Summary

An allylsodium–sodium alloxide mixture was obtained by cleaving diallyl ether with sodium metal. This mixture reacted with 2-bromooctane to give a high yield of 4-methyl-1-decene.

For comparative purposes, 4-methyl-1-decene was also synthesized by a Grignard reaction, and allyl 1-methylheptyl ether was prepared by a Williamson reaction.

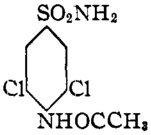
EVANSTON, ILLINOIS RECEIVED MAY 29, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WELLESLEY COLLEGE]

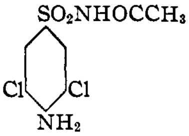
Acetylation of 3,5-Dichlorosulfanilamide

BY MARGARET K. SEIKEL

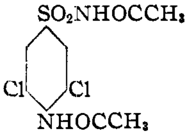
Preliminary attempts to acetylate 3,5-dichlorosulfanilamide, I,[1] led to a mixture of products. Specific conditions, therefore, have been developed by which each of the four possible acetyl derivatives, II, III, IV and V can be obtained directly from the parent compound in good yields.[2] These four derivatives have been identified,[3] and the hydrolysis of each in different media has been studied in respect to products and speed.



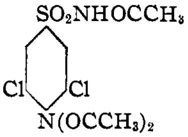
II



III



IV



V

The acetylation of 3,5-dichlorosulfanilamide and the properties of its acetyl derivatives are in general in agreement with material in the literature. The presence of the two chlorine atoms ortho to the amino nitrogen distinguishes I from sulfanilamide because of the resultant decrease in basicity. Sulfanilamide is soluble in acid while I separates even from hot concentrated hydrochloric acid solution.[1] Only three acetyl derivatives of sulfanilamide have been reported,[4] the N^4-acetyl,[5] the N^1-acetyl,[6] and the N^1, N^4-diacetyl.[6a,6b,7] Unsuccessful preliminary attempts were made in the present work to obtain a triacetyl derivative by the method used to triacetylate I. Such negative results check work on diacetylation of substituted anilines, in which the presence of diortho substituents was shown to favor diacetylation markedly.[8]

The markedly greater effect which the sulfuric acid catalyst has on the speed of monoacetylation *versus* that of diacetylation of an amino nitrogen with diortho substituents by acetic anhydride mentioned by Smith and Orton[9] was noticed and evidence obtained on the dependence of the rate of monoacetylation on the amount of acid. Smaller amounts of sulfuric acid were used than have generally been reported.[9,10] The use of an acetic acid solution to retard diacetylation of the amino group[9,10a] was confirmed in studying the preparation of IV.

Differential acetylation of the amino group and the amido group in I by acetic anhydride has been accomplished and distinguishes I from sulfanilamide and its non-diortho substituted derivatives. First, this was attained by controlling the amount of sulfuric acid used. The amino group acetylated at room temperature with low concentrations of sulfuric acid (0.001 ml. per 0.5 ml. of acetic anhydride) while the amido groups remained for the most part unacetylated even in the presence of excess anhydride. With higher concentrations (0.01 ml. per 0.5 ml. of anhydride) both acetylated. It is felt that the local heating effect of rapid monoacetylation may have promoted the diacetylation. Secondly, reactions in basic media (aqueous alkali or pyridine) led first to acetylation of the amido group. Sodium hydroxide solutions have been used in acetylation of amines containing acid groups,[11] but no preparations of N-acetylsulfonamides employing hydroxide solutions have been discovered. Acetic anhydride in pyridine solution has been used in recent years for acetylating the N^1-nitrogen of sulfanilamide and its deriva-

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[1] Seikel, THIS JOURNAL, **62**, 1214 (1940), and "Organic Syntheses," **24**, 47 (1944).

[2] During the work each of the five compounds has been obtained from and converted into all of the others with the exception of II to and from III and III from V.

[3] Their structures are proven by the fact that only III contains a diazotizable amino group, by strongly acidic imidic hydrogen in III, IV and V, by their logical conversion into one another on hydrolysis or further acetylation, by the fact that IV can yield two different monoacetyl derivatives (II and III) on hydrolysis, by the relatively great instability of the third acetyl group in V, and by the fact that V may be reprecipitated unchanged from a bicarbonate solution.

