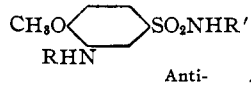
TABLE X

DERIVATIVES OF 4-METHOXY-3-AMINOBENZENESULFONAMIDE:[a]



No.	R	R'	M. p., °C.	Anti-strep. activity	Anti-mening. activity	Formula	Nitrogen analyses, % Calcd.	Found
1	CH_3CO	H	225.5	0	±	$C_9H_{12}O_4N_2S$	11.47	11.34
2	CH_3CO	CH_2CH_2OH	152–153	0	0	$C_{11}H_{16}O_5N_2S$	9.72	9.85
3	CH_3CO	$CH_2CHOHCH_3$	146–147	0	0	$C_{12}H_{18}O_5N_2S$	9.27	9.36
4	CH_3CO	$CH_2COH(CH_3)_2$	125	0	±	$C_{13}H_{20}O_5N_2S$	8.86	9.09
5	H	H	142–142.5	0	0	$C_7H_{10}O_3N_2S$	13.86	13.53
6	H	$CH_2CHOHCH_3$	102	0	0	$C_{10}H_{16}O_4N_2S$	10.77	10.90

[a] Usually small glistening white crystals. Yields varied from 60 to 84%. Slightly soluble in water. Recrystallized from water, excepting number 4 which was recrystallized from dilute ethanol.

Summary

A variety of *p*-acylamidobenzenesulfonamides, *p*-acylamidobenzenesulfonalkanolamides, *p*-aminobenzenesulfonalkanolamides, *p*-alkyl- and *p*-aralkylaminobenzenesulfonalkanolamides, *p*-carbethoxyaminobenzenesulfonamides, *p*-acylamidobenzenesulfonmorpholides, *p*-aminobenzenesulfonmorpholide, *p*-acyl- and *p*-aminobenzenesulfonanilides and derivatives of 4-methoxy-3-aminobenzenesulfonamide have been prepared.

All show less antistreptococcal activity than sulfanilamide but practically all are much less toxic.

The antimeningococcal activity of many is equivalent to that found in sulfanilamide.

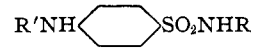
URBANA, ILLINOIS RECEIVED JUNE 16, 1939

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND JOHNS HOPKINS UNIVERSITY MEDICAL SCHOOL]

Sulfanilamide Derivatives. II

BY ROGER ADAMS, P. H. LONG AND ALLENE JEANES[1]

In the previous paper[2] it was demonstrated that the acyl groups in acylamidobenzenesulfonalkanolamides greatly reduced the toxicity of the molecule. The antistreptococcal activity was generally lower than that of sulfanilamide but the therapeutic ratio in many instances was more favorable. Consequently, a variety of other substituted acyl substituents has been introduced either directly or indirectly into the molecule. The compounds studied are shown below.



where R = $-CH_2CHOHCH_3$ and

R' = $HOOC(CH_2)_2CO-$ I

$C_2H_5OOC(CH_2)_2CO-$ II

$CH_3CHOAcCO-$ III

where R = $-CH_2CH_2OH$ and

R' = $HOCH_2CH_2NHCO(CH_2)_2CO-$ IV

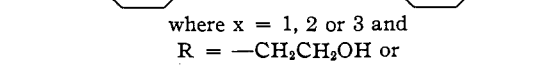
CH_3OCH_2CO- V

where R = H and

R' = $NH_2CO(CH_2)_2CO-$ VI

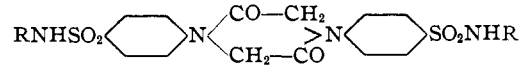
$CH_3CHOAcCO-$ VII

$CH_3CHOHCO-$ VIII

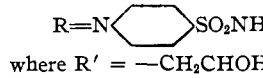


where x = 1, 2 or 3 and

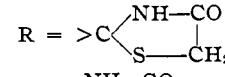
R = $-CH_2CH_2OH$ or $-CH_2CHOHCH_3$



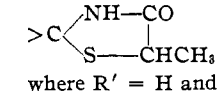
where R = H or $-CH_2CH_2OH$ or $-CH_2CHOHCH_3$



where R' = $-CH_2CHOHCH_3$ and

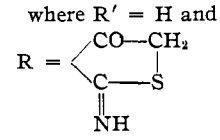


IX



X

where R' = H and



XI

All the compounds were prepared either (1) by introduction of the sulfonyl chloride grouping into

(1) The authors are indebted to The Chemical Foundation for grants which made possible the work described in this communication.

