chiometric ratios have been calculated. The higher order of magnitude of these formation constants indicates a high degree of stability of the complex.

REFERENCES

(1) Cohen, J., and Lach, J. L., THIS JOURNAL, 52, 132 (1963).
(2) *Ibid.*, 52, 137(1963).
(3) French, D., Levine, M. L., Pazur, J. H., and Nordberg, E., *J. Am. Chem. Soc.* 71, 353(1949).
(4) Higuchi, T., and Lach, J. L., THIS JOURNAL, 43, 349(1954).
(5) Wall, F. T., and Banes, F. W., *J. Am. Chem. Soc.*, 67, 898(1945).
(6) Schlenk, H., Sand, D. M., and Tillotson, J. A., *ibid.*, 77, 3587(1955).
(7) Higuchi, T., and Zuck, D. A., THIS JOURNAL, 42, 138(1953).
(8) Higuchi, T., Sciarrone, B. J., and Haddad, A. F., *J. Med. Pharm. Chem.*, 3, 195(1961).
(9) Poole, J. W., and Higuchi, T., THIS JOURNAL, 48, 592(1959).

Potential Hypoglycemic Sulfonylureas

By KARL A. NIEFORTH†, GLENN L. JENKINS, and ADELBERT M. KNEVEL

A series of *N'*-alkyl-*N*-*p*-phenylbenzenesulfonylureas and *N,N'*-bis(*N*-alkylcarbamyl) 4,4'-biphenyldisulfonamides has been prepared for pharmacological studies of their hypoglycemic activities.

ALTHOUGH SULFONYLUREAS have been reported in the literature for several years, it was not until 1955 that the hypoglycemic activity of these compounds was recognized and reported. Since that time, the interest in synthesizing compounds of this type has increased considerably and has resulted in a few marketable compounds. The purpose of this paper is to extend research in this area to include the biphenyl nucleus.

Early work in the area of hypoglycemics was centered around derivatives of guanidine (1, 2). Several years later, various derivatives of isopropylthiadiazole were investigated and found to be active hypoglycemics (3). This work (3) may also be considered to be the start of the use of sulfonamides in controlling the symptoms of diabetes. In 1955, a sulfonylurea compound was found to be very active in lowering the blood sugar concentration in diabetics (4). After this work was reported, new active compounds began appearing at a rapid rate (5–8). It is now generally accepted that the sulfonylurea function is a source of hypoglycemic compounds. The work in this paper is based on that assumption and is conducted in two parts. The first part is the synthesis of *N'*-alkyl-*N*-*p*-phenylbenzenesulfonylureas (VII); the second part is the synthesis of *N,N'*-bis(*N*-alkylcarbamyl)4,4'-biphenyldisulfonamides (XIV).

Biphenyl (I) was sulfonated according to a published procedure (9) and gave good yields of 4-biphenylsulfonic acid (II). This in turn was reacted with phosphorus pentachloride using carefully controlled conditions to form 4-biphenylsulfonyl chloride (III). If the conditions were not controlled, varying amounts of 4,4'-biphenyldisulfonyl chloride (X) were found in the reaction mixture. The sulfonyl chloride was heated in ammonia water forming 4-biphenylsulfonamide (IV). The sulfonylurea (V) was prepared (10) upon reaction of the sulfonamide with *n*-butylisocyanate in the presence of triethylamine. Because of the difficulty in preparing the various isocyanates needed in this project, an alternate route was used to prepare the remainder of the compounds in Part I (11).

In Part II, biphenyl(VIII) was sulfonated with an excess of sulfuric acid to form 4,4'-biphenyldisulfonic acid (IX) (12). The reaction between 4,4'-biphenyldisulfonic acid and phosphorus pentachloride was controlled to prevent the formation of 4,4'-dichlorobiphenyl. 4,4'-Biphenyldisulfonyl chloride (X) was heated with ammonia water to form 4,4'-biphenyldisulfonamide (XI). From this point, the reactions in Part II are the same as those utilized in Part I. One compound (XII) was synthesized by the reaction of 4,4'-biphenyldisulfonamide and *n*-butylisocyanate. The remainder of the compounds was prepared by the alternate route (XI-XIV).