[4] The references given do not presume to be complete.

[5] Gelmo, *J. prakt. Chem.*, [2] **77**, 371 (1908); Scudi, THIS JOURNAL, **59**, 1481 (1937); Miller, Rock and Moore, *ibid.*, **61**, 1199 (1939).

[6] (a) Crossley, Northey and Hultquist, *ibid.*, **61**, 2950 (1939); (b) Huang-Minlon and Lo, *J. Chinese Chem. Soc.*, **9**, 61 (1942); (c) Braz, *J. Applied Chem.* (*U. S. S. R.*), **17**, 508 (1944), *C. A.*, **41**, 4061 (1945).

[7] Scudi, *Ind. Eng. Chem.*, *Anal. Ed.*, **10**, 347 (1938).

[8] Ulffers and von Janson, *Ber.*, **27**, 93 (1894); Sudborough, *J. Chem. Soc.*, **79**, 533 (1901); Raiford, Taft and Lankelma, THIS JOURNAL, **46**, 2051 (1924); Hodgson, *J. Soc. Dyers and Colourists*, **46**, 187 (1930); Dubsky, *Chem. Z.*, **36**, 677, 697 (1912).

[9] Smith and Orton, *J. Chem. Soc.*, **93**, 1242 (1908).

[10] (a) Blanksma, *Chem. Weekblad*, **6**, 717 (1909); (b) Skraup, *Monatsh.*, **19**, 458 (1898); (c) Chattaway and Irving, *J. Chem. Soc.*, 143 (1933).

[11] For example, Chattaway, *ibid.*, **2495** (1931).

tives, but in all cases discovered the N^4-amino groups have been protected or had not been formed.[12] This protection is necessary because under these conditions sulfanilamide yields the N^4-acetyl derivative.[13]

The ease of hydrolysis of the acetyl groups in II, III, IV and N^1,N^4-diacetylsulfanilamide depends on the relationship of the acidity or basicity of the media with the acidity or basicity of the compound or its hydrolysis product. This means that the ease of hydrolysis of the N^4-acetyl groups (the products have weakly basic groups) varied inversely with the basicity of the nitrogen atoms in alkaline hydrolysis[14] and directly for neutral or acidic hydrolysis. Similarly the acidic N^1-acetyl derivatives were more stable than the N^4-acetyl derivatives in basic solution, less in acid. The N^1-acetyl derivative of sulfanilamide appeared to be more stable to base than III. The ready hydrolysis of the second N^4-acetyl group in V checked results on diacetanilide and its derivatives.[15]

A mole for mole complex, VI, of I and III was isolated. It separated from solutions containing approximately mole for mole proportions of its two constituents, although the solubility of one is three times that of the other. Similar complexes have been reported for sulfanilamide and its derivatives.[16]

Experimental[17]

N^4-Acetyl-3,5-dichlorosulfanilamide, II

Preparation.—To 0.5 g. (0.00207 mole) of I,[18] powdered, 0.5 ml. (0.00528 mole, 2.5 times the theoretical amount) of acetic anhydride containing 0.001 ml. of concentrated sulfuric acid per 0.5 ml. of acetic anhydride was added at room temperature,[19] and the mixture stirred and ground continually. Separation of a new solid, with an evolution of heat, caused the mixture to become dry. When it no longer tested positively for a free aromatic amino group (half an hour or more), it was treated with 5 ml. of saturated sodium bicarbonate solution reinforced with solid bicarbonate. From the basic mixture II was filtered out, washed with bicarbonate until free from the acidic by-products, and then with water until free from bicarbonate. Crude products melted between 230–240° if properly prepared and weighed from 0.40–0.47 g., 70–80% yields. From the filtrate 0.07–0.15 g. (10–20% yields) of acidic by-products, melting between 180–200°, was obtained by acidification. Solution of this in dilute hydroxide and reprecipitation converted it all into IV, m. p. around 200°, proving that V had been present also.