(2) Adams, Long and Johanson, THIS JOURNAL, **61**, 2342 (1939).

the properly substituted anilide followed by treatment with ammonia or an amine, or (2) by introduction of the proper acyl group into sulfanilamide or into sulfonalkanolamide.

Only a few of the products showed any antistreptococcal activity. Compound II and the isopropanol derivative of the diketopiperazide showed very slight, and compound V, moderate activity.

Experimental

Succinanil.—This was prepared by a modification of the method of Tingle and Cram.[3]

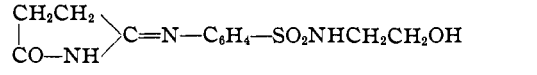
A mixture of 170 cc. of freshly distilled aniline and 225 g. of pulverized succinic acid was heated in an open flask in an oil-bath at 140–150° for four hours. The mixture was then distilled at atmospheric pressure which, due to the high temperature necessary, converted the succinic acid monoanilide into the anil. The distillate was crystallized from 95% ethanol: colorless needles, m. p. 156–158°; yield, 246 g. (75%). Menschutkin[4] reports the same melting point.

Mono-(*p*-aminosulfonylphenyl)-succinamide (VI).—Succinanil was treated with five moles of chlorosulfonic acid according to the method in "Organic Syntheses."[5] After heating to 60–65° for two hours, the product was poured slowly into well-stirred crushed ice and water. The crude sulfonyl chloride was washed and used directly.

To an excess of ice-cold 28% aqueous ammonia, 60 g. of the crude, moist sulfonyl chloride was added. The chloride dissolved and a mass of white crystals separated. The mixture was heated to 70° for a half hour and was then cooled. The product was purified by recrystallization from water, using norite; white needles, m. p. 234–238° with decomposition.

Anal. Calcd. for $C_{10}H_{13}N_3O_4S$: N, 15.50. Found: N, 15.55.

Succinamide Derivative (IV).—The crude acid chloride from chlorosulfonic acid and succinanil was treated with 2 molecules of ethanolamine dissolved in 7% aqueous potassium hydroxide (containing 2.5 moles of potassium hydroxide for each mole of acid chloride) and heated to 70° for a half hour. After neutralization and concentration to small volume, a thick oil was obtained. This was dissolved in butanol and two crystalline products separated. The first and main fraction was a granular product which formed slowly in the undisturbed solution; the second, a by-product, glistening plates which formed rapidly after removal of the first fraction. This by-product was probably the compound



as shown by analysis. After recrystallization from butanol, and washing with dry ether, the first product melted at 137–142°; the second at 85–93°.

Anal. (m. p. 137–142°). Calcd. for $C_{14}H_{21}N_3O_6S$: N, 11.70. Found: N, 11.35 (m. p. 85–93°) Calcd. for $C_{12}H_{15}N_3O_4S$: N, 14.14. Found: N, 14.20.

Succinamide Derivative (I).—The product from the acid chloride and isopropanolamine was obtained in the same manner as described for the ethanolamine. It remained as an oil, however, and was hydrolyzed directly by boiling for ten minutes with the calculated quantity of 10% aqueous potassium hydroxide and then acidifying with concentrated hydrochloric acid. Addition of a small amount of water gave a gummy precipitate which was dried and then crystallized from water, using norite: colorless needles, m. p. 179–192° with decomposition; yield, 30 g. from 60 g. of succinanil.

Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: N, 8.48. Found: N, 8.71.

The ethyl ester (II), produced by the action of ethanol and a drop of sulfuric acid, was purified from very dilute ethanol; white crystals, m. p. 125–128°.

Anal. Calcd. for $C_{15}H_{22}N_2O_6S$: N, 7.82. Found: N, 7.94.

(*p*) - Methoxyacetamidobenzenesulfon - (β - hydroxyethyl)-amide (V).—The *p*-methoxyacetamidobenzene sulfonyl chloride was prepared in the usual way from methoxyacetanilide and chlorosulfonic acid. It was condensed with ethanolamine (2 moles) in 7% aqueous potassium hydroxide and the mixture heated to 60° during the course of five minutes. On cooling the product separated. The reaction mixture was neutralized, the substance filtered and purified from water; white crystals, m. p. 125–127°.