EXPERIMENTAL[1]

4-Biphenylsulfonic Acid and 4,4'-Biphenyldisulfonic Acid.—These compounds were prepared by reacting biphenyl with sulfuric acid. The quantities of sulfuric acid depended on the desired acid (9, 12). The salts of the sulfonic acids were formed by dissolving the acids in alcohol and adding concentrated solutions of potassium or sodium hydroxide to the alcoholic solutions.

4-Biphenylsulfonyl Chloride.—Twenty grams

Received April 19, 1962, from the Research Laboratories, School of Pharmacy, Purdue University, Lafayette, Ind.
Accepted for publication June 12, 1963.
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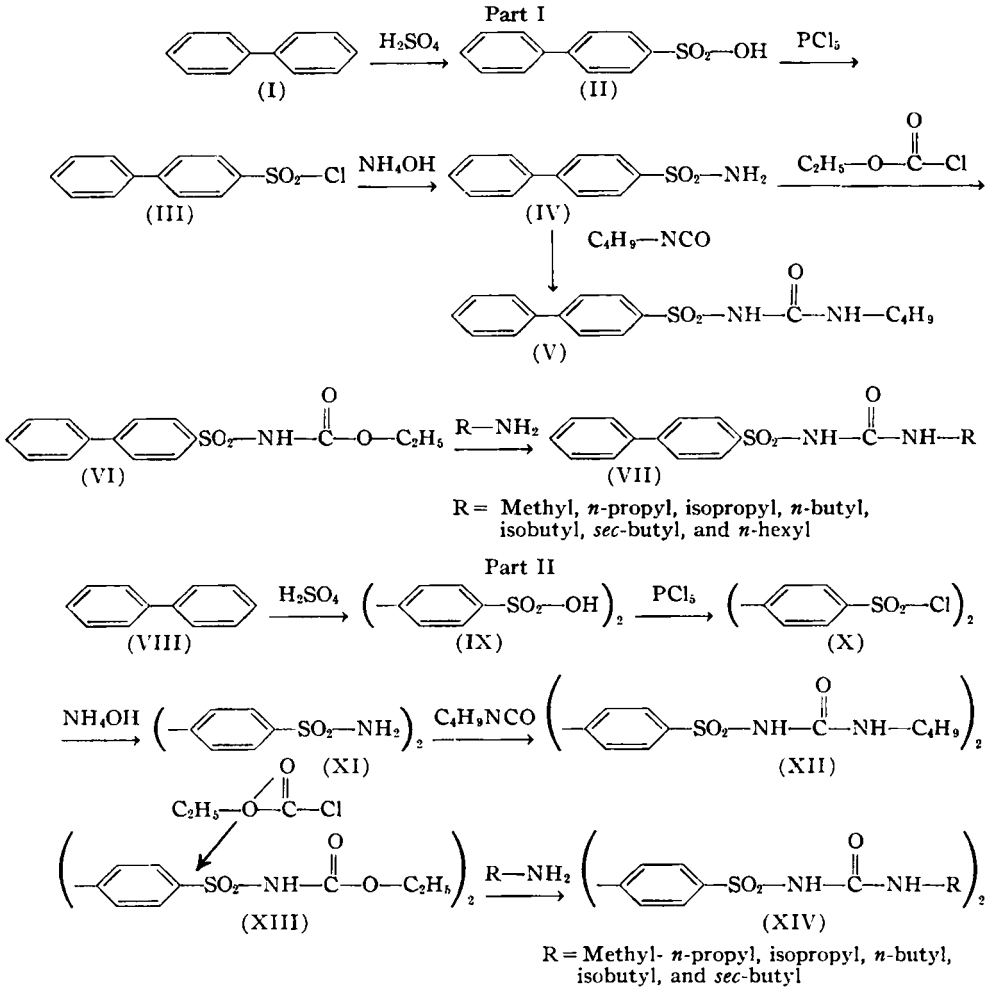
[1] Sulfur determinations were carried out by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, 164 Banbury Road, Oxford, England, and Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut fur Kohlenforschung, Hohenweg 17, Mulheim (Ruhr), Germany.