Changed conditions produced the following results. Increase in concentration of sulfuric acid, even doubling it, gave a faster reaction but led to more by-product. Decrease gave too slow a reaction without eliminating the by-product. Longer times did not lead to further acetylation. Powdering the amide and frequent stirring of the heterogeneous mixture are imperative for a complete reaction. Since II is soluble in hydroxide, bicarbonate must be employed in isolating it.

II may also be obtained by hydrolysis of the higher acetylated products.

Properties.[20]—The compound could not be diazotized and coupled nor was it titratable, but it is soluble in excess 0.1 *N* alkali. It could be further acetylated.

N^1-Acetyl-3,5-dichlorosulfanilamide, III

Preparation. From I in Aqueous Alkali.—To a stirred solution of 0.25 g. (0.00104 mole) of I[18] in 5 ml. of 0.5 *N* sodium hydroxide, warmed to 50–55°, alternate additions of 50–55°, alternate additions of 0.02-ml. portions of acetic anhydride and drops of 0.5 *N* sodium hydroxide were made. Rates of addition were controlled to maintain a *p*H of about 11. The reaction was complete when the *p*H could be lowered to 7 without precipitation of unreacted I; this occurred after about 0.4 ml. (0.086 acid equivalent) of anhydride and 15–24 ml. (0.075–0.12 equivalent) of base had been added, an operation requiring about twenty minutes. After a trace of unreacted I which separated on cooling had been removed, III was precipitated from the filtrate by reducing the *p*H to about 3 with excess 6 *N* hydrochloric acid. This constituted a 79–83% yield (0.23–0.245 g.), melting around 205–207°.

A study of different temperatures showed that at 25° more of the reagents and a longer time were required, probably because the rate of hydrolysis of the anhydride was decreased less than the rate of acetylation. At 75° more unreacted material was isolated, probably because of its increased solubility.

From I in Pyridine Solutions.—A mixture of 0.25 g. (0.00104 mole) of I[18] dissolved in the least boiling pyridine (0.35 ml.) and 0.12 ml. (0.0013 mole, 1.25 times the theoretical amount) of acetic anhydride was heated for fifteen minutes on the steam-bath. III was obtained by diluting with water, stirring to crystallize the oil, adding 1 ml. of concentrated hydrochloric acid to reduce the *p*H to 1, and cooling for fifteen minutes. The yield was 0.28 g. (96%), the melting point 209.5–210.5°. This product contained as its main impurity a 4–8% recovery of I which could be isolated by bicarbonate extraction, but recrystallizing from 25% alcohol once was an easier purification. This yielded pure material, m. p. 196–197°, in an 87% over-all yield.

Incomplete reactions resulted with less anhydride or shorter times. Lower yields without better melting points resulted if the crude material was extracted with bicarbonate and the product reprecipitated.

From IV by hydrolysis.[21]—A solution of 5.3 g. (0.0163 mole) of IV, m. p. 202.5–203°, in 144 ml. of 0.25 *N* sodium hydroxide (0.036 mole or 1.1 times the theoretical amount) was refluxed for four hours. The by-product I was isolated in an 11% yield (0.40 g.) by neutralizing with 6 *N* hydrochloric acid using phenolphthalein, cooling, filtering and washing with bicarbonate. III could be isolated most easily by reheating the filtrate, acidifying strongly with excess concentrated hydrochloric acid (3 ml.) and cooling the milky solution. The yield was 65% (3.00 g.), m. p. 203.5–204°.

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(12) Lo and Chu, THIS JOURNAL, **66**, 660 (1944); Chu, *ibid.*, **67**, 812 (1945); Tozer and Smiles, *J. Chem. Soc.*, 2056 (1938). Acyl chlorides have been used with pyridine, footnote 6a; with sodium hydroxide, English, Chappell, Bell and Roblin, THIS JOURNAL, **64**, 2516 (1942).

(13) Huang-Minlon, Lo and Chu, *J. Chinese Chem. Soc.*, **8**, 194 (1941).

(14) *Cf.* Sapozhnikova, *J. Applied Chem.* (*U. S. S. R.*), **17**, 370 (1944); *C. A.*, **39**, 2688 (1945), and Zehender, *Helv. Chim. Acta*, **26**, 1346 (1943).

