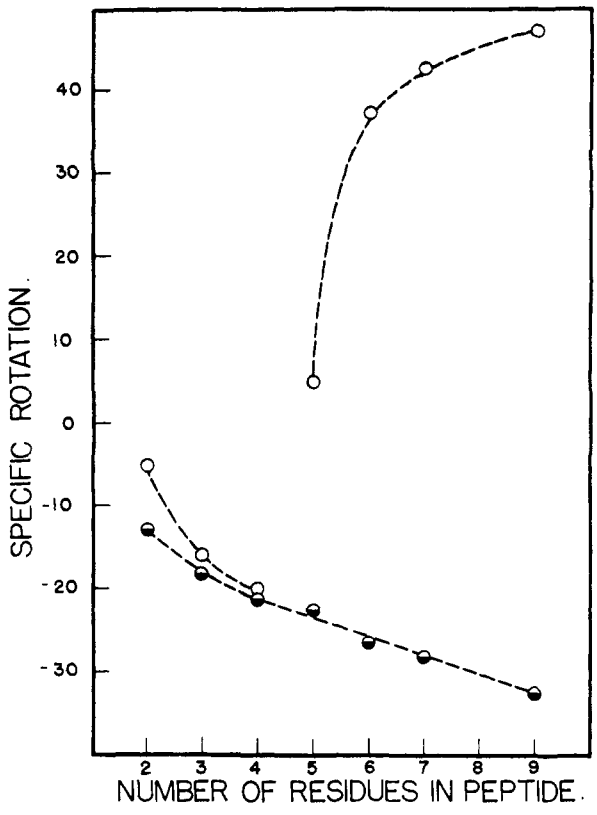

Fig. 1.—Optical activity of peptide derivatives as a function of solvent and number of residues. All rotations were measured in dioxane (open circles) and dichloroacetic acid (half-filled circles) at 2% concentration except the hepta- and nonapeptides in dioxane solution. These rotations were measured on a 1.43% and 0.22% solution, respectively.

Another explanation for positive optical rotations has been offered by Blout and Doty[4] for low molecular weight peptides. By polymerizing the γ-benzyl-α-amino acid anhydride of glutamic acid they obtained polydisperse oligomeric γ-benzyl-L-glutamate ($\overline{DP}$ 5.2), and found a concentration and solvent dependent positive rotation. This they ascribe to an associated β-form in solution.

The optical activities in dioxane of our di-, tri- and tetrapeptides were completely independent of concentration even at concentrations as high as 20%. On the other hand, the pentapeptide and hexapeptide showed decided concentration dependencies [+5° at 3% to −29° at 0.1%], and [+35 at 2% to 0° at 0.05%], respectively, while the heptamer and nonamer exhibited little or no concentration dependence.

In addition, a second solid form of these pure oligomers has been isolated by the technique of carefully heating the hexamer or higher in dioxane until precipitation occurred. The resulting solid is completely insoluble in dioxane. By heating, most probably, hydrogen bonds are broken and the peptide chain rearranges in a manner analogous to protein denaturation.[5] The chain is then able to associate as a β-extended structure which is insoluble in dioxane. This second solid form can be reconverted to the original by dissolving it in a hydrogen bond breaking solvent such as N,N-dimethylformamide and precipitating the peptide with ethanol.

We suggest the alternate possibility that the positive rotations for these oligomeric peptides are due to formation of intramolecular hydrogen bonds of the type found in the α-helix[6] of high molecular weight polyglutamic acid esters. The di-, tri-, and tetrapeptides indicate no detectable association or enhanced optical activity above that found for the solvated random coil in dichloroacetic acid. The penta and higher peptides, on the other hand, show both association[7] and enhanced optical rotations. On this basis we believe that the association is dependent upon a prior folding of the peptide chain.

Acknowledgment.—We gratefully acknowledge the support for this research given by the National Association of Glue Manufacturers.

Proc. Natl. Acad. Sci., **43**, 213 (1957); (e) E. R. Blout and R. H. Karlson, THIS JOURNAL, **80**, 1259 (1958).

(4) P. Doty, A. M. Holtzer, J. H. Bradbury and E. R. Blout, *ibid.*, **76**, 4493 (1954).

(5) C. H. Bamford, A. Elliott and W. E. Hanby, "Synthetic Polypeptides," Academic Press, Inc., New York, N. Y., 1956, p. 333.

(6) L. Pauling and R. B. Corey, *Proc. Natl. Acad. Sci.*, **37**, 241 (1951).

