regarded as apomorphine 4,O-glucuronide. In this structure, the bulk of glucuronic acid becomes proximal to the apomorphine molecule. Due to spatial interaction, this may distort and inhibit the relative coplanarity of the alkaloidal molecule, with the result that resonance of the biphenyl part of the apomorphine molecule would be decreased. This steric inhibition of resonance would explain the hypsochromic shift in the electronic absorption spectrum observed for this molecule.

Since both metabolites were hydrolyzed by β-glucuronidase, an enzyme known to be specific for β-glucosidic linkage, they may be regarded as 3,O and 4,O-β-glucuronides, respectively.

On the basis of evidence presented for the closely related morphine glucuronide (6, 7), the "bound" metabolites of apomorphine may be assumed to exist in the zwitterion form.

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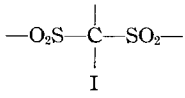
Synthesis of N-Substituted Methanedisulfonamides and N′-Substituted Methanedisulfonylureas

By WAYNE V. KESSLER† and GLENN L. JENKINS

The preparation of various derivatives of methanedisulfonic acid is reported. These include fifteen N-substituted methanedisulfonamides and four N′-substituted methanedisulfonylureas.

SEVERAL INVESTIGATORS (1–6) have observed the similarities between the chemical structure of methanedisulfonic acid and the chemical structures of certain therapeutically useful organic sulfur and malonic acid derivatives. Certain sulfonamides, sulfones, sulfoxides, and sulfides have been used as chemotherapeutic agents (7). Numerous aliphatic sulfone derivatives (I) and malonic acid derivatives (II) have hypnotic properties. The similarities between the chemical structures of these compounds and that of methanedisulfonic acid (III) is apparent. These observations have induced the synthesis of many derivatives of methanedisulfonic acid for pharmacological and chemotherapeutical evaluation (3–6).



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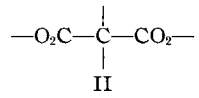

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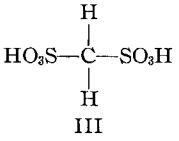

III

The discovery of the therapeutic value of various sulfur-containing compounds in recent years has intensified the research in this area. The recent preparation of new sulfonylureas (8, 9) for evaluation as hypoglycemic agents and N-substituted alkanesulfonamides from methane- and ethanesulfonic acid (10) for evaluation in the treatment of experimental traumatic shock and as bacteriostatic and bactericidal agents may be cited as examples.

This investigation was conducted with the purpose of synthesizing new derivatives of methanedisulfonic acid which might possess useful pharmacological or chemotherapeutical activity. These derivatives are N-substituted methanedisulfonamides (X) and N′-substituted methanedisulfonylureas (XI).

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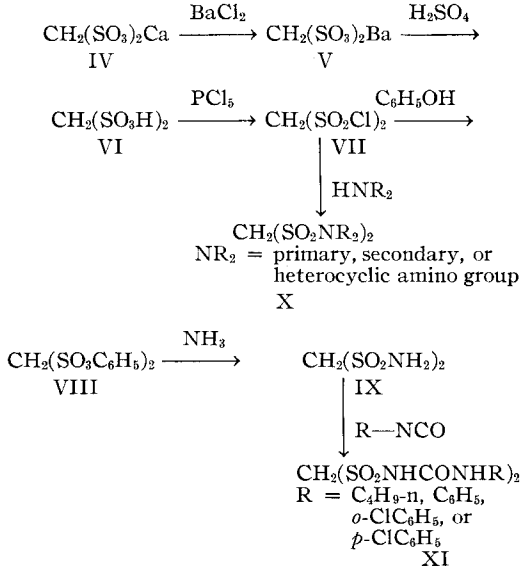
† Fellow of the Purdue Research Foundation. Present address: Purdue University, Bionucleonics Department, Lafayette, Ind.

Calcium methanedisulfonate (IV) was available and was used for the starting material. It was converted to the barium salt (V) with barium chloride solution (4), and the barium salt was treated with aqueous sulfuric acid to form methanedisulfonic acid (VI) (2). The product obtained in this manner was sufficiently pure for the preparation of the acid chloride.

The acid chloride (VII) was prepared by the action of phosphorus pentachloride upon the dry acid (2, 11). It was purified by fractional distillation under reduced pressure and was reacted with phenol to form diphenyl methanedisulfonate (VIII) (11). Methanedisulfonamide (IX) was obtained by heating a benzene solution of the diphenyl ester with an excess of liquid ammonia in a bomb (11).

The N-substituted methanedisulfonamides were synthesized from the acid chloride and the appropriate amines (3, 11). Twice the calculated amount of amine was used to serve as the hydrogen chloride acceptor. The N′-substituted methanedisulfonylureas were synthesized by a method similar to that used by Kurzer (12) for the preparation of N-aryl-N′-arylsulfonylureas. The disodium salts of three of these compounds were prepared to facilitate their purification.

The scheme used in this synthesis was as indicated.



EXPERIMENTAL

All melting points reported in this paper are uncorrected and were determined by the open capillary tube method. Nitrogen and sulfur determinations were done by Dr. Alfred Bernhardt.[1] Sodium determinations were done by nonaqueous titrations with acetous perchloric acid.