(15) For example, see Bistrzycki and Ulffers, *Ber.*, **27**, 92 (1894), and Ruggli and co-workers, *Helv. Chim. Acta*, **16**, 468 (1933); **24**, 711 (1941).

(16) Sevag. THIS JOURNAL, **65**, 110 (1943); Burton and Walker, *J. Chem. Soc.*, 656 (1943); Lur'e. *J. Gen. Chem.* (*U. S. S. R.*), **16**, 209 (1946), *C. A.*, **41**, 414 (1947).

(17) All melting points are uncorrected and were taken by the method described in Mulliken, "Identification of Organic Compounds," Vol. I, p. 218, on a 360° thermometer immersed in sulfuric acid to the −10° point.

(18) M. p. 208–209°. Compare with earlier work, footnote 1.

(19) Larger quantities of reactants, *i. e.*, 5.0 g. of amide, were cooled before mixing and during half the reaction time.

(20) See Table I also.

(21) This followed Crossley, Northey and Hultquist's method for N^1-acetylsulfanilamide (footnote 6a). The main change was decrease in strength and amount of alkali.

If 2.5 *N* base was employed in excess (1.25 times the theoretical amount), the product was largely hydrolyzed. Half normal alkali was usable. At least three hours of refluxing was necessary for an essentially complete reaction.

Properties.[20]—Crude samples of III melted higher than the pure material and required two recrystallizations before they melted below 200°. The compound dissolved readily in bicarbonate, titrated with 0.1 *N* alkali using phenolphthalein and diazotized and coupled. It could be further acetylated.

N^1,N^4-Diacetyl-3,5-dichlorosulfanilamide, IV

Preparation. Method I.—To 0.25 g. (0.00104 mole) of I,[18] powdered, were added 0.75 ml. of glacial acetic acid and 0.3 ml. (0.0032 mole, 1.5. times the theoretical amount) of acetic anhydride containing 0.01 ml. of concentrated sulfuric acid per 0.5 ml. of the anhydride. Spontaneous monoacetylation occurred in less than one minute, and then the mixture was heated to boiling. Heating was continued until, about a minute after total (or in large runs partial) solution of the precipitate, the mixture suddenly solidified. After cooling it was dissolved in 3 *N* sodium hydroxide, and IV was precipitated by adding 6 *N* hydrochloric acid until the *p*H was 3 and by icing. The product, washed with water carefully until free of chloride, was dehydrated at 110° and then weighed 0.27 g. (83% yield), m. p. 198.5–200°. In other runs 85–96% yields resulted with melting points between 196–201°. Twelve grams of I have been employed, and both II and III have been used as the starting material.

With less sulfuric acid the monoacetylation and the solidification were slower, and the latter did not coincide with completion of the acetylation. The amount of anhydride was increased and the ratio of acetic anhydride to acetic acid was varied from 1:3 to 2:1 without apparent differences. Acetic acid must be used to precipitate the products, visibly signifying the completion of the reaction. The treatment with hydroxide was necessary to convert the by-product, V, into IV, and a 3 *N* solution kept the volume small and the concentration too low for precipitation of the salt of the product. Air drying of the product left it in the hydrated form.

Method II.—The method of preparation of II was adapted to the preparation of IV by increasing the sulfuric acid content to 0.01 ml. per 0.5 ml. of anhydride. The reaction was complete in ten minutes and the product was isolated as in Method I. The yields were 86–96%, the melting points, 199–201°. III was also employed as the starting material. In fact, this compound acetylated slowly with less sulfuric acid (0.001 ml. per 0.5 ml. of anhydride), and although tests showed that the reaction was not quite complete after several hours, 75–81% yields of material, m. p. 197–200°, were isolated.

The small excess of anhydride which was used, 1.25 times the theoretical amount, often led to incomplete reactions unless it were pure and the mixture well-stirred. Larger volumes of reagent are recommended. The reaction was incomplete in five minutes, the bicarbonate insoluble II being isolated.

