(2) G. B. Fink and M. R. Juchau, *J. Pharm. Sci.*, **53**, 325(1964).

(3) L. C. Mark, *Clin. Pharmacol. Ther.*, **4**, 504(1963).

(4) M. Sparberg, *Ann. Int. Med.*, **59**, 914(1963).

(5) S. K. Arya, K'un Chang, and C. F. Martin, *J. Pharm. Sci.*, **56**, 1520(1967).

(6) H. M. Taylor and C. R. Hauser, "Organic Syntheses," vol. 43, Wiley, New York, N. Y., 1963, p. 25.

(7) J. B. Niederl, R. T. Roth, and A. A. Plentl, *J. Amer. Chem. Soc.*, **59**, 1901(1937).

(8) C. F. Martin and V. L. Narayanan *J. Org. Chem.*, **26**, 2127 (1961).

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* Present address: Department of Pharmacology, College of Medicine, University of Illinois at the Medical Center, Chicago, IL 60680

N-Phenylacetylsulfamide: Sulfone Analog of Anticonvulsant Acylureas

CECIL C. CHAPPELOW, Jr.*, and WILLIAM J. ROST†

Abstract □ *N*-Phenylacetylsulfamide was synthesized under three different conditions. If ethyl acetate was used as a solvent, a higher yield of the monoacylated product was obtained than if pyridine was used as the solvent. If the lithium salt of sulfamide was used, a maximum yield of the diacylated product and a minimum yield of the monoacylated product were obtained. The *N*-phenylacetylsulfamide was less than half as active as trimethadione when tested as an anticonvulsant in the cat.

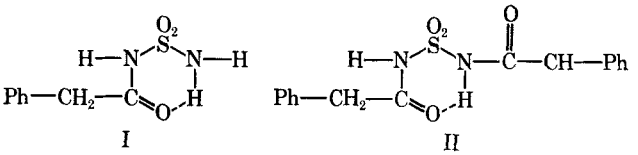
Keyphrases □ *N*-Phenylacetylsulfamide—synthesis, three methods □ Acylureas—synthesis of sulfone analog □ Anticonvulsant acylureas—synthesis of the sulfone analog *N*-phenylacetylsulfamide

The acylureas such as phenacemide[1], Ph—CH_2—CO—NH—CO—NH_2, represent a class of anticonvulsant drugs. Hence, it was desired to prepare the sulfone analog, Ph—CH_2—CO—NH—SO_2—NH_2, for comparison. A search of the literature revealed that only a few simple acyl derivatives of sulfamide have been prepared and characterized (1).

To prepare the desired compound, phenylacetyl chloride and sulfamide were condensed. Even though an equimolar ratio of the two chemicals was employed, an appreciable amount of *N,N'*-bis(phenylacetyl)sulfamide was obtained. If ethyl acetate was used as the solvent, a 40% yield of the monoacylated product and 15% yield of the diacylated product were obtained. If the reaction was run in pyridine, a 30% yield of the monosubstituted product and an 8% yield of the disubstituted product were obtained.

In an attempt to increase the yield of the monoacylated product and/or decrease the yield of the diacylated product, the reaction was run with the lithium salt of sulfamide. Unexpectedly, this reaction gave only a 10% yield of the monoacylated and a 42% yield of the diacylated products. The high yield of the diacylated product was probably the result of a transmetallation reaction between the *N*-lithiosulfamide and the monoacylated products.

Inspection of the NMR spectra of *N*-phenylacetylsulfamide and *N,N'*-bis(phenylacetyl)sulfamide revealed an unusually large chemical shift for one of the nitrogen-bonded protons of these compounds. These shifts are indicative of intramolecular hydrogen bonding (2). Based on these data, it is proposed that in solution the monosubstituted and disubstituted compounds exist as the following intramolecular hydrogen-bonded structures:



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These structures are compatible with most of the general rules governing the formation of intramolecular hydrogen-bonded rings set forth by Wheland (3). Also, the formation of an intramolecular hydrogen bond structure for *N*-phenylacetylsulfamide would explain the high incidence of disubstitution, especially in the reaction where *N*-lithiosulfamide was employed as the reactant.

An exchange reaction of *N*-phenylacetylsulfamide and deuterium oxide was conducted according to the procedures of Ouchi and Moeller (4). This was readily driven to completion by employing an excess of deuterium oxide. NMR analysis of the reaction product confirmed the structure assignment and revealed the location of all nitrogen-bound proton signals.

N-Phenylacetylsulfamide was studied for activity as a potential petit mal anticonvulsant by recording its protective ability, as compared to the standard anticonvulsant, trimethadione, against pentylenetetrazol-in-

[1] Phenurone.

duced electrographic spiking in each of eight CNS sites in the cat. The areas studied were the central lateral nucleus of the thalamus, anterior dorsal nucleus of the thalamus, dorso-lateral nucleus of the thalamus, mesencephalic reticular formation, central hippocampus, head of the caudate nucleus, anterior amygdala, and the fronto-occipito cortex. Recordings were made on a Grass model 7 polygraph using model 7P5 EEG preamplifiers. Recording electrodes were made of nichrome wire and stereotaxically implanted into each recording site. Recordings were made following administration of convulsant doses of pentylenetetrazol to cats protected and unprotected by trimethadione and *N*-phenylacetylsulfamide.

Findings indicate that *N*-phenylacetylsulfamide was less than 0.5 times as effective as the standard, trimethadione, on a molar basis as an anticonvulsant tested against convulsant doses of pentylenetetrazol. The compound was also found to lack significant anticonvulsant activity against the excitant effects of pentylenetetrazol at considerably higher dose levels. At these higher dose levels, the compound exhibited strong emetic properties.