N-Substituted Methanedisulfonamides.—These compounds were prepared by the following general procedure: In a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer, dropping funnel, and reflux condenser carrying a calcium chloride tube, were placed 0.4 mole of the appropriate amine and 250 ml. of anhydrous benzene. The stirrer was started and a solution of 0.1 mole of methanedisulfonyl chloride in 75 ml. of anhydrous benzene was added, dropwise, over a period of one hour. After all the acid chloride had been added, the reaction mixture was refluxed and stirred for one to fifteen hours and was then cooled. The sulfonamide was separated from the amine hydrochloride and was then recrystallized from a suitable solvent until a constant melting point was obtained. Data for these compounds are listed in Table I.

Disodium N′-Substituted Methanedisulfonylureas.—These compounds were prepared by procedures similar to that used for the preparation of disodium N,N′-bis-(N-phenylcarbamyl)methanedisulfonamide: In a 100-ml. round-bottomed flask, fitted with a reflux condenser and a mechanical stirrer, were placed 17.4 Gm. (0.1 mole) of methanedisulfonamide, 31.4 Gm. (0.264 mole) of phenyl isocyanate, and 4 ml. of triethylamine. This mixture was heated on a steam bath for twelve hours with stirring. The methanedisulfonamide gradually dissolved, and after about three hours the reaction mixture began to solidify and form a yellow viscous mass. At the end of the reaction, the reaction mixture, while still hot, was dissolved by stirring with 240 ml. of 4% sodium hydroxide solution in divided portions at 70°. The residual insoluble solid was filtered from the hot solution and washed with a small amount of boiling water. These washings were added to the main filtrate. Two grams of decolorizing charcoal was added to the filtrate, and this mixture was stirred at 60° for one-half hour. The mixture was then filtered, and the filtrate was set aside for several hours. The disodium derivative crystallized upon cooling. The filtrate was finally placed in an ice water bath for two hours, after which time the product was collected on a Büchner funnel and recrystallized from an ethanol-water mixture until a constant melting point was obtained. Data for these compounds are listed in Table II.

N,N′-Bis-(N,*n*-butylcarbamyl)methanedisulfonamide.—In a 200-ml. round-bottomed flask, fitted with a reflux condenser and a mechanical stirrer, were placed 26.1 Gm. (0.15 mole) of methanedisulfonamide, 39.7 Gm. (0.4 mole) of *n*-butyl isocyanate, and 6 ml. of triethylamine. This mixture was heated on a steam bath for twelve hours with stirring. The methanedisulfonamide gradually dissolved, and after about one hour the reaction mixture began to solidify and form a yellow mass. At the end of the reaction, the reaction mixture, while still hot, was dissolved in 360 ml. of 4% sodium hydroxide solution. The resulting solution was cooled and extracted with two 100-ml. portions and one 50-ml. portion of benzene. It was then acidified with glacial acetic acid and cooled in an ice water bath for one hour. The product, which precipitated during the acidification, was collected and recrystallized three times from 95% ethanol. The

[1] Mikroanalytisches Laboratorium im Max-Planck Institut für Kohlenforschung, Kaiser Wilhelm Platz 1, Mülheim (Ruhr), Germany.

TABLE I.—N-SUBSTITUTED METHANEDISULFONAMIDES

$R_2N—SO_2CH_2SO_2—NR_2$

NR_2	Formula	Recrystallizing Solvent	Yield, %	M. P., ° C.	Nitrogen, % Calcd.	Nitrogen, % Found
Benzylamino[a]	$C_{15}H_{18}N_2O_4S_2$	Dioxane-H_2O	38.1	213.5–214.5	7.90	7.97
1-Phenylethylamino[b,c,d]	$C_{17}H_{22}N_2O_4S_2$	EtOH-dioxane-H_2O	35.6	156 –158	7.32	7.11
2-Phenylethylamino[b,e]	$C_{17}H_{22}N_2O_4S_2$	EtOH-dioxane	26.7	164 –166	7.32	7.21
4-Methylpiperazino[b,e]	$C_{11}H_{24}N_4O_4S_2$	Abs. EtOH	37.9	149 –150	16.46	16.12
2,6-Dimethylmorpholino[b,f]	$C_{13}H_{26}N_2O_6S_2$	Abs. EtOH	54.6	164 –170[l]	7.56	7.62
2,5-Dimethoxyanilino[b,g]	$C_{17}H_{22}N_2O_8S_2$	EtOH-dioxane	75.3[k]	139 –140	6.27	6.20
2,5-Diethoxyanilino[b,h]	$C_{21}H_{30}N_2O_8S_2$	Abs. EtOH	66.9[k]	125 –126	5.57	5.45
2-Methyl-5-nitroanilino[i]	$C_{15}H_{16}N_4O_8S_2$	Dioxane	64.4[k]	243.5–245[m]	12.61	12.51
N-Benzylanilino[b,c]	$C_{27}H_{26}N_2O_4S_2$	EtOH-dioxane	78.7	147.5–148.5	5.53	5.72
N-Ethyl-*o*-toluino[c,d]	$C_{19}H_{26}N_2O_4S_2$	EtOH-dioxane-H_2O	67.7[k]	155 –157	6.82	6.76
N-Ethyl-*m*-toluino[c]	$C_{19}H_{26}N_2O_4S_2$	EtOH-H_2O	61.9[k]	104.5–105.5	6.82	6.53
N-Ethyl-*p*-toluino[c,j]	$C_{19}H_{26}N_2O_4S_2$	EtOH-H_2O	76.1[k]	125.5–127	6.82	7.06
N-Benzyl-*o*-toluino[c,d,j]	$C_{29}H_{30}N_2O_4S_2$	EtOH-dioxane	79.7[k]	206 –207	5.24	5.18
N-Benzyl-*m*-toluino[c,d]	$C_{29}H_{30}N_2O_4S_2$	Abs. EtOH	66.0[k]	144.5–145.5	5.24	5.17
N-Benzyl-*p*-toluino[c,d,j]	$C_{29}H_{30}N_2O_4S_2$	EtOH-dioxane	84.9[k]	170 –171.5	5.24	5.29

