7–9 Å. gave a dextrorotatory product. An hydroxylation with left circularly polarized light, with the development of levorotation, remains to be carried out before the asymmetric synthesis can be considered to be proved conclusively.

The precision and accuracy of polarimetric measurements in the region of very low rotations, such as is encountered in photoasymmetric work, are discussed.

An expedient visual method, suggested by Dr. A. F. Turner, for determining the principal angles of incidence and azimuth for metallic mirrors for the 2535–7–9 Å. band is described.

A 6.6% yield of diethyl tartrate was obtained by the photochemical hydroxylation of diethyl fumarate with non-polarized ultraviolet radiation, according to the method of Milas and co-workers.

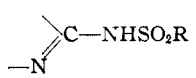
RECEIVED OCTOBER 12, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MAY AND BAKER, LTD.]

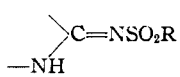
Sulfonamides of the Indole Group

BY H. J. BARBER

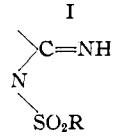
Although the sulfonamide derivatives of a vast number of heterocyclic systems have been described in the past few years, those of indole appear to have been overlooked, as judged from the literature which has reached this country. The derivatives now described, which were prepared in 1938, have little chemotherapeutic interest, but certain novel features in their chemistry make publication desirable. It is established beyond reasonable doubt that the common sulfonamide heterocycles, Sulfapyridine, Sulfathiazole and Sulfadiazine, are 2-substituted derivatives of the two tautomeric forms of the heterocyclic systems I and II and not substituted derivatives of the imino form III.[1]



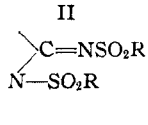
I



II

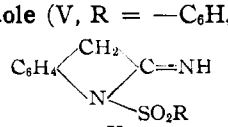


III

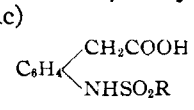


IV

It is striking that derivatives of type III are not normally encountered in condensing sulfonyl chlorides with amino heterocycles. When two sulfonyl residues enter, as, for example, in the case of 2-aminothiazole, they give 1,2-disulfonyl derivatives IV,[2] from which the sulfonyl group in position 1 is readily removed, leaving the 2-arylsulfonamide heterocycles. 2-Amino-indole, however, with acetylsulfanilyl chloride, yielded **1-*p*-acetamido-benzenesulfonyl-2-imino-2,3-dihydroindole** (V, R = $-C_6H_4NHAc$)

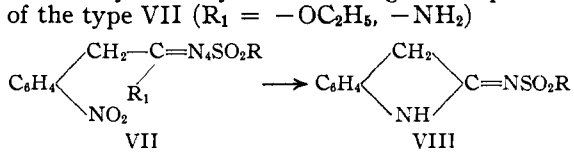


V

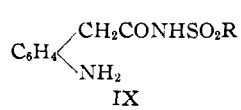


VI

the structure being proved by hydrolysis to **2-sulfanilylaminophenylacetic** acid VI (R = $-C_6H_4NH_2$). If the unlikely migration of the sulfanilyl group is excluded, loss of ammonia could not have occurred without loss of the sulfonyl group unless the latter was in the 1 position. Further support for this came from the fact that the same sulfonamide was readily obtained by condensation of *o*-aminobenzyl cyanide with acetylsulfanilyl chloride. Attempts were made to prepare the isomeric 2-sulfanilylaminoindole by methods involving the condensation of *o*-nitrophenylacetimino ethyl ether or *o*-nitrophenylacetamidine with acetylsulfanilyl chloride to give compounds of the type VII (R_1 = $-OC_2H_5$, $-NH_2$)



VII VIII



IX

which on reduction of the $-NO_2$ group to NH_2 were expected to undergo intramolecular condensation with loss of alcohol or ammonia to give the required compound VIII.

Various difficulties were encountered particularly in the reduction of the nitro compounds VII (R_1 = $-OC_2H_5$, R = $-C_6H_4NO_2$, or $-C_6H_4NHAc$). Catalytic reduction caused fission into unidentified indole derivatives and simpler sulfanilamide derivatives. Stannous chloride reduced the nitro group but the acid conditions effected partial hydrolysis of the imino ether with the resultant formation of the amide IX. As was expected, this did not cyclise as smoothly as the iminoether might have done, and only very small quantities of the required **2-sulfanilyl indole VIII** were obtained, together with various unidentified products. Though the yields were impractical, the method could probably be developed and might have application to other heterocycles where it is desired to locate the sulfonyl group on a substituent nitrogen atom with some certainty, but further investigation was not undertaken

(1) Shepherd, Bratton and Blanchard, THIS JOURNAL, **64**, 2532 (1942).