(0.075 mole) of sodium 4-biphenylsulfonate was heated at 100° for 1 hour in an oil bath with 16 Gm. (0.075 mole) of phosphorus pentachloride. At the end of the heating period, the semisolid mass was poured into a beaker and allowed to solidify (13). The melting point of a purified sample agreed with the reported melting point of 115°. The crude sulfonyl chloride was washed with several small portions of cold water to remove any of the starting materials and by-products before using it to prepare the sulfonamide.

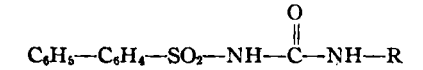
4,4′-Biphenyldisulfonyl Chloride.—In a 1-L. flask fitted with a condenser were placed 122 Gm. (0.32 mole) of potassium 4,4′-biphenyldisulfonate and 175 Gm. (0.85 mole) of phosphorus pentachloride. The flask was shaken thoroughly to mix the powders and heated on an oil bath at 100° for 20 hours. The reaction mixture was poured into ice water and filtered. The residue was filtered and washed with three portions of cold water to remove any starting material and by-products. For identification purposes, one batch was recrystallized from glacial acetic acid and was melted at the reported melting point of 205–206°. All other batches were reacted in the crude state.

Biphenylsulfonamides.—Both sulfonamides used in this work were prepared simply by boiling the crude sulfonyl chlorides with an excess of concentrated ammonia water for 1 hour. The only precaution taken was to add the ammonia water to the sulfonyl chloride slowly enough to prevent a rapid reaction and resulting effervescence.

Sulfonylureas.—*Method A* (*10*).—In a 100-ml. flask fitted with a condenser were placed the sulfonamide and at least a twofold excess of *n*-butylisocyanate dissolved in 10 ml. of triethylamine. The mixture was heated on an oil bath at 100° for 20 hours. The resin which formed was dissolved in 4% sodium hydroxide and treated with charcoal. The clear colorless solution was acidified by pouring it into a cooled solution of acetic acid. The product was filtered and recrystallized from 70% aqueous alcohol. Data for these compounds are listed in Tables I and II.

Method B (*11*).—The first step in this method involved the synthesis of a sulfonylurethan. Fourteen grams (0.06 mole) of 4-biphenylsulfonamide, 200 ml. of anhydrous acetone, and 15 Gm. of anhydrous potassium carbonate were placed in a three-necked flask. The suspension was heated to boiling and 10 Gm. (0.1 mole) of ethyl chlorocarbonate was added dropwise over a period of 1 hour.

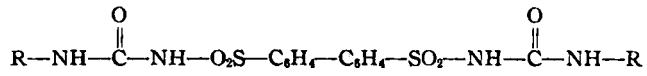
TABLE I.—ALKYL-*N*-*p*-PHENYLBENZENESULFONYLUREAS



R	Molecular Formula	Method of Synthesis[a]	Yield, %	M. p.[b]	Sulfur Analysis—Calcd.	Sulfur Analysis—Found
Methyl	$C_{14}H_{14}N_2O_3S$	B	48	240–241	11.05	10.96
n-Propyl	$C_{16}H_{18}N_2O_3S$	B	60	186.5 to 188	9.82	9.78
Isopropyl	$C_{16}H_{18}N_2O_3S$	B	52	183–184	9.82	9.99
n-Butyl	$C_{17}H_{20}N_2O_3S$	A	28	177–178	9.42	9.35
Isobutyl	$C_{17}H_{20}N_2O_3S$	B	63	211–212	9.42	9.14
sec-Butyl	$C_{17}H_{20}N_2O_3S$	B	45	180–181	9.42	9.55
n-Hexyl	$C_{19}H_{24}N_2O_3S$	B	53	151 to 152.5	7.77	7.92

[a] The methods refer to *Methods A* and *B* discussed in the *Experimental* section; the yield is based on the final reaction. [b] The melting points were determined by the open capillary method and are uncorrected.