Methods I and II were combined. A 0.25 g. (0.00104 mole) sample of I was treated with 0.5 ml. (0.00528 mole, 2.5 times the theoretical amount) of acetic anhydride containing 0.01 ml. of sulfuric acid and boiled for one minute. An 86% yield of IV was obtained, m. p. 198–200°. This variation is less tedious than Method II but lacks the visible end-point of Method I.

Properties.[20]—IV could be effectively purified only by recrystallization from water.[22] It separated as a monohydrate, stable at room temperature, dehydrated by heat or by cold alcohol, indistinguishable by melting point. IV could not be diazotized and coupled, was soluble in bicarbonate solution and titrated with 0.1 *N* alkali with phenolphthalein. It could be further acetylated.

N^1,N^4,N^4-Triacetyl-3,5-dichlorosulfanilamide, V

Preparation.—A mixture of 0.25 g. (0.00104 mole) of I[18] and 1.5 ml. (0.0158 mole, 5 times the theoretical amount) of acetic anhydride containing 0.0001–0.00001 ml. of concentrated sulfuric acid per 0.5 ml. of anhydride was agitated at room temperature until monoacetylation occurred, a process requiring one to six minutes depending on the amount of acid, and then refluxed for fifteen minutes. The clear solution was worked up either by stirring it with water or by dissolving it in bicarbonate solution reinforced with solid bicarbonate and precipitating V with 6 *N* hydrochloric acid. The product weighed about 0.32 g. (84% yield) and melted at 201°. By this same method II, III and IV were converted to V. When sulfanilamide was subjected to this method, only the N^1,N^4-diacetyl derivative, m. p. 248.5–249° (recorded, 253.5–255°[6a]) was obtained even after three hours of refluxing.

Higher concentrations of sulfuric acid (0.0005 to 0.01 ml. per 0.5 ml. of anhydride) yielded successively darker and finally lower melting products. When it was omitted, no reaction occurred at room temperature even after several hours and about two and one-half hours of refluxing were necessary to complete the reaction. Less anhydride produced lower melting products even with longer times. Although in some cases the reaction appeared complete in five minutes, fifteen minutes was more reliable. With the small concentrations of sulfuric acid, longer refluxing did no harm. Hydroxide cannot be used for dissolving the reaction mixture as it hydrolyzes the third acetyl group producing IV. Even the bicarbonate solution must be acidified at once to prevent this.

Properties.[20]—V dissolved in bicarbonate and titrated with 0.1 *N* alkali using phenolphthalein, but it did not diazotize and couple. It could be reprecipitated unchanged from bicarbonate solution if the solution did not stand.

Complex of N^1-Acetyl-3,5-dichlorosulfanilamide and 3,5-Dichlorosulfanilamide, VI

Preparation.—When 0.022 mole each of I (0.53 g.) and III (0.62 g.) were recrystallized together from 60 ml. of 25% alcohol, the distinctive curly crystals of VI separated in a 90% yield, m. p. 178–178.5°. The same substance resulted when III was partially hydrolyzed by boiling one day in aqueous solution.

Properties.[20]—Repeated recrystallizations from water, dilute alcohol or dilute acetic acid did not change the melting point. In fact, the same melting point was obtained by powdering together mole for mole amounts of the constituents. The complex diazotized and coupled, titrated with 0.1 *N* alkali and partially dissolved in bicarbonate leaving I as a residue.

Hydrolysis Studies

By Hot Concentrated Hydrochloric acid.—To 0.25-g. samples of II, III, IV and V concentrated hydrochloric acid was added with boiling at such a rate that solution occurred in five minutes. The volumes (not critical) varied between 3–12 ml. Refluxing caused the precipitation of I to commence in seven to twenty minutes of total heating time, a time partially dependent on the volume. After thirty minutes the solutions were cooled and sometimes diluted with water; I was obtained in pure form[18] in 90–100% yields. The reactions, as evidenced by the crystals and the melting points of the products, were complete within fifteen to twenty-five minutes, but the results were not considered reliable enough to differentiate between the rates of hydrolysis.