Anal. Calcd. for $C_{11}H_{16}N_2O_5S$: N, 9.72. Found: N, 9.80.

***p* - (α - Acetoxypropionamido) - benzenesulfonamide (VII).**—A solution of 16 g. of α-acetoxypropionyl chloride (1 mole) in dry ether was added slowly to 35 g. of sulfanilamide (2 moles) in dry ether. After stirring overnight, the precipitate was filtered and treated with water, followed by dilute hydrochloric acid. The product was purified from water, using norite; white crystals, m. p. 192.5°.

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$: N, 9.79. Found: N, 9.70.

The same product was also obtained from α-acetoxypropionanilide and chlorosulfonic acid, followed by treatment with aqueous ammonia.

***p* - (α - Hydroxypropionamido) - benzenesulfonamide (VIII).**—A mixture of 0.75 g. (1 mole) of the acetoxy compound just described and 4 cc. of 1.5 *N* aqueous sodium hydroxide was heated at 50–55° for three and one-half hours. At the end of the reaction, the solution was made slightly acid, and the product filtered. It was purified by recrystallization from water; transparent prisms, m. p. 196°.

Anal. Calcd. for $C_9H_{12}N_2O_4S$: N, 11.47. Found: N, 11.50.

***p* - (α - Acetoxypropionamido - N - (2 - hydroxy - 1-propyl)-benzenesulfonamide (III).**—Addition of 25 g. of α-acetoxypropionanilide to 73 g. of chlorosulfonic acid according to the usual procedure gave little evolution of gas until the mixture was heated to 30°, when the reaction became vigorous. The reaction mixture was held be-

(3) Tingle and Cram, *Am. Chem. J.*, **37**, 596 (1907).
(4) Menschutkin, *Ann.*, **162**, 166 (1872).
(5) "Org. Syntheses," Coll. Vol. I, p. 7.

TABLE I

DERIVATIVES OF DIBASIC ACIDS

	M. p., °C.	Solvent	Nitrogen analyses, % Calcd.	Found
$[(p)\text{-}HOCH_2CH_2NHSO_2C_6H_4NHCO]_2CH_2$	203–208 (dec.)	H_2O	11.20	11.36
$[(p)\text{-}CH_3CHOHCH_2NHSO_2C_6H_4NHCO]_2CH_2$	173–176 (dec.)	H_2O	10.60	10.80
$[(p)\text{-}HOCH_2CH_2NHSO_2C_6H_4NHCOCH_2]_2$	243–250 (dec.)	EtOH	10.89	11.26
$[(p)\text{-}CH_3CHOHCH_2NHSO_2C_6H_4NHCOCH_2]_2$	265–270 (dec.)	EtOH	10.33	10.50
$[(p)\text{-}HOCH_2CH_2NHSO_2C_6H_4NHCOCH_2]_2CH_2$	196–198	H_2O	10.60	10.70
$[(p)\text{-}CH_3CHOHCH_2NHSO_2C_8H_4NHCOCH_2]_2CH_2$	187–190	EtOH	10.07	10.04

tween 30–60° for three hours, cooled and added very slowly to a well-stirred mixture of ice and water. The sticky gum which formed was washed with ice water, then condensed immediately. The sulfonyl chloride was assumed to be 50% pure.

The sulfonyl chloride was added gradually in the cold to a cold solution of 2 moles of isopropanolamine in 30 cc. of 7% aqueous potassium hydroxide. The mixture was warmed to 60° during the course of ten minutes, filtered and neutralized with hydrochloric acid. Concentration of the solution at room temperature to a small volume resulted in the separation of an oil. By cooling and standing, this solidified and was purified from water using norite; white crystals, m. p. 97–103°.

Anal. Calcd. for $C_{14}H_{20}N_2O_6S$: N, 8.13. Found: 8.03.

