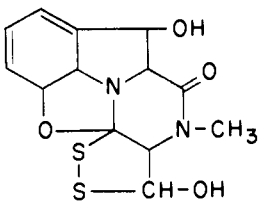
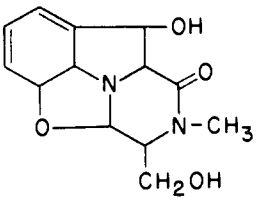
THE STRUCTURE OF GLIOTOXIN

Sir:

The formulas proposed earlier for gliotoxin and *de*thiogliotoxin (I, II)[1,2] are not compatible with

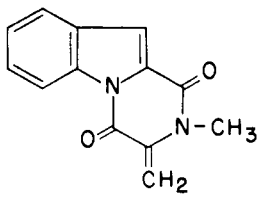


I

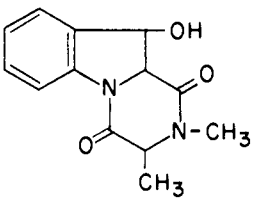


II

several recent experimental observations. These include the transformation of gliotoxin on short contact with alkaline alumina at 20° into the compound $C_{13}H_{10}N_2O_2$ (III),[3] and the lack of satisfactory correspondence in chemical and spectroscopic properties between the synthetic 10-hydroxypyrazinoindole derivative IV and a degradation product, anhydro*de*thiogliotoxin, which had been assigned this chemical constitution.[4]

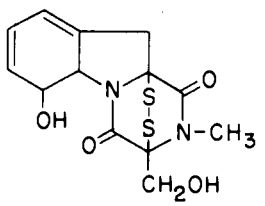


III

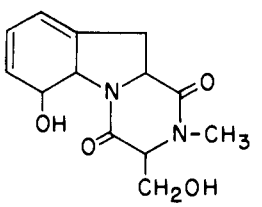


IV

We have now deduced the structure V for gliotoxin. This expression permits the unambiguous interpretation of the extensive transformations of gliotoxin and *de*thiogliotoxin (VI) into degradation



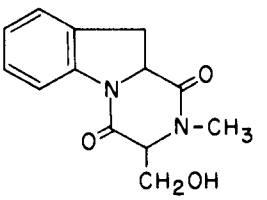
V



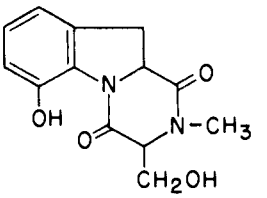
VI

products of known structure, and leads directly to satisfactory formulations for several derived substances of hitherto unknown or uncertain structure and genesis. For example, the long-known anhydro*de*thiogliotoxin is now given the structure VII, and a new series of transformations,[5] described below, is uniquely formulable in terms of the new structures.

*De*hydro*de*thiogliotoxin, $C_{13}H_{14}N_2O_4$, [m.p. 252–254°, $[\alpha]^{25}D$ − 217 ± 7°, $\lambda\lambda_{max}$ (log ϵ) 220 mμ (4.19), 262 mμ (3.82), 292 mμ (3.47)] is formed when *de*thiogliotoxin is heated over palladium-charcoal in boiling xylene. Its chemical behavior and ultraviolet absorption are consistent with formula VIII.[6]

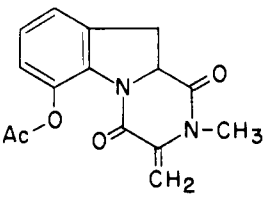


VII



VIII

Acetic anhydride at 230° converts *de*hydro*de*thiogliotoxin to an alkali-insoluble, colorless, crystalline compound of the formula $C_{15}H_{14}N_2O_4$ [m.p. 185–186°, $[\alpha]^{25}D$ + 1.3 ± 1.3°]. The chemical behavior and the absorption spectra in the ultraviolet and infrared regions support the formulation of the acetylated derivative as IX.



IX

Treatment of the acetylated compound with saturated methanolic ammonia at 20° converts it slowly to a very sparingly soluble, colorless, crystalline compound, $(C_7H_7NO_2)_n$, which decomposes at *ca.* 360°, without melting. This product exhibits a striking resemblance to the very insoluble dimeric substances produced by the action of ammonia and other bases on dipeptides or 2,5-piperazinediones containing a serine unit.[7]

Chemical and stereochemical considerations exclude attachment of a disulfide bridge in gliotoxin at any positions other than 3 and 11. It is now clear that gliotoxin is an anhydrodipeptide related to the amino acids serine and phenylalanine, and it is particularly worthy of note that the α-carbon atoms of the coöperating α-thio-α-amino acid units must have the same absolute configuration.

(1) J. R. Johnson and J. B. Buchanan, THIS JOURNAL, **75**, 2103 (1953).

(2) J. R. Johnson, "The Structure of Gliotoxin," in "The Roger Adams Symposium," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 60–90.

(3) John S. Warner, Doctoral Thesis, Cornell University, 1953.

(4) L. R. Harper, Doctoral Thesis, Cornell University, 1954.

(5) Malcolm R. Bell, Doctoral Thesis, Cornell University, 1956.

(6) The late Professor E. A. Braude (Imperial College) informed one of us (R.B.W.) privately (23 March 1956) that his associates R. L. Erskine and G. Lowe had effected the dehydrogenation of gliotoxin itself, using tetrachloro-*o*-benzoquinone in *o*-dichlorobenzene at 100°. Professor Braude rightly regarded the preparation of dehydrogliotoxin [m.p. 184–185°, $\lambda\lambda_{max}$ (log ϵ) 214 mμ (4.34), 270 mμ (3.72), 298 mμ (3.67)] as providing confirmatory evidence for the presence of the unusual cyclohexadiene moiety in gliotoxin, but otherwise formulated the change in terms of the old structure I. It is now clear that *de*hydrogliotoxin is the analog of the *de*hydro*de*thio compound VIII which we had prepared prior to receiving Professor Braude's communication.

(7) M. Bergmann and collaborators, *Ann.*, **445**, 17 (1925); **448**, 38 (1926); **458**, 40 (1927).

(8) We wish to acknowledge the generous support of the National Institutes of Health and the National Science Foundation.

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