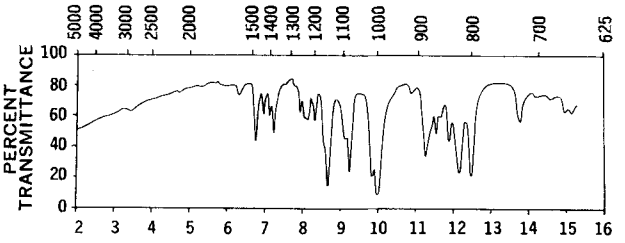
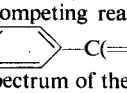


Figure 5—*IR spectrum of Compound III.*

of starting material present at any time may be calculated as:

$$\% \text{ Compound I} = \frac{\text{integral I}}{\text{integral I} + \text{II} + \text{III}} \times 100 \quad \text{(Eq. 1)}$$

Calculations on this basis were made for the spectra run at various time intervals. The data are shown in Table I.

Interferences—If oxygen is not excluded from the system in this experiment, a competing reaction involving the formation of the diketone Cl—  —C(=O)—C(=O)—CH_3 will result. Figure 6 is the NMR spectrum of the diketone. It is obvious from the chemical shift of the methyl group in the diketone spectrum that this material is easily detected in the reaction mixture if it is present.

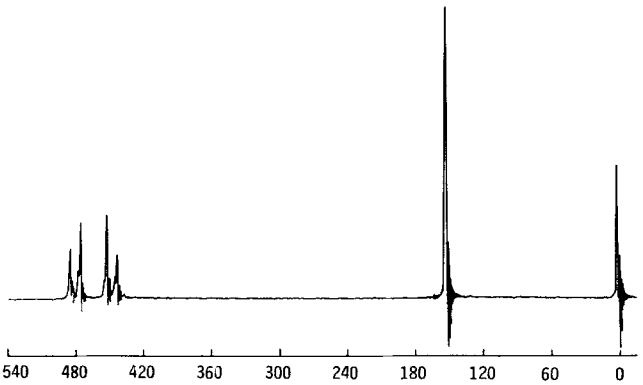


Figure 6—*NMR spectrum of diketone.*

Table I—Percent I, II, and III at Various Time Intervals

Hours	Percent I	Percent II and III
0	100	—
66	83.3	16.7
72	83.3	16.7
91	84.4	15.6
96	82.6	17.4
114	77.3	22.7
120	75.7	24.3
138	75.5	24.5
140	76.0	24.0
144.5	73.1	26.9
166	70.7	29.3
168	70.4	29.6
238	69.9	30.1

CONCLUSION

NMR has been used successfully to monitor the enolization of 1-*p*-chlorophenyl-1-hydroxy-2-propanone. In this study, an unexpected product (III) was formed. This material was isolated and identified by IR, NMR, and mass spectral data.

REFERENCES

(1) R. Warren and J. Zarembo, *J. Pharm. Sci.*, **59**, 840(1970).
(2) *Ibid.*, **60**, 307(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 18, 1970, from the *Research and Development Division, Smith Kline & French Laboratories, Philadelphia, PA 19101*

Accepted for publication January 8, 1971.

The authors are grateful to Dr. L. M. Jackman for helpful discussions of the spectra presented, and to Mr. John Messina for technical assistance in obtaining the spectra presented here.

New Compounds: 2,4-Dinitrobenzenesulfenamides

M. J. KORNET, T. C. HO, and L. ISENBERG

Abstract □ A compilation of 2,4-dinitrobenzenesulfenamide derivatives of 72 amines is given. Fifty-one of the derivatives are described for the first time.

Keyphrases □ 2,4-Dinitrobenzenesulfenamide derivatives—compilation and description of 72 amines □ Amines, 2,4-dinitrobenzenesulfenamide derivatives—description, compilation

In the course of other studies with 2,4-dinitrobenzenesulfenyl chloride (I), the authors found that this reagent is excellent for the derivatization of amines. This observation was made earlier by Billman *et al.* (1) who characterized 14 amines by converting them into the corresponding 2,4-dinitrobenzenesulfenamides (Scheme I):

$$2,4\text{-}(O_2N)_2C_6H_3SCl + 2R_2NH \rightarrow 2,4\text{-}(O_2N)_2C_6H_3SNR_2 + R_2NH \cdot HCl$$

Scheme I

Subsequently, Kharasch (2) showed that I can also be used for the preparation of derivatives of many other functional groups. Tables containing the physical properties of such derivatives have since been published (3).

