temperature,[6] we suggest that in dilute solution and in the molten state the isotactic and block polymers of optically active α-olefins are at least in part spiralized and that helices of a single screw sense largely prevail.

(6) For the highly stereoregular fractions of poly-(S)-3-methyl-1-pentene which have a very low solubility and high melting point it is possible that the solutions of the polymers still contain crystalline molecular aggregates which undergo dissociation by increasing the temperature. In this case, the decrease of the optical activity by increasing the temperature, could be attributed to the dissociation of the crystalline aggregates having high optical activity to dissolved less optically active macromolecules, which may change or eventually loose their spiralized conformation. G. Natta, M. Farina, M. Peraldo, P. Corradini, G. Bressan and P. Ganis (*Rend. Acc. Naz. Lincei*, April, 1960) have found crystalline molecular aggregates in solutions of some di-isotactic polymers. We are particularly indebted to Prof. Natta and his co-workers for the discussion on this point.

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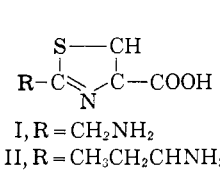
DEGRADATION OF THIOSTREPTON. THIOSTREPTOIC ACID

Sir:

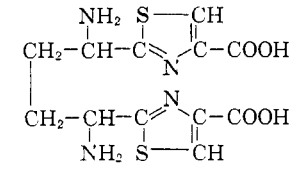
Earlier publications from this Laboratory have described the isolation and characterization[1] as well as the biological properties[2,3] of the antibiotic thiostrepton. Kenner, *et al.*,[4] have isolated the 4-thiazolecarboxylic acids I and II from acid hydrolysates of the antibiotic. This Communication presents our own degradative studies with thiostrepton.

Separation of water-soluble components of acid hydrolysates (6 *N* HCl, 16 hours at 105°) by countercurrent distribution, then partition chromatography, led to the isolation of L-threonine, L-isoleucine, L-alanine, and of D-cystine.[5] The identity of these components was ascertained by comparison with authentic samples on paper chromatograms, by infrared spectra and by measurement of their optical rotation. No other conventional amino acids were found. From a partial hydrolysate (6 *N* HCl at room temperature) L-isoleucyl-L-alanine[6] was obtained in crystalline form and identified by paper chromatographic separation of the components liberated by hydrolysis before and after dinitrophenylation.

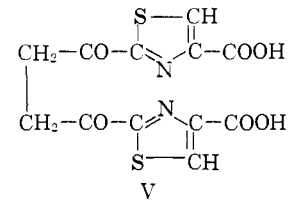
Hydrolysis of thiostrepton with a 1:1 mixture of concentrated hydrochloric and formic acids[7] furnished in addition to the previously isolated[4] thiazolecarboxylic acids[8] I and II,[9] the keto acid III[10] and the hitherto unknown amino acid IV designated by us as *thiostreptoic acid.*



I, R = CH_2NH_2
II, R = $CH_3CH_2CHNH_2$
III, R = CH_3CH_2CO



IV



V

The crystalline acid IV was isolated from the hydrolysate after removal of impurities by butanol extraction. The dihydrate melts at 235–237° (dec.); $[\alpha]^{23}D \pm 0$ (*c*, 1.0 in 1 *N* HCl); $\lambda_{max}^{1N\ HCl}$ 236 mμ (ε = 15,000); *Anal.* weight loss at 110°: 9.7; calcd. for 2 H_2O: 9.5; calcd. for $C_{12}H_{14}O_4N_4S_2$: C, 42.1; H, 4.12; N, 16.4; S, 18.7. Found: C, 42.3; H, 4.21; N, 16.4; S, 18.6. On Whatman No. 1 paper in a system of 1-butanol–acetic acid–water (4:1:1) thiostreptoic acid moves somewhat faster than cystine, R_f = 0.08–0.10. In 1 *N* HCl it forms a crystalline dihydrochloride, which, when dissolved in water, deposits the free acid. Treatment of IV in water with acetic anhydride in the presence of triethylamine yields the corresponding N,N'-diacetyl derivative, m.p. 275–277° (dec.). *Anal.* Weight loss at 110°, 10.4; calcd. for 3 H_2O: 11.2; calcd. for $C_{16}H_{18}O_6N_4S_2$: C, 45.3; H, 4.26; S, 15.1. Found: C, 45.3; H, 4.38; S, 15.1. On both a reaction with dinitrofluorobenzene IV forms mono- and bis-dinitrophenyl derivative.[11] The former is ninhydrin positive. From the specific absorption of the monodinitrophenyl derivative at 355 mμ a molecular weight of about 500 was calculated. Titration of monodinitrophenylthiostreptoic acid with alkali and acid gave neutralization equivalents of 257 and 539, respectively (mol. wt., 508). Reduction of IV with sodium in liquid ammonia and then acid hydrolysis[12] led to a mixture, in which alanine and cystine were identified by paper chromatography. Oxidation of thiostreptoic acid

(1) J. Vandeputte and J. D. Dutcher, "Antibiotics Annual, 1955-1956," Medical Encyclopedia, Inc., New York, N. Y., p. 560.