By 3 *N* Hydrochloric Acid.—Small powdered samples of II, III and IV were suspended in 3 *N* hydrochloric acid in closed flasks and allowed to stand at room temperature. Visible changes such as needle growth slowly occurred. The products were worked up by fractional crystallization or bicarbonate extraction. After eight months II yielded 36% of I, and 25% of unhydrolyzed material was recovered. After seven and one-half weeks, III yielded 80% of I and a trace of VI. After two weeks and five days IV yielded 46% of II. **After three weeks**

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[22] The solutions were cloudy, even after hot filtration, but no hydrolysis product could be isolated.

TABLE I

ANALYSIS AND PHYSICAL PROPERTIES

Compound	Formula	N, %		Neut. eq.		M. p., °C.[c]	Recrystallization		Recov.	G./100 me. H$_2$O	
		Calcd.	Found[a]	Calcd.	Found[b]		Solvents	Ml./g.	%	Cold	Hot[j]
I	$C_6H_6Cl_2N_2O_2S$					208–209	Glacial AcOH[o]	7–11	78–88	0.009[d]	0.3
II	$C_8H_8Cl_2N_2O_3S$	9.90	10.03			239.5–240	Glacial AcOH[k]	10–12	70	.081[d]	1
III	$C_8H_8Cl_2N_2O_3S$	9.90	9.98	283.1	284.8	197.5–198	25% EtOH[p]	60–100	70–93	.027[e,f]	0.3
IV	$C_{10}H_{10}Cl_2N_2O_4S$	8.62	8.83	325.2	325.1	203.5–204.5[c]	H_2O	60–75	80–90	.156[e]	2
IV H[l]	$C_{10}H_{10}Cl_2N_2O_4S\cdot H_2O$[g]			343.2	343.8	as IV	As IV				
V	$C_{12}H_{12}Cl_2N_2O_5S$	7.63	7.70	367.2[h]	367.4	201.5–202[c]	50% acetone	20–30	80–95	.025[e]	0.2
VI	$C_{14}H_{14}Cl_4N_4O_5S_2$			524	536	179.5–180.5	H_2O[m]	100–150	86–88	.047[e]	0.8
DAS[n]	$C_{10}H_{12}N_2O_4S$			256.3	257.2	256 dec.[i]	H_2O ($NaHCO_3$)	150–170			0.6

[a] Best of two checking results. [b] Determined by titration in water or alcohol, with phenolphthalein indicator. Best of two to six checking results given. [c] Varied to some extent with rate of heating, especially with IV and V. Melting point given for V occurred when temperature was raised fast enough over 200° so that melt when first formed was practically colorless. [d] Determined by evaporating a saturated solution to dryness. [e] Determined by titrating a saturated aqueous solution. [f] Much less soluble than the corresponding N^1-acetylsulfanilamide which Crossley and co-workers (footnote 6a) reported as 0.9% at room temperature. Frisk [*Acta Med. Scand.*, *Suppl.*, **142**, 1–199 (1943), *C. A.*, **38**, 4692 (1944)] reported 1260 mg. % for N^1-acetyl- and 415 mg. % for sulfanilamide. In both cases N^1 acetylation has increased the water solubility three times. [g] % H$_2$O. Calcd.: 5.25. Found[a]: 5.22. [h] Sap. eq., calcd.: 183.6. Found[a]: 182.4. See text. [i] Recorded m. p. 253.5–255°, footnote 6a. [j] Approximate, at 100°. [k] With 25% EtOH, 35–50 ml./g., 75–88% recovery. [l] Hydrate. [m] With 25% EtOH, 30–40 ml./g., 85–93% recovery. With 25% AcOH, 12–20 ml./g., 75–90% recovery. [n] Diacetylsulfanilamide. [o] Also 95% EtOH. [p] Also dil. AcOH or H$_2$O.

N^1,N^4-diacetylsulfanilamide was 50% unhydrolyzed, but only a 23% yield of the rather soluble sulfanilamide could be isolated by exact neutralization.

