4-caproyl-	152.5–153	..	$C_{17}H_{28}O_5N_2S_2$	6.93	6.85
N^1-1-Butanesulfonyl-N^4-*n*-caproyl-	182–183	28	$C_{16}H_{26}O_5N_2S_2$	7.17	7.12

The preparation of these compounds from the alkanesulfonanilides V, by the action of chlorosulfonic acid and subsequent conversion of the sulfonyl chloride to the amide, was unsatisfactory. Under conditions similar to those used for the preparation of acylaminobenzenesulfonyl chlorides[1] from acylanilides, the sulfonanilides were found to undergo cleavage with the formation of the sulfonyl chloride VII and an aminobenzenesulfonic acid VIII. None of the desired sulfonyl chloride VI was obtained. The cleavage products were isolated in yields of 50–76% from 1-butanesulfonanilide and benzenesulfonanilide and 20% from ethanesulfonanilide.

At a lower temperature ethane- and 1-butanesulfonanilide were not cleaved. The product was a sulfonyl chloride which appeared to be a homogeneous substance and analyzed correctly for the desired compound VI. On treating with ammonia this product was converted to an amide which was difficult to purify. However, after several recrystallizations a low yield of the amide I, identical with that prepared from sulfanilamide, was obtained.



Derivatives in which an alkanesulfonyl group is attached to the amide nitrogen (N^1) also have been prepared. The N^1-alkanesulfonylsulfanilamides II were obtained from sulfanilamide and a sulfonyl chloride in aqueous alkali or by the catalytic reduction of the corresponding nitro compound. The N^1-alkanesulfonyl-N^4-acylsulfanilamides IV were prepared from the N^4-acylsulfanilamides[1] III and an alkanesulfonyl chloride or from the N^1-alkanesulfonylsulfanilamide II and an acyl chloride.

These sulfonyl derivatives of sulfanilamide are listed in Table I. Preliminary results against experimental streptococcal infection in mice, after treatment with a single dose of these compounds, indicate that the introduction of the sulfonyl group into the N^4-position of the sulfanilamide molecule markedly reduces its therapeutic effect. Introduction into the N^1-position also reduces the effectiveness but to a less extent. However, all of these compounds are relatively non-toxic.[4]

Experimental Part[5]

N^4-Alkanesulfonylsulfanilamides, I.—Sulfanilamide (0.1–0.2 mole) was dissolved in pyridine (40–50 cc.) and the alkanesulfonyl chloride (5–10% excess) added in small portions with vigorous stirring. After the addition was complete, the red solution was refluxed gently for thirty minutes. The cooled solution was poured into a mixture of concentrated hydrochloric acid and crushed ice. The product was separated and recrystallized from water or alcohol and water. The yields of crude product were 70–90% and recrystallized 50–70%. The melting points and analyses of these compounds are given in Table I.

Action of Chlorosulfonic Acid on Alkanesulfonanilides.—(a) Fifty-eight grams of chlorosulfonic acid was cooled to 10° in an ice-bath and 21.4 g. (0.1 mole) of 1-butanesulfonanilide added slowly with stirring over a fifteen to thirty minute period while maintaining the temperature below 20°. After fifteen minutes, the ice-bath was removed and the reaction mixture allowed to

(4) We are indebted to Messrs. G. W. Webster and Harry J. Pratt for the pharmacological testing of these compounds.

(5) All melting points are uncorrected.

stir at room temperature for two hours. It was then poured into ice and water. The 1-butanesulfonyl chloride, which separated as an oil, was taken up in petroleum ether and filtered from the insoluble material. From this ether extract a 67% yield of 1-butanesulfonyl chloride was obtained, b. p. 108–109° (33 mm.). The solid material (9.1 g.) did not melt and after recrystallizing from water was analyzed. The analysis and properties indicated an aminobenzenesulfonic acid. Similar results were obtained when the reaction was carried out at 0 to 10° for fifteen hours.

Under the same conditions ethanesulfonanilide gave 20% of ethanesulfonyl chloride and benzenesulfonanilide gave 71% of benzenesulfonyl chloride.

(b) The reactions were carried out as in (a), except that the temperature was kept at 0 to 8° during the entire period of the reaction. On pouring into ice and water a white solid separated which was removed by filtration and thoroughly washed with cold water. There was no evidence of cleavage and the product had the properties expected of an alkanesulfonamidobenzenesulfonyl chloride. With 1-butanesulfonanilide the yield of crude product was 19.0 g., m. p. 120–123°. This was recrystallized from benzene or toluene and naphtha to a constant melting point of 126–128°.

Anal. Calcd. for $C_{10}H_{14}O_4NS_2Cl$: N, 4.49; Cl, 11.40. Found: N, 4.40; Cl, 11.60.