More recently, I was advocated for the characterization of pharmaceutically important organic compounds such as barbituric acid, phenylbutazone, and saccharin (4). In addition, sulfenamides are valuable precursors for a number of pharmaceutically useful sulfonamides (5). In the biochemical area, Fontana *et al.* (6) and Scoffone *et al.* (7) showed that I may be used to determine both the cysteine and tryptophan content in polypep-

Table I—2,4-Dinitrobenzenesulfenamide Derivatives of Amines

Amine	Melting Point	Formula	Percent Nitrogen—Calcd.	Percent Nitrogen—Found
4-Acetylaniline	207–208.5°	$C_{14}H_{11}N_3O_5S$	12.61	12.50
2-Aminoaniline	166°[a]	$C_{12}H_{10}N_4O_4S$	18.30	18.56
2-Amino-4-methylpyridine	210.5–212.5°	$C_{12}H_{10}N_4O_4S$	18.30	18.38
Ammonia	119.5–120.5°[b]			
Aniline	142.5–143°[b]			
Benzylamine	86–87°	$C_{13}H_{11}N_3O_4S$	13.77	13.82
N-Benzylaniline	134.5–135°[b]			
Benzylethylamine	74–75°	$C_{15}H_{15}N_3O_4S$	12.61	12.57
Benzylmethylamine	99–101°	$C_{14}H_{13}N_3O_4S$	13.16	13.12
Benzyl *n*-propylamine	84–85°	$C_{16}H_{17}N_3O_4S$	12.10	12.02
2-Bromoaniline	146–147°	$C_{12}H_8BrN_3O_4S$	11.35	11.49
3-Bromoaniline	160–160.5°	$C_{12}H_8BrN_3O_4S$	11.35	11.41
4-Bromoaniline	180.5–181°[b]			
n-Butylamine	88.5–89°[b]			
tert-Butylamine	89.5–90.5°	$C_{10}H_{13}N_3O_4S$	15.49	15.70
2-Chloroaniline	125–126°	$C_{12}H_8ClN_3O_4S$	12.90	12.94
3-Chloroaniline	148.5–149.5°	$C_{12}H_8ClN_3O_4S$	12.90	12.94
4-Chloroaniline	164–164.5°[b]			
5-Chloro-2-methylaniline	204–206°	$C_{13}H_{10}ClN_3O_4S$	12.37	12.48
Cyclohexylamine	109.5–110°[b]			
N-Cyclohexylaniline	114–116°	$C_{18}H_{19}N_3O_4S$	11.25	11.23
Cyclohexylethylamine	96–96.5°	$C_{14}H_{19}N_3O_4S$	12.92	13.02
Cyclohexylmethylamine	95.5–96°[b]			
Dibenzylamine	106–107°	$C_{20}H_{17}N_3O_4S$	10.63	10.64
2,5-Dichloroaniline	156–157°	$C_{12}H_7Cl_2N_3O_4S$	11.67	11.62
Dicyclohexylamine	128.5–130.5°	$C_{18}H_{25}N_3O_4S$	11.07	10.91
Diethylamine	99–100°[b]			
N,*N*-Diethylaniline	146–147°[b,c]			
Diisobutylamine	108.5–109.5°	$C_{14}H_{21}N_3O_4S$	12.84	12.84
Diisopropylamine	98–99°	$C_{12}H_{17}N_3O_4S$	14.04	13.85
N,*N*-Dimethylaniline	175–176°[b,c]			
2,4-Dimethylaniline	160.5–161.5°	$C_{14}H_{13}N_3O_4S$	13.16	13.20
2,5-Dimethylaniline	172.5–174.5°	$C_{14}H_{13}N_3O_4S$	13.16	13.35
2,6-Dimethylaniline	202–203°	$C_{14}H_{13}N_3O_4S$	13.16	13.05
Diphenylamine	150–151.5°	$C_{18}H_{13}N_3O_4S$	11.44	11.47
Di-*n*-propylamine	95.5–97°	$C_{12}H_{17}N_3O_4S$	14.04	13.94
4-Ethoxylaniline	138–139°	$C_{14}H_{13}N_3O_5S$	12.53	12.64