TABLE II.—*N*,*N*′-BIS(*N*-ALKYLCARBAMYL)4,4′-BIPHENYLDISULFONAMIDES



R	Molecular Formula	Method of Synthesis	Yield, %	M. p.[b]	Sulfur Analysis—Calcd.	Sulfur Analysis—Found
Methyl	$C_{16}H_{18}N_4O_6S_2$	B	67	220	15.03	15.15
n-Propyl	$C_{20}H_{26}N_4O_6S_2$	B	70	215	13.29	13.31
Isopropyl	$C_{20}H_{26}N_4O_6S_2$	B	83	227	13.29	13.15
n-Butyl	$C_{22}H_{30}N_4O_6S_2$	A[a]	80	237	12.36	12.69
Isobutyl	$C_{22}H_{30}N_4O\,S_2$	B	63	228	12.36	12.06
sec-Butyl	$C_{22}H_{30}N_4O_6S_2$	B	81	218	12.36	12.65

[a] *Method B* resulted in 32% yield. [b] The melting points of the compounds in Table II were determined on a Kofler melting point apparatus. All compounds decomposed upon melting. The decompqsition was evidenced by the evolution of a gas and the formation of 4,4′-diphenyldisulfonamide which melted at 305°.

The mixture was stirred at reflux for 12 hours. When the reaction was complete, any insoluble material was filtered off and the solution carefully acidified with diluted hydrochloric acid. The precipitate was dissolved in sodium carbonate solution and any insoluble material removed. The solution was acidified and extracted with several small portions of ether. The ethereal extract was dried over exsiccated sodium sulfate; then the ether was removed. The product, *N*-*p*-phenylbenzenesulfonylurethan (VI) was recrystallized from 80% aqueous ethanol yielding 11.5 Gm. (47%) of an analytical sample melting at 81 to 82.5°.

Anal.—Calcd. for $C_{15}H_{15}NO_4S$: S, 10.50. Found: S, 10.59.

N,*N*′-Bicarbethoxy-4,4′-biphenyldisulfonamide (XIII) was prepared in the same manner with the following modification. Since the product was not very ether soluble, it was recrystallized after acidification of the sodium bicarbonate solution. Starting with 5 Gm. (0.016 mole) of 4,4′-biphenyldisulfonamide, the yield of final product was 6 Gm. (82%) melting at 180–182°.

Anal.—Calcd. for $C_{18}H_{20}N_2O_8S_2$: S, 14.03. Found: S, 13.63.

The sulfonylureas were prepared from the corresponding sulfonylurethan in the following manner. The sulfonylurethan obtained above was dissolved in a primary amine warming to 80° if necessary. The excess amine was removed using a water aspirator leaving a gummy amine salt of the sulfonylurethan. This was pyrolyzed at 130° and 5 mm. Hg for 3 to 6 hours depending on the time necessary for the salt to lose its gummy appearance or for the bubbling to stop. After pyrolysis, the product was dissolved in sodium bicarbonate solution and treated with charcoal if deemed necessary. The alkaline solution was acidified with diluted hydrochloric acid and the resulting solid recrystallized from 70% aqueous alcohol. Data for these compounds are listed in Tables I and II.

REFERENCES

(1) Frank, E., Nothmann, M., and Wagner, A., *Klin. Wochschr.*, **5**, 2100(1926).
(2) Frank, E., *Deut. Med. Wochschr.*, **53**, 1845(1927).
(3) Loubatieres, A., *Compt. Rend. Soc. Biol.*, **138**, 830 (1944).
(4) Franke, H., and Fuchs, J., *Deut. Med. Wochschr.*, **80**, 1449(1955).
(5) Haak, E., *Arzneimittel-Forsch.*, **8**, 444(1958).
(6) Shah, M., *J. Sci. Ind. Res. India*, **18B**, 202(1960).
(7) Kessler, W., and Jenkins, G., THIS JOURNAL, **50**, 842 (1961).
(8) Holland, G., Jaeger, D., Wagner, R., Laubach, G., McLamore, W., and P'an, S., *J. Med. Pharm. Chem.*, **3**, 99 (1961).
(9) Fusco, R., and Renieri, L., *Gazz. Chim. Ital.*, **78**, 435(1948).
(10) Kurzer, F., *J. Chem. Soc.*, **1951**, 1258.
(11) Marshall, F., and Sigal, M., *J. Org. Chem.*, **23**, 927 (1958).
(12) Pollak, J., and Riesz, E., *Monatsh.*, **53**, 90(1929).
(13) Feldmann, J., *Helv. Chim. Acta*, **14**, 751(1931).