EXPERIMENTAL[2]

The melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. The IR spectra of the compounds were determined on a Perkin-Elmer model 137 Infracord recording spectrophotometer. The spectra were run as mineral oil mulls. A Varian Associates model A-60 NMR spectrometer was used to determine the proton magnetic resonance spectra. Tetramethylsilane was used as a standard reference, and hexadeuterodimethylsulfoxide was used as the solvent.

Synthesis of Phenylacetylsulfamide and *N,N'*-Bis(phenylacetyl)-sulfamide Using Pyridine—To a rapidly stirred solution of sulfamide (9.6 g., 0.1 mole) in 100 ml. of pyridine, phenylacetyl chloride (19.0 g., 0.11 mole) was added dropwise over 30 min. The addition was accompanied by a slight temperature rise. After addition was complete, the reaction mixture was stirred for 6 hr. while the temperature was maintained at 60°. Then the reaction mixture was poured onto cracked ice and stirred until the ice melted. The resultant two-phase mixture was extracted twice with 100-ml. portions of chloroform. The extracts were combined, washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue (23.0 g.), an orange-colored semicrystalline solid, was dissolved in absolute alcohol, and the two products were obtained by repeated concentration and cooling in the following order:

N,N'-Bis(phenylacetyl)sulfamide—Crude product (2.5 g.), m.p. 166–168° dec., which after one recrystallization from absolute alcohol gave 2.0 g. (7% yield) of final product, a white powder m.p. 170–171° dec. The IR spectrum of the product has an intense band at 3500 cm.$^{-1}$ (—NH—), a sharp intense band at 1710 cm.$^{-1}$ (C=O), a broad band centered at 1160 cm.$^{-1}$ (SO_2), and a characteristic series of three bands at 760, 710, and 690 cm.$^{-1}$ (aromatic). The NMR spectrum has a sharp singlet at 3.55δ (—CH_2—), another sharp singlet at 7.17δ (—C_6H_5), and a broad singlet centered at 12.25δ (—NH— — —O=C).

Anal.—Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.64; H, 4.84; N, 8.25; S, 9.56.

N-Phenylacetylsulfamide—Crude product (8.0 g.), m.p. 153° dec., which after one extraction with hot benzene and two recrystallizations from absolute alcohol, gave 7.0 g. (30% yield) of final product, a white powder, m.p. 164–165°. The IR spectrum had a sharp band at 3800 cm.$^{-1}$ and a moderately broad band at 3500 cm.$^{-1}$ (—NH— and —NH_2), an intense band at 1690 cm.$^{-1}$ (C=O), a broad intense band centered at 1135 cm.$^{-1}$ (SO_2), and a characteristic series at 865, 810, 765, and 695 cm.$^{-1}$ (aromatic). The NMR spectrum has a sharp singlet at 3.48δ (—CH_2—), a second sharp singlet at 7.15δ (—C_6H_5 and —NH_2), and a broad singlet centered at 11.43δ (—NH— — —O=C).

Anal.—Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.79; H, 4.93; N, 12.71; S, 14.71.

***N*-Phenylacetylsulfamide Using Ethyl Acetate**—The previously described reaction was repeated using the same amount of reactants, except that 200 ml. of ethyl acetate was employed as the solvent according to the procedure of Anderson and Degering (5). The by-product HCl distilled out of the reaction mixture, and the products were isolated by concentrating and cooling the reaction mixture. A 40% yield of *N*-phenylacetylsulfamide and a 15% yield of *N,N'*-bis(phenylacetyl)sulfamide were obtained.

***N*-Phenylacetylsulfamide *via* *N*-Lithiosulfamide**—To a stirred solution of sulfamide (9.60 g., 0.1 mole) in 300 ml. of tetrahydrofuran, a 15% solution of *n*-butyllithium in hexane (6.4 g., 0.1 mole) was added dropwise. After refluxing the resultant slurry of *N*-lithiosulfamide for 30 min., phenylacetyl chloride (15.5 g., 0.1 mole) was added dropwise with stirring. The reaction mixture was refluxed for 30 min. The resultant clear solution was evaporated to dryness, and the residue was extracted with boiling ethyl acetate. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated until a precipitate began to separate. A crude product was obtained by the addition of toluene and subsequent cooling. Recrystallization from absolute ethanol yielded 7.0 g. (41.9%) of *N,N'*-bis(phenylacetyl)sulfamide, m.p. 171–172°, and 2.2 g. (10.0%) of *N*-phenylacetylsulfamide, m.p. 155–158°.

These products had IR absorption and NMR spectra identical to the previously reported product.

[2] Elemental analyses were performed by the Analytic Laboratory of the Midwest Research Institute, Kansas City, Mo.

REFERENCES

(1) E. F. Degering, "An Outline of Organic Nitrogen Compounds," University Lithoprinters, Ypsilanti, Mich., 1945, pp. 481–484.

(2) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, pp. 434, 435.

(3) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed., Wiley, New York, N. Y., 1949, pp. 151–153.

(4) A. Ouchi and T. Moeller, *J. Org. Chem.*, **29**, 1865(1964).

(5) C. H. Anderson and E. F. Degering, *Proc. Indian Acad. Sci.*, **56**, 134(1946).

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* Present address: Midwest Research Institute, Kansas City, MO 64110

† To whom all requests for reprints and information should be directed.