(2) Jensen and Thorsteinsson, *Dansk Tids. Farm.*, **15**, 41 (1941).

since our knowledge of the sulfonamide field indicated that derivatives of this type were unlikely to be of much therapeutic importance.

The required intermediates, **o-nitrophenylacetimino ethyl ether** and the corresponding **amidine**, were obtained without difficulty and condensed smoothly with acetylsulfanilyl chloride to give **N-acetylsulfanilyl-2-nitrophenylacetimino-ethyl ether** VII, (R = $-C_6H_4NHAc$, R_1 = $-OC_2H_5$) and **amidine** VII (R = $-C_6H_4NHAc$, R_1 = $-NH_2$), respectively. Incidentally, the fact that the latter product exhibits dimorphism, whereas the isomeric substance from the sulfonyl imino ether and ammonia does not, is the most clear-cut demonstration of the type of isomerism so far found.[3] The product from the amidine and the sulfonyl chloride exhibits a reversible change

$$\alpha\text{-form, m. p. } 165^\circ \underset{\text{Boiling acetic acid}}{\overset{\text{Boiling alcohol}}{\rightleftharpoons}} \beta\text{-form, m. p. } 181^\circ.$$

The product from the sulfonyl imino ether and ammonia has m. p. 191° and is unaltered by boiling with either alcohol or acetic acid.

Experimental

Condensation of Acetylsulfanilyl Chloride with 2-Aminoindole.[4]—Aminoindole (1.0 g.) dissolved in acetone (10 cc.) to which sodium hydroxide (0.6 g.) in water (2 cc.) had been added, was treated with a solution of acetylsulfanilyl chloride (1.8 g.) in acetone (5 cc.). After being shaken vigorously for a few minutes, the solution was poured into water and the alkaline solution charcoaled and filtered. Acidification with acetic acid threw out a brown semi-crystalline product (1.0 g.) which was purified by several crystallizations from dilute acetic acid, from which it formed diamond plates, m. p. 207–208°. *Anal.* Calcd. for $C_{16}H_{15}O_3N_3S$: N, 12.76. Found: N, 12.6. Condensation in pyridine gave amorphous products difficult to crystallize.

Condensation of Acetylsulfanilyl Chloride with *o*-Aminobenzyl Cyanide.—*o*-Aminobenzyl cyanide (3.7 g.) was dissolved in pyridine (20 cc.) and acetylsulfanilyl chloride (6.7 g.) added. After warming for a few minutes the wine-red solution was poured into water and the crude product (7.5 g. = 80%) removed. Crystallized from glacial acetic acid, it had m. p. 211° and was identical with, but purer than, the product from 2-aminoindole. *Anal.* Calcd. for $C_{16}H_{15}O_3N_3S$: N, 12.75; S, 9.75. Found: N, 12.5; S, 9.6.

Hydrolysis of Above Sulfonamide. (a) Aqueous Sodium Hydroxide.—The above acetyl compound (1.0 g.) was dissolved in 2 *N* sodium hydroxide (10 cc.) and boiled for one hour under reflux. The solution was neutralized, charcoaled and filtered, and then made faintly acid to congo red. The product separated in short heavy prisms, m. p. 215–216°. It was readily soluble in dilute acids and in sodium bicarbonate. *Anal.* Calcd. for $C_{14}H_{14}O_4N_2S$: N, 9.15; S, 10.4. Found: N, 9.2; S, 10.1.

(b) **Alcoholic Sodium Ethoxide.**—The acetyl compound (17 g.) was refluxed for two hours with a solution of sodium (8 g.) in ethyl alcohol (200 cc.). The solution was poured into water (800 cc.) and acidified with acetic acid. The crude product (6.9 g.) which separated was purified by solution in dilute acid (charcoal) and reprecipitation by sodium acetate and crystallization from 60% acetic acid, m. p. 178°. It was insoluble in sodium bicarbonate *Anal.* Calcd. for $C_{14}H_{13}O_2N_3S$: N, 14.6. Found: N, 14.5, 14.5.

***o*-Nitrophenylacetamidine hydrochloride,** from the nitrile via the imino ether in the usual way (yield 81%), formed hexagonal plates from alcohol, m. p. 215–216°. *Anal.* Calcd. for $C_8H_9O_2N_3$·HCl: N, 19.5. Found: N, 19.1.

Condensation of *o*-Nitrophenylacetimino Ether with Acetylsulfanilyl Chloride.—*o*-Nitrophenylacetimino ether hydrochloride (2.6 g.) dissolved in pyridine (10 cc.) was treated with acetylsulfanilyl chloride (2.5 g.) and heated for ten minutes at 70° and left to stand for two hours. The solution was poured into water and the product, which rapidly solidified, was crystallized from alcohol; long prisms, m. p. 162–163°; yield, 44%. *Anal.* Calcd. for $C_{18}H_{19}O_6N_3S$, N, 10.4. Found: N, 10.5.