(7) Poly-γ-benzyl glutamates also exhibit association in solvents such as chloroform and dioxane; P. Doty, J. H. Bradbury and A. M. Holtzer, THIS JOURNAL, **78**, 947 (1956).

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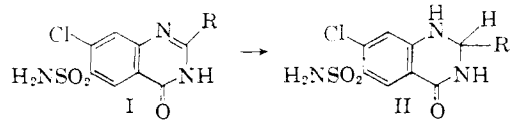
QUINAZOLINONE SULFONAMIDES AS DIURETIC AGENTS

Sir:

In view of the great current interest in orally active diuretic agents, which are neither organic mercurial compounds nor primarily carbonic anhydrase inhibitors,[1,2] we wish to report on a series of highly active 7-chloro-6-sulfamyl-4(3H)-quinazolinones (I) and 7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinones (II).



These compounds cause a marked natriuresis and chloruresis in rats and dogs on oral administration, but at the same time cause only a relatively small increase in potassium excretion.

In general, minor variations in R from H to lower alkyl have very little effect on the over-all activity observed in this series but do affect slightly the dose-response curves and the Na^+, Cl^- and K^+ excretion ratios as observed experimentally.[3]

Conversion of the quinazolinones (I) to the 1,2,3,4-tetrahydroquinazolinones (II) results in an enhancement of oral diuretic activity on a dose/kg.

(1) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957).

(2) Annals of the New York Academy of Sciences, "Chlorothiazide and Other Diuretic Agents," Vol. 71, pp. 321-478 (1958).

(3) We are indebted to Dr. J. R. Cummings and his associates of the Experimental Therapeutics Research Section, Pearl River Laboratories, for the pharmacological data reported.

basis in animals. It also reduces K^+ excretion as compared to Cl^- excretion.

Chlorosulfonation and amination of 5-chloro-*o*-acetotoluide (III) yielded 5-chloro-4-sulfamyl-*o*-acetotoluide (IV) (m.p. >265°; *Anal.* Calcd, for $C_9H_{11}N_2O_3SCl$: C, 41.1; H, 4.20; N, 10.6; S, 12.2; Cl, 13.5. Found: C, 41.0; H, 4.31; N, 10.6; S, 11.9; Cl, 13.8) which was oxidized with $KMnO_4$ to N-acetyl-4-chloro-5-sulfamylanthranilic acid (V) (m.p. 254–256°; *Anal.* Calcd, for $C_9H_9N_2O_5SCl$: C, 36.9; H, 3.08; N, 9.57; S, 11.0; Cl, 12.1. Found: C, 37.3; H, 3.60; N, 9.92; S, 10.7; Cl, 12.3). Treatment of V with urethan at 180–190° gave I (R = CH_3) directly (m.p. >320°; *Anal.* Calcd, for $C_9H_8N_3O_3SCl$: C, 39.6; H, 2.93; N, 15.3; S, 11.7; Cl, 13.0. Found: C, 39.3; H, 3.25; N, 15.2; S, 11.5; Cl, 12.9). Alternately, V was hydrolyzed to 4-chloro-5-sulfamylanthranilic acid VI (m.p. 275°; *Anal.* Calcd. for $C_7H_7N_2O_4SCl$: C, 33.5; H, 2.79; N, 11.2; S, 12.8; Cl, 14.2. Found: C, 33.3; H, 2.85; N, 11.1; S, 12.6; Cl, 14.1) which on fusion with formamide at 170–175° gave I (R = H) (m.p. 310–315°; *Anal.* Calcd. for $C_8H_6N_3O_3SCl$: C, 37.0; H, 2.31; N, 16.2; S, 12.3; Cl, 13.7. Found: C, 37.1; H, 2.60; N, 15.8; S, 12.4; Cl, 13.6).

Reduction of the 4(3H)-quinazolinones (I) with $NaBH_4$ in the presence of $AlCl_3$ gave highly active compounds of the 1,2,3,4-tetrahydro-4-quinazolinone structure (II), for example; 7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone (II, R = H) (m.p. 256–258°; *Anal.* Calcd. for $C_8H_8N_3O_3SCl$: C, 36.7; H, 3.06; N, 16.1; S, 12.3. Found: C, 37.2; H, 3.30; N, 16.2; S, 12.2) and 7-chloro-2-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone (II, R = CH_3) (m.p. 275°; *Anal.* Calcd. for $C_9H_{10}O_3N_3SCl$: C, 39.2; H, 3.63; N, 15.3; S, 11.7; Cl, 12.9. Found: C, 39.1; H, 3.60; N, 15.1; S, 11.8; Cl, 12.7). A number of other compounds in this series have been prepared and will be reported at a later date.