4-Ethoxycarbonylaniline	153.5–155.5°	$C_{15}H_{13}N_3O_6S$	11.57	11.50
Ethylamine	66–66.5°[b]			
2-Fluoroaniline	148–149.5°	$C_{12}H_8FN_3O_4S$	13.59	13.68
4-Fluoroaniline	139.5–141°	$C_{12}H_8FN_3O_4S$	13.59	13.59
Furfurylamine	115–115.5°	$C_{11}H_9N_3O_5S$	14.23	14.07
Hexamethylenimine	126–128°	$C_{12}H_{15}N_3O_4S$	14.14	14.13
2-Hydroxyaniline	192.5–193.5°	$C_{12}H_9N_3O_5S$	13.68	13.67
4-Hydroxyaniline	155–156°[b]			
2-Iodoaniline	153.5–154°	$C_{12}H_9IN_3O_4S$	10.07	10.33
2-Methoxyaniline	155–156°	$C_{13}H_{11}N_3O_5S$	13.08	13.29
3-Methoxyaniline	145–146°	$C_{13}H_{11}N_3O_5S$	13.08	13.05
4-Methoxyaniline	158–159°[b]			
2-Methoxycarbonylaniline	161.5–162°	$C_{14}H_{11}N_3O_6S$	12.03	12.32
4-Methoxycarbonylaniline	188–190°	$C_{14}H_{11}N_3O_6S$	12.03	12.08
4-Methoxy-2-nitroaniline	192–193°[a]	$C_{13}H_{10}N_4O_7S$	15.30	15.38
Methylamine	99–99.5°[b]			
2-Methylaniline	155–156°[b]			
3-Methylaniline	142.5–143.5°	$C_{13}H_{11}N_3O_4S$	13.77	13.80
4-Methylaniline	161–161.5°[b]			
N-Methyl-4-nitroaniline	160–161°	$C_{13}H_{10}N_4O_6S$	16.00	15.83
3-Methylpiperidine	95–96°	$C_{12}H_{15}N_3O_4S$	14.14	14.24
4-Methylpiperidine	59–60°	$C_{12}H_{15}N_3O_4S$	14.14	14.20
Morpholine	164.5–165°[b]			
1-Naphthylamine	188.5–189°[b]			
2-Naphthylamine	167–168°[b]			
2-Nitroaniline	204.5–206°	$C_{12}H_8N_4O_6S$	16.66	16.75
3-Nitroaniline	172.5–173°	$C_{12}H_8N_4O_6S$	16.66	16.74
4-Nitroaniline	181–182.5°[a]	$C_{12}H_8N_4O_6S$	16.66	16.82
1-Phenylethylamine	99–100°	$C_{14}H_{13}N_3O_4S$	13.16	13.29
Piperidine	151.5–152.5°	$C_{11}H_{13}N_3O_4S$	14.84	15.03
1,3-Propanediamine[d]	105–107°	$C_{15}H_{14}N_6O_8S_2$	17.86	17.54
n-Propylamine	94–94.5°[b]			
Pyrrolidine	147–149°	$C_{10}H_{11}N_3O_4S$	15.61	15.35
1,2,3,4-Tetrahydroisoquinoline	157.5–159.5°	$C_{15}H_{13}N_3O_4S$	12.68	12.59
2,4,6-Trimethylaniline	170–171°	$C_{15}H_{15}N_3O_4S$	12.61	12.55

[a] Decomposition point. [b] Data are taken from *Reference 3*. [c] *Para*-sulfide, not amide. [d] Bis compound.

tides and proteins.

In this paper, the physical properties of 51 new 2,4-dinitrobenzenesulfenamides are described. A total of 72 amines have now been derivatized, and the present compilation should be of value in the qualitative identification of these compounds.

EXPERIMENTAL[1]

Melting points were determined with the Fisher-Johns melting-point apparatus and are corrected.

The procedure for 2,4-dinitrobenzenesulfenamide formation was identical to the one reported (3) except that methylene chloride was used as the reaction solvent. The results are summarized in Table I.