On conversion to the amide with concentrated ammonia both the crude and recrystallized sulfonyl chloride gave an amide melting at 148–155°. After several recrystallizations from dilute alcohol it melted at 159.5–160.5° and was identical with the N^4-1-butanesulfonylsulfanilamide prepared from sulfanilamide and 1-butanesulfonyl chloride.

Ethanesulfonanilide gave 19.5 g. of crude product, m. p. 118–122°. On recrystallization from benzene or toluene it melted constantly at 127–128°. A mixed melting point with the sulfonyl chloride from the 1-butanesulfonanilide gave a depression of 20°.

Anal. Calcd. for $C_8H_{10}O_4NS_2Cl$: N, 4.93; Cl, 12.53. Found: N, 4.70; Cl, 12.57.

The crude amide melted at 162–170°. After recrystallization from dilute alcohol, the melting point was 175–176° and was not depressed by N^4-ethanesulfonylsulfanilamide.

Benzenesulfonanilide gave only 4% of a product corresponding to the sulfonyl chloride VI and 25% of the cleavage products.

N^1-Alkanesulfonylsulfanilamides.—(a) To 100 cc. of 10% sodium hydroxide 17.2 g. (0.1 mole) of sulfanilamide was added and shaken until completely dissolved. Twenty grams of 1-butanesulfonyl chloride was added in portions during twenty minutes with vigorous agitation and constant cooling. After all of the sulfonyl chloride had reacted, the solution was neutralized with dilute hydrochloric acid and chilled. The unreacted sulfanilamide was removed and the filtrate made acid with hydrochloric acid. The N^1-1-butanesulfonylsulfanilamide was recrystallized from water; yield 9.0 g., 31%, m. p. 203–205°. Similar results were obtained using 1-pentanesulfonyl chloride and phenylmethanesulfonyl chloride (Table I). The diazo color tests showed the presence of the free amino group in these compounds.

(b) In a similar manner a 64% yield of 1-butanesulfonyl-*p*-nitrobenzenesulfonamide was obtained from *p*-nitrobenzenesulfonamide and 1-butanesulfonyl chloride. This was recrystallized from a concentrated water solution by the addition of concentrated hydrochloric acid, m. p. 117–118.5°.

Anal. Calcd. for $C_{10}H_{14}O_6N_2S_2$: N, 8.70. Found: N, 8.63.

This compound was reduced catalytically, using PtO_2, to the N^1-1-butanesulfonylsulfanilamide, m. p. 204.5°, yield 73%.

N^1-Alkanesulfonyl-N^4-acylsulfanilamides.—(a) To a solution of 5.4 g. (0.02 mole) of N^4-caproylsulfanilamide[1] in 50 cc. of 10% sodium hydroxide, 5.0 g. (0.03 mole) of 1-butanesulfonyl chloride was added with constant cooling and vigorous agitation. The addition required about ten minutes. The solution was diluted with two volumes of water, neutralized with dilute hydrochloric acid and the unreacted material removed by filtration. The filtrate was made strongly acid with hydrochloric acid. The precipitated product was removed, redissolved in sodium carbonate solution and reprecipitated with acid. The yield of N^1-1-butanesulfonyl-N^4-caproylsulfanilamide was 2.7 g. (35%), m. p. 180–182°. After recrystallization from water and alcohol, it melted at 182–183°. The 1-pentanesulfonyl compound was prepared in a similar manner from 1-pentanesulfonyl chloride.

From N^4-acetylsulfanilamide and 1-butanesulfonyl chloride the N^1-1-butanesulfonyl-N^4-acetylsulfanilamide was prepared.

(b) N^1-1-Butanesulfonyl- and N^1-1-pentanesulfonylsulfanilamide were treated with caproyl chloride in pyridine or aqueous alkali solution to give 50–80% yields of the N^1-alkanesulfonyl-N^4-caproylsulfanilamides.

All of the N^1-alkanesulfonyl derivatives (II and IV) are strong acids, readily soluble in bicarbonate solutions. The readily soluble sodium and potassium salts give neutral aqueous solutions.

Summary

1. Thirteen N^1- and N^4-alkanesulfonyl derivatives of sulfanilamide are described.

2. Pharmacological results indicate that the introduction of a sulfonyl group into sulfanilamide markedly reduces the activity against streptococcal infections in mice.

3. Under conditions similar to those used for the chlorosulfonation of acylanilides, alkanesulfonanilides are cleaved by chlorosulfonic acid to give the alkanesulfonyl chloride and an aminobenzenesulfonic acid. Cleavage does not occur, however, at lower temperatures.

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