[a] The reaction solvent was anhydrous toluene instead of anhydrous benzene. The solution of amine was refluxed while the acid chloride was added. Both the sulfonamide and amine hydrochloride precipitated from the reaction mixture. The sulfonamide was separated as the disodium derivative by recrystallization of the reaction product from 2 *N* sodium hydroxide solution. The free sulfonamide was obtained by acidification of a hot solution of the disodium derivative with concentrated hydrochloric acid. [b] The temperature of the reaction mixture was maintained at about 20° by external cooling during the addition of the acid chloride. [c] The amine hydrochloride precipitate was filtered from the reaction mixture and washed with benzene. The washings were added to the main filtrate and the combined solution was evaporated to dryness to obtain the impure sulfonamide. [d] The impure sulfonamide was washed with several portions of ethanol-water mixture before recrystallization. [e] Both the sulfonamide and amine hydrochloride precipitated from the reaction mixture. The combined precipitate was washed with benzene, air dried, washed with water, and finally dissolved in a minimum amount of acetone. This solution was added to an excess of water and the resulting impure sulfonamide was collected. [f] Neither the amine hydrochloride nor the sulfonamide precipitated from the reaction mixture. The benzene was removed from the reaction mixture and the resulting yellow syrup was washed with ethanol-water mixture to remove amine hydrochloride. [g] Not all the amine hydrochloride precipitated. The benzene was removed from the reaction mixture, the residue was washed with water, the resulting solid was dissolved in a minimum amount of acetone, and this solution was added to an excess of water. The impure sulfonamide was collected and decolorized with charcoal. [h] Both the sulfonamide and amine hydrochloride precipitated from the reaction mixture. The combined precipitate was washed with benzene, air dried, and washed with water to obtain the impure sulfonamide. [i] The solid which precipitated from the reaction mixture was washed with benzene, air dried, washed thoroughly with water acidified with hydrochloric acid, and dissolved in warm 2 *N* sodium hydroxide solution. This solution was extracted with benzene and acidified with concentrated hydrochloric acid. The resulting solid was washed with water and dissolved in a minimum amount of acetone. This solution was added to an excess of water and the resulting impure sulfonamide was collected. [j] A crystal of amine hydrochloride was added to the cool reaction mixture to induce crystallization of the amine hydrochloride. [k] The yield is based on 0.2 mole of amine and 0.05 mole of acid chloride. [l] Softened at 164° and was completely liquid at 170°. [m] With decomposition.

TABLE II.—DISODIUM N′-SUBSTITUTED METHANEDISULFONYLUREAS

$RNHCON(Na)SO_2CH_2SO_2N(Na)CONHR$

R	Formula	Yield, %	M. P., °C.	Sulfur, % Calcd.	Sulfur, % Found	Sodium, % Calcd.	Sodium, % Found
Phenyl	$C_{15}H_{14}N_4O_6S_2Na_2$	23.9	282.5–284[a]	14.05	13.88	10.08	10.21
p-Chlorophenyl	$C_{15}H_{12}Cl_2N_4O_6S_2Na_2$	11.2	284 –284.5[a]	12.21	12.36	8.76	8.78
o-Chlorophenyl	$C_{15}H_{12}Cl_2N_4O_6S_2Na_2$	19.0	245[b]	12.21	12.04	8.76	8.90

[a] With decomposition. [b] Began to sinter above 200° and rapidly turned brown with effervescence above 245°.

yield was 26.1 Gm. (46.8%); m. p. 200.5–202° (with effervescence).

Anal. Calcd. for $C_{11}H_{24}N_4O_6S_2$: N, 15.05; S, 17.22. Found: N, 14.82; S, 16.85.

SUMMARY

1. The objective of this research project was the synthesis of methanedisulfonic acid derivatives for pharmacological and bacteriological evaluation.

2. Fifteen new N-substituted methanedisulfonamides have been synthesized.

3. Four new N′-substituted methanedisulfonylureas have been synthesized.

4. Sufficient quantities of these compounds are available for pharmacological and bacteriological evaluation.

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