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RECEIVED AUGUST 19, 1959

THE MECHANISM OF ACID-CATALYZED AROMATIC HYDROGEN EXCHANGE[1]

Sir:

Because rates of aromatic hydrogen exchange in strong aqueous acid are proportional to Hammett's acidity function, h_0, this reaction is thought to proceed by the A-1 mechanism,[2] which, in this case, demands a reaction sequence of at least three steps. The evidence for all other electrophilic aromatic substitutions, however, demands nothing more complex than a two-step reaction sequence.[3] An analogous mechanism for aromatic hydrogen exchange would involve a slow proton transfer (A-S_E2 reaction), a reaction whose acidity dependence is not known with certainty.[4] Since there is no reason to consider hydrogen fundamentally different from other electrophilic reagents, it seems desirable to re-examine the mechanism of aromatic hydrogen exchange to see whether it is not, in fact, an A-S_E2 reaction.

The A-1 reaction can be distinguished from the A-S_E2 reaction by the form of its acid catalysis: The A-1 reaction is catalyzed only by hydronium ion, whereas the A-S_E2 reaction shows general acid catalysis.[5] This difference cannot be observed with the usual aromatic substrates because these react at appreciable rates only in strong mineral acids. The accelerating influence of a methoxy group on this reaction is, however, very strong, and a prediction based on known partial rate factors[6] leads to the expectation of measurable rates in dilute aqueous acid for molecules bearing a sufficient number of suitably arranged methoxy groups. This prediction is borne out by experiment: 1,3,5-trimethoxybenzene-2-*t* has an exchange half-life of approximately 30 minutes in 0.05 *N* strong acid. The rate of exchange is proportional to the first power of hydronium ion concentration over the range 1.3×10^{-5} to 5×10^{-2} *N*. In buffers, at constant hydronium ion concentration, the rate is also proportional to buffer concentration; Fig. 1 shows that rate changes by a factor of 3.5 with a change of 10 in acetate

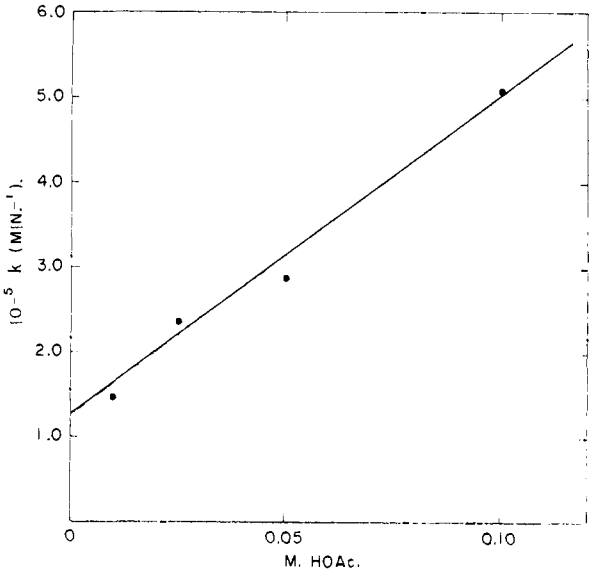

Fig. 1.—Dependence of rate of nuclear hydrogen exchange in 1,3,5-trimethoxybenzene on acetate buffer concentration at constant hydronium ion concentration.

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

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(3) L. Melander, *Arkiv Kemi*, **2**, 211 (1950); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 279; P. W. Robertson, *J. Chem. Soc.*, 1267 (1954); P. B. D. de la Mare, T. M. Dunn and J. T. Harvey, *ibid.*, 923 (1957); H. Zollinger, *Experientia*, **12**, 165 (1956); A. J. Kresge, unpublished work on mercuration; A. J. Kresge and D. P. N. Satchell, *Tetrahedron*, in press.

(4) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 942 (1957); A. J. Kresge and D. P. N. Satchell, *Chem. and Ind.*, 1328 (1958); L. Melander and P. C. Myhre, *Arkiv Kemi*, **13**, 507 (1959).

(5) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, p. 124; A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 204; F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 943 (1957).

(6) D. P. N Satchell, *J. Chem. Soc.*, 3911 (1956).