Action of Ammonia on Acetanilide Sulfonyl-*o*-nitrophenylacetimino Ether.—The sulfonyl derivative (0.5 g.) was stirred with alcoholic ammonia (3 cc. 6%). Reaction was immediate and after two minutes the product was filtered and washed with alcohol; yield 0.4 g., m. p. 191°. Recrystallization from ethyl alcohol (short heavy prisms) or acetic acid (long interlaced prisms) did not affect the m. p. *Anal.* Calcd. for $C_{16}H_{16}O_5N_4S$ N, 14.9. Found: N, 14.4.

Condensation of *o*-Nitrophenylacetamidine with Acetylsulfanilyl Chloride.—*o*-Nitrophenylacetamidine hydrochloride (15 g.) was suspended in acetone (70 cc.) and a solution of caustic soda (5.6 g.) in water (15 cc.) was added. The whole was vigorously stirred while a solution of acetylsulfanilyl chloride (17 g.) in acetone (100 cc.) was run in rapidly. Reaction was immediate and, after ten minutes of stirring, water (*ca.* 500 cc.) was added and the crystalline product removed; yield, 26.5 g. (100%); m. p. 160–161°. Crystallization from glacial acetic acid (150 cc.) gave the pure product m. p. 165°. Found: N, 14.7. Crystallization from alcohol gave a product of m. p. 181–182° (diamond plates). Found: N, 14.5. The two forms may be interconverted by boiling with the appropriate solvent.

Reduction of Acetanilide Sulfonyl-*o*-nitrophenylacetamidine.—The sulfonyl compound (38 g.) was added over three-fourths of an hour to a vigorously stirred solution of stannous chloride (130 g.) in hydrochloric acid (260 cc., d. 1.16) at 5–10°. More hydrochloric acid (100 cc.) was added during the reaction, to thin the stiff paste formed. The mixture was diluted with water (2 liters) and filtered. The product was suspended in hot water (400 cc.) and converted to the sodium salt with a slight excess of caustic soda. After cooling the sodium salt was filtered and washed with dilute alkali. It was dissolved in boiling water, filtered and acidified with dilute acid. It formed short heavy prisms, m. p. 247°; yield, 60%. *Anal.* Calcd. for $C_{16}H_{17}O_4N_3S$, C, 55.3; H, 4.9; N, 12.1. Found: C, 55.6; H, 4.4; N, 11.5, 11.8. Repeated crystallizations from, or prolonged boiling in, glacial acetic acid, gave products of lower m. p., having analytical figures suggesting further acetylation. The sodium salt was sparingly soluble in water and formed fine matted needles from dilute alkali.

2-Sulfanilamidoindole.—The above sulfonamide IX (R = C_6H_4NHAc) (3 g.) was boiled for two hours with sodium hydroxide (25 cc., 2 *N*). The solution was diluted and acidified with 2 *N* acetic acid. The small quantity of product which separated was crystallized from 90% pyridine as prisms, m. p. 236–237° dec. *Anal.* Calcd. for $C_{14}H_{13}O_2N_3S$: C, 58.5; H, 4.6; N, 14.6. Found: C, 58.6, 59.0; H, 4.8, 4.7; N, 14.1.

The product was insoluble in sodium bicarbonate and soluble in 5 *N* hydrochloric acid.

Reduction of Acetanilide Sulfonyl-*o*-nitrophenylacetimino Ether.—The sulfonyl derivative (1 g.) dissolved in acetone (20 cc.) was reduced in presence of platinum oxide catalyst (0.05 g.). After removal of acetone, the tarry residue was extracted with ether, leaving a crystalline residue which on crystallization from alcohol yielded pure acetanilide-*p*-sulfonamide. No other sulfonamide was isolated.

(3) Barber, *J. Chem. Soc.*, 102 (1943).

(4) Since this paper was submitted, Elliott and Robinson, *J. Chem. Soc.*, 632 (1944), have reported their failure to obtain this product.

Condensation of *o*-Nitrophenylacetimino Ether with *p*-Nitrobenzenesulfonyl Chloride.—The normal method of condensation of pyridine failed to give clean products. *o*-Nitrophenylacetimino ether base (8.4 g.) was melted with *p*-nitrobenzenesulfonyl chloride (4.4 g.). Reaction was immediate and the temperature rose to 80°. Some ethyl chloride was evolved, as normally occurs.[8] The melt, after a few minutes at 90°, was extracted successively with ether and water and the residue (4.9 g.) m. p. 115° (incomplete) was recrystallized from alcohol. The mixture was taken up in boiling ethyl acetate (30 cc.) and the product which separated on cooling (0.5 g., m. p. 157–158°) was removed. After a crystallization from ethyl acetate this had m. p. 159° and was identified as *o*-nitrophenylacetamide (Calcd.: N, 15.55. Found: N, 15.4). The ethyl acetate liquors were concentrated and successive crops removed. These were crystallized from 1:1-benzene/light petroleum mixture to give the required ***p* - nitrobenzenesulfonyl - 2 - nitrophenylacetimino ether,** m. p. 123°; yield 2.55 g. *Anal.* Calcd. for $C_{16}H_{13}O_7N_3S$: N, 10.7. Found: N, 10.8.