Dibasic Acid Derivatives of the Type $(p)\text{-}RNHSO_2C_6H_4NHCO(CH_2)_xCONHC_6H_4SO_2NHR(p)$.—These were all prepared by the same general method. The dianilides of malonic, succinic and glutaric acids were synthesized, the first by the action of aniline on diethyl malonate,[6] the latter two by the action of aniline on the dibasic acid chlorides in dry ether. The dianilides were converted to the corresponding disulfonyl chlorides by the method described in "Organic Syntheses."[5] These products were then condensed with ethanolamine and isopropanolamine dissolved in 7% aqueous potassium hydroxide and more alkali was added during the course of the reaction to maintain alkalinity. The reactions were completed by heating for a half hour at 70°. Neutralization caused precipitation of the products which were then recrystallized, using norite, from water or alcohol. The products separated as white crystals upon slow cooling.

Diketopiperazine Derivatives of the Type

$$(p)\text{-}RNHSO_2C_6H_4\text{—}N\begin{matrix}CO\text{—}CH_2\\ \diagup\quad\diagdown\\ CH_2\text{—}CO\end{matrix}N\text{—}C_6H_4SO_2NHR\text{-}(p)$$

Compound in which R = $-CH_2CH_2OH$.—N,N'-Diphenyldiketopiperazine[7] was converted into the corresponding disulfonyl chloride and then condensed with ethanolamine in the usual way. The product was purified from water; white microcrystals, m. p. 260–270° with decomposition.

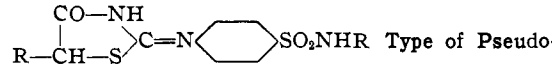
Anal. Calcd. for $C_{20}H_{24}N_4O_8S_2$: N, 10.93. Found: N, 11.00.

Compound in which R = $-CH_2CHOHCH_3$.—This substance was prepared like the above using isopropanolamine; white needles, m. p. 280–284° with decomposition.

Anal. Calcd. for $C_{22}H_{28}N_4O_8S_2$: N, 10.37. Found: N, 10.66.

Compound in which R = H.—Made in a similar manner with ammonia, the product was purified from water; white microcrystals, m. p. 325° with decomposition.

Anal. Calcd. for $C_{16}H_{16}N_4O_6S_2$: N, 13.20. Found: N, 13.20.



Type of Pseudothiohydantoin Derivatives.—The above structure for the following compounds was assigned on the basis of those suggested by Wheeler and Johnson[8] for the stable and labile forms of aryl-substituted pseudothiohydantoins.

Isopropanolamine Compound (IX).—*p*-Chloroacetamidobenzenesulfonyl chloride was prepared from *p*-chloroacetanilide and chlorosulfonic acid in the usual way and then condensed with isopropanolamine. An oil which separated from the reaction mixture was removed and the desired isopropanolamine derivative obtained by concentration of the solution. On purification from water, it formed colorless needles, m. p. 125–129°.

Anal. Calcd. for $C_{11}H_{15}N_2O_4SCl$: N, 9.13. Found: N, 9.10.

This product was treated with 1.5 moles of ammonium thiocyanate in sufficient absolute ethanol to dissolve it. The mixture was boiled gently for one and one-half hours and then the solvent removed by means of a current of air. The resulting product was crystallized from water, using norite; yellow needles, m. p. 209–212°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4S_2$: N, 12.76. Found: N, 12.87.

Isopropanolamine Compound (X).—α-Bromopropionanilide was converted with chlorosulfonic acid to the sulfonyl chloride and then condensed with isopropanolamine. The product melted at 140–143° after purification from ethanol. It was then dissolved in absolute ethanol and refluxed gently for one and one-half hours with one and one-half moles of ammonium thiocyanate. Much longer heating caused no further change. Removal of the solvent at room temperature gave a mixture of an oil and a solid, which was converted into a solid by agitation with 2.5% sodium carbonate solution. Acidification of the basic filtrate from this treatment gave more of the same substance as a white solid.

The combined solids from the sodium carbonate treatment were dissolved in boiling water, a small amount of a highly insoluble yellow product was removed, and the solution allowed to cool. The desired compound sepa-

(6) Reissert and Moré, *Ber.*, **39**, 3300 (1906).

(7) Kuhara, *Am. Chem. J.*, **24**, 168 (1900).

(8) Wheeler and Johnson, *ibid.*, **28**, 121 (1902).

rated slowly, sometimes only after agitation and concentration of the solution. A second recrystallization from water gave white needles, m. p. 190–192°.