By Water.—Hot saturated aqueous solutions of 0.15–1.0 g. of II, III, IV, V, VI and N^1,N^4-diacetylsulfanilamide were refluxed for many hours. The products generally separated on cooling. When necessary, they were purified by bicarbonate extraction or recrystallization. II, after forty-seven hours, was recovered unhydrolyzed in a 94% yield, and the residue from the filtrate gave only a faint test for a free amino group. After twenty-four hours, III was quantitatively converted to VI, but after sixty-five hours a 58% yield of I was obtained and from the filtrate a 22% yield of VI. After forty-seven hours, IV was hydrolyzed to II (74% yield), and residues from the filtrate gave evidence of a free amino group. V, after four and one-half hours, produced a 29% yield of II and 45–56% yields of IV. VI, after seventy-two hours, had been converted to I (95% yield) with only traces of acidic material remaining. Diacetylsulfanilamide, treated as IV, yielded only 46% of the N^4-acetyl derivative, but 5% of the original was recovered and 12% of the soluble sulfanilamide.

By Saturated Sodium Bicarbonate Solution.—When 0.2 g. of V stood overnight in bicarbonate solution (8 ml.), acidification produced an 84% yield of IV. Another study showed a lowering of the melting point of the product in twenty minutes which reached 30° in six hours. Treatment of VI with bicarbonate left a residue of I (49% yield) and produced a 42% yield of II on acidification.

By Sodium Hydroxide.—Small samples (0.001 mole) of II and III were treated by the method described for the preparation of III from IV, using 1.1 equivalents of 0.5 *N* alkali. The minimum time for complete hydrolysis of II was three hours, as determined by the melting point of the product, and a 71% yield of I was isolated. In the same length of time only 46% of III was converted to I, 50% being recovered. The use of stronger base (2.5 *N*) for the hydrolysis of II had no adverse effects. The basic hydrolysis of IV is described under the preparation of III. V was hydrolyzed instantaneeously to IV on solution in excess cold 0.1 *N* alkali; immediate back-titration gave the theoretical saponification equivalent.

By Acetic Acid, Glacial.—After refluxing in saturated acetic acid solution for an hour, a 0.25-g. sample of IV was recovered in an 88% yield. Similar treatment of V for one, one and one-half, and two hours produced 70–85% yields of IV in crude form, an extra 10% of less pure material being recovered from the filtrate. Solution of each in dilute alkali raised its melting points to over 200°; therefore the impurity was unhydrolyzed V.[23]

By Acetic Acid, 25%.—When 0.25-g. samples of IV and V were refluxed in saturated 25% acetic solution, II was isolated. For example, after one hour IV gave a 23% yield of II and 48% of acidic material, while V gave a 26% yield of II and 45% of IV.

Summary

1. N^4- and N^1-monoacetyl-, N^1,N^4-diacetyl- and N^1,N^4,N^4-triacetyl-3,5-dichlorosulfanilamide have been prepared directly from 3,5-dichlorosulfanilamide either with a sulfuric acid catalyst or in a basic media. The amount of sulfuric acid has been shown to be critical in certain cases.

2. Hydrolysis studies have shown that the N^1-acetyl group is more stable to basic hydrolysis and less stable to neutral or acidic hydrolysis than the N^4-acetyl group.

3. A complex of 3,5-dichlorosulfanilamide and its N^1-acetyl derivative has been isolated.

4. The properties of 3,5-dichlorosulfanilamide and its acetyl derivatives differ from those of sulfanilamide and its derivatives. These differences include the easy formation of a triacetyl derivative, the selective acetylation of the N^1-amido group in sodium hydroxide or pyridine solution, the greater instability of the N^1-acetyl group to basic hydrolysis, and the greater stability of the N^4-acetyl group to neutral and acidic hydrolysis. The decreased basicity of the N^4-amino group in 3,5-dichlorosulfanilamide due to the diortho substituents accounts in general for these differences.

WELLESLEY, MASS.

RECEIVED DECEMBER 23, 1947

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(23) The incompleteness of the hydrolysis of V in glacial acetic acid probably pointed to an equilibrium condition. This could result if a reaction occurred similar to that reported for the action of acetic acid on diacetanilide by Tassinari, *Gazz. chim. ital.*, **24**, I, 444 (1894).