REFERENCES

(1) J. H. Billman, J. Garrison, R. Anderson, and B. Wolnak, *J. Amer. Chem. Soc.*, **63**, 1920(1941).

(2) N. Kharasch, *J. Chem. Educ.*, **33**, 585(1956).

(3) R. B. Langford and D. D. Lawson, *ibid.*, **34**, 510(1957).

(4) R. T. Coutts and S. J. Storey, *Can. J. Pharm. Sci.*, **2**, 22(1967).

(5) J. Korman, *J. Org. Chem.*, **23**, 1769(1958), and references therein.

(6) A. Fontana, E. Scoffone, and C. A. Benassi, *Biochemistry*, **7**, 980(1968).

(7) E. Scoffone, A. Fontana, and R. Rocchi, *ibid.*, **7**, 971(1968).

[1] Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. 2,4-Dinitrobenzenesulfenyl chloride was obtained from Matheson Scientific.

ACKNOWLEDGMENTS AND ADDRESSES

Received October 23, 1970, from the *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication December 8, 1970.

COMMUNICATIONS

Distribution of Ampicillin Administered Orally in Three Different Forms in Rabbit

Keyphrases ☐ Ampicillin distribution—rabbit ☐ Distribution, rabbit—anhydrous, trihydrate, and metampicillins

Sir:

Many physicochemical factors, like particle size (1), salt form (2), ester form (3), or crystal form (4), can affect the dissolution rate and the pharmacokinetics of antibiotics. Particularly, different plasma levels of antibiotic after administration of anhydrous or trihydrate ampicillin (5) and different biliary levels of antibiotic after administration of ampicillin or metampicillin have been described (6). We have reported the distribution of ampicillin in the rabbit after oral administration of three forms of 6-[D(−)-α-aminophenylacetamido]-penicillanic acid: anhydrous ampicillin (AA), trihydrate ampicillin (TA), and metampicillin (MA) (condensation product of ampicillin with formaldehyde).

Sixty male New Zealand rabbits, 2.8 ± 0.3 kg., were fed on a pellet diet with water *ad libitum* and kept at 21 ± 1° and relative humidity 50 ± 4%. The fasting animals were treated orally in random order with 50 mg./kg. of the ampicillins, the amounts of which were expressed as 6-[D(−)-α-aminophenylacetamido]penicillanic acid, and with a mean particle diameter of 14 ± 7 μ. At random order, the animals were killed by bleeding 0.5, 1, 2, and 4 hr. after antibiotic administration; all specimens of blood were taken with a sterile syringe. The kidney, liver, stomach, duodenum, lung, brain, heart, spleen, and muscle were aseptically homogenized for 5 min. with a 0.2 *M* buffer phosphate solution, pH 7; the homogenates were centrifuged for 10 min. at 3000 r.p.m., and assays were performed on the supernatants. The assays of ampicillin (in terms of micrograms per milliliter or micrograms per gram) were carried out on the same day the test was made.

Ampicillin levels were assayed by the cup-plate method, with *Bacillus subtilis* FB27 as the test organism. Samples of plasma, supernatants, and antibiotic standards were diluted when necessary in phosphate buffer, pH 7; several tests were also made with ampicillin-free plasma and supernatants, and no antibacterial activity was detected. The standard solutions were made with plasma or supernatants from untreated animals.

No statistical differences were evident (Table 1) in the distribution of the ampicillin administered as anhydrous ampicillin, trihydrate ampicillin, or condensation product with formaldehyde. Sutherland and Robinson (7) also found that the activities demonstrated by the condensation products of ampicillin with acetone or formaldehyde corresponded closely with the rates to which these compounds hydrolyzed to ampicillin.

(1) G. Harvey and J. O. Alexander, *Lancet*, **1**, 327(1962).

(2) E. Nelson, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 96(1959).

(3) E. Nelson, *Chem. Pharm. Bull.*, **10**, 1099(1962).

(4) J. D. Mullins and T. J. Macek, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 245(1960).

(5) J. W. Poole, G. Owen, J. Silverio, J. N. Freyhof, and S. Rosenman, *Curr. Ther. Res.*, **10**, 292(1968).

(6) M. De Vecchi Pellati, F. Falcone, and F. Perraro, *Minerva Med.*, **61**, 946(1970).