Anal. Calcd. for $C_{13}H_{17}N_3O_4S_2$: N, 12.24. Found: N, 12.22.

3 - (*p* - Aminosulfonylphenyl) - pseudothiohydantoin (XI).—A mixture of 7.5 g. of *p*-chloroacetamidobenzenesulfonamide[9] in 150 cc. of absolute ethanol and 3.5 g. of ammonium thiocyanate was refluxed for thirty minutes. Longer heating produced no further change. The precipitate that formed was filtered, washed with 5 g. of aqueous sodium carbonate and recrystallized from water with norite. From the slow cooling of the solution, a colorless non-crystalline precipitate was obtained which darkened from 238°, melted at 258°, with decomposition.

Anal. Calcd. for $C_9H_9N_3O_3S_2$: N, 15.49. Found: N, 15.26.

(9) Jacobs and Heidelberger, THIS JOURNAL, **39**, 2429 (1917).

Summary

A number of sulfanilamide derivatives was prepared in which the amino group was substituted by various complex acyl groups and the amido group by ethanol and isopropanolamine. None showed activity comparable with sulfanilamide.

URBANA, ILLINOIS RECEIVED JUNE 16, 1939

[CONTRIBUTION FROM THE INTERNATIONAL LEPROSY CENTER, RIO DE JANEIRO]

Alepric, Aleprylic, Aleprestic and Aleprolic Acids, New Homologs of Chaulmoogric Acid

BY HOWARD IRVING COLE AND HUMBERTO T. CARDOSO

In analyzing *Hydnocarpus wightiana* oil by the method described by us[1] the high optical rotation and iodine numbers of the lower boiling fractions of ethyl esters indicated that there must be present at least one more optically active fatty acid besides those already known (chaulmoogric, hydnocarpic and gorlic[2] acids). By repeated fractional vacuum distillation of 200 l. of *H. wightiana* ethyl esters and fractional crystallization of the free acids we have succeeded finally in isolating two new homologs of chaulmoogric acid. The presence of two other homologs has been proved and they have been obtained 70.5 and 42% pure, respectively. Lack of sample prevented further purification. Because of their relationship to the treatment of leprosy we have named these four new homologs, alepric, aleprylic, aleprestic and aleprolic acids.

Alepric acid is the next lower homolog to hydnocarpic acid, differing from it by C_2H_4, having the formula $C_{14}H_{24}O_2$. Our final sample still contained a small amount of another unsaturated acid as indicated by the iodine number and optical rotation. The acid is colorless when liquid, white when solid, almost odorless and melts at 48°. The melted acid upon solidifying forms characteristic beautiful branching crystals rising above the surface of the acid. They are very similar to those already reported by us as characteristic of hydnocarpic and chaulmoogric acids.[3] Our purest sample of alepric acid gave a specific optical rotation of +77.12°. The theoretical value from the molecular weight–optical rotation curve is +80°.

Aleprylic acid is the next lower homolog to alepric acid containing two carbon atoms and four hydrogen atoms less than the latter. It has the formula $C_{12}H_{20}O_2$. It was obtained absolutely pure. It crystallizes in the same characteristic manner as the other homologs. Aleprylic acid melts sharply at 32° and has a specific optical rotation of +90.78°. It is colorless when liquid, white when solid and has a slight aromatic odor when warmed.

Aleprestic acid is the next lower homolog to aleprylic acid differing from it by C_2H_4 and having the formula $C_{10}H_{16}O_2$. It was obtained only 70.5% pure (Table I, 51W, 2) based upon its specific optical rotation which would be +100.5° as determined from the curve for the other homologs of this series of acids.

Although the next homolog to aleprestic acid may be present, our experimental data neither prove nor disprove its presence (Table I, 49W, 3, 4 and 5). On the other hand the second homolog below aleprestic acid is definitely proven to be present by the boiling point of the ethyl ester and the optical rotation and iodine number (Table I, 49W, 1). Computed from its rotation value we have obtained it 42% pure. We have named this lowest homolog aleprolic acid. It differs from aleprestic acid by C_4H_8 and has the

(1) Cole and Cardoso, THIS JOURNAL, **60**, 614 (1938).
(2) *Ibid.*, **60**, 612 (1938).
(3) *Ibid.*, **59**, 963 (1937).