Attempted Reduction of Above.—Two grams dissolved in acetone (50 cc.) was reduced catalytically in the usual way (0.1 g. of platinum oxide) giving an uptake of 12 H in sixty-five minutes. After filtration from catalyst, the acetone was removed at low temperature *in vacuo*. The residue had a strong indole-like odor and was soluble in ether. No pure product was isolated and it was clear that the sulfonyl group had been split off.

The author's thanks are due to the Directors of Messrs. May & Baker Ltd., England, for permission to publish this work, and to Mr. S. Bance for the semi-micro analyses.

Summary

1. When 2-aminoindole is condensed with acetylsulfanilyl chloride, the sulfonyl residue enters in the 1 position.

2. A method of obtaining the isomeric 2-sulfanilyl derivative by use of appropriate sulfanilyl amidines or imino ethers is outlined.

3. It is suggested that this method might find other similar applications in this field.

DAGENHAM, ENGLAND RECEIVED AUGUST 24, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Composition of the Solid Secretion Produced by Primula Denticulata[1]

BY WALTER C. BLASDALE

A distinguishing feature of a large percentage of the species of *Primula* is the secretion of white or yellow solids commonly designated by botanists as farina. They are produced by minute, two-celled, gland-tipped hairs found on the leaves, scapes, calyces, or more rarely the petals. The chemical nature of the secretion of *P. pulverulenta* was studied by Hugo Müller[2] who found it to consist of flavone associated with small amounts of a wax-like component. Later Brunswick,[3] by the use of a microchemical test devised by Klein,[4] found that flavone was present in the secretions of 25 of the species of *Primula* as well as three of the closely related genus *Dionysia*. This test involved the subjection of fragments of farina-bearing tissue or of minute portions of farina scraped from it, to the fumes of concentrated hydrochloric acid, at a temperature of 40°, in a sublimation ring. If flavone was present a microscopic examination of the tissue or the cover glass revealed bundles of fine white or yellow needle-like crystals.

Appreciable differences in the color and consistency of the secretions of the different species suggest that additional components, both colorless and colored, should be looked for. Macroscopic study of them is rendered difficult because of difficulty of procuring enough plants upon which they are found. The seed of many species is unobtainable, many are difficult to grow, and the yield of farina-bearing tissue per plant is very small. During the past fifteen years I have been able to grow sufficient plants of twenty-one of the farina-bearing species to make a partial study of their secretions possible. This paper is concerned chiefly with the secretion of *P. denticulata*. I desire to express my obligation to Mr. Charles Koch of this Laboratory for microcombustions of several of the products separated.

(1) Original manuscript received January 11, 1943.

(2) Müller, *J. Chem. Soc.*, **107**, 872 (1915).

(3) Brunswick, *Ber. Akad. Wiss. Wien.*, [1] **131**, 221 (1922).

(4) Klein, *ibid.*, [1] **131**, 23 (1922).

Experimental Part

Separation of Farina.—Owing to the sticky nature of the secretion and the small amount of farina-bearing tissue available, mechanical separation of it was not feasible. The procedure finally adopted was to treat the dried and coarsely powdered leaves and flower heads for twenty minutes, at room temperature, with a three-fold volume of benzene and allow the filtered extract to evaporate spontaneously. The dry residue consisted of white crystals and green amorphous matter, the total equaling about 4% of the tissue used. The same procedure applied to non-farinate leaves of the same species yielded nearly 2% of a green sticky mass from which no crystals could be obtained even by use of a variety of solvents. It seems probable that none of the crystals in the extract from the farina-bearing tissue came from the tissue itself.

Some Properties of Flavone.—It was soon apparent that most of the crystalline material present in the benzene extract was flavone. In separating it from the other components constant use was made of a boiling solution of 6 *N* hydrochloric acid. Although acid addition products of several flavone derivatives have been isolated,[5] these compounds hydrolyze at once unless the concentration of the acids used in their preparation is left high. It was found that constant boiling hydrochloric acid dissolved 2.65 g. of flavone per liter but about 90% separated, on standing at room temperature, as long fine needles. This may be attributed to its low melting point as compared with those of its derivatives. By treating the benzene extract with large volumes of 6 *N* acid twice, the flavone was almost completely separated from the large amounts of plant pig-

(5) Perkin, *J. Chem. Soc.*, [2] **69**, 1439 (1896).