(2) J. F. Pagano, M. J. Weinstein, H. A. Stout and R. Donovick, *ibid.*, 1955-1956, p. 554.

(3) B. A. Steinberg, W. P. Jambor and Lyda O. Suydam, *ibid.*, 1955-1956, p. 562.

(4) G. W. Kenner, R. C. Sheppard and C. E. Stehr, *Tetrahedron Letters*, 23 (1960).

(5) In thiostrepton this D-amino acid occurs in the reduced form, as shown by the absence of a reaction for disulfides in the antibiotic and the positive test for sulfhydryl after hydrolysis. Moreover, the behavior of this amino acid during fractionation by countercurrent distribution or by partition chromatography was characteristic of cysteine rather than cystine.

(6) Isoleucine and alanine were also found in a diketopiperazine formed during pyrolysis of the antibiotic at 250° *in vacuo*.

(7) G. L. Miller and V. du Vigneaud, *J. Biol. Chem.*, **118**, 101 (1937).

(8) The fact that acid hydrolysis of the product obtained from thiostrepton by reduction with sodium in liquid ammonia yields glycine and α-aminobutyric acid indicates that the thiazolecarboxylic acids I and II, and probably also IV, are present as such in the parent molecule and not, for instance, as thiazolines.

(9) In these studies, 11 was isolated as a crystalline salt with *p*-hydroxyazobenzene-*p*'-sulfonic acid. *Anal.* Calcd. for $C_{19}H_{20}O_6N_4S_2$: C, 49.1; H, 4.34; S, 13.8. Found: C, 48.9; H, 4.46; S, 13.7.

(10) The acid III, probably formed as a secondary degradation product from II, was found to be identical with the acid isolated by P. Brookes, A. T. Fuller and J. Walker (*J. Chem. Soc.*, 689 (1957)) from *Micrococcin P.* A homologous keto acid was reported as a secondary degradation product from bacitracin A (J. R. Weisiger, W. Hausmann and L. C. Craig, THIS JOURNAL, **77**, 3123 [1955]).

(11) A. R. Battersby and L. C. Craig, THIS JOURNAL, **73**, 1887 (1951); **74**, 4023 (1952).

(12) P. Brookes, R. J. Clark, B. Majhofer, M. P. V. Mijovic and J. Walker, *J. Chem. Soc.*, 925 (1960).

with $KMnO_4$ in dilute NaOH[13] gave the diketo acid V, m.p. 280–290° (dec.); λ_{max}^{alc} 293 mμ (ε = 9,000); *anal.* Calcd. for $C_{12}H_8O_6N_2S_2$: C, 42.3; H, 2.37; S, 18.8. Found: C, 42.4; H, 2.19; S, 18.5, in addition to a small amount of 4-thiazolecarboxylic acid. The above data permit the assignment of structure IV to thiostreptoic acid. Unambiguous proof was provided by a synthesis of V.

Succindialdehyde was treated with potassium cyanide and the resulting cyanhydrin benzoylated *in situ*.[13,14] As expected, two isomers, the meso form and the racemate of α,δ-dibenzoyloxyadipic acid dinitrile were isolated, m.p. 135–137°; and m.p. 212–216°; *anal.* Calcd. for $C_{20}H_{16}O_4N_2$: C, 69.0; H, 4.63; N, 8.04. Found: C, 68.9; H, 4.60; N, 7.93 for the lower melting and C, 69.0; H, 4.81; N, 8.10 for the higher melting isomer. The lower melting isomer was used in the subsequent steps. Treatment with hydrogen sulfide in dimethylformamide in the presence of triethanolamine[13,14] furnished α,δ-dibenzoyloxyadipic acid dithioamide, m.p. 203–205°; *anal.* Calcd. for $C_{20}H_{20}O_4N_2S_2$: N, 6.73; S, 15.4. Found: N, 6.94; S, 15.4, which was condensed with ethyl bromopyruvate to give the diethyl ester of 2,2′-(1,4-dibenzoyloxytetramethylene)-bis-[4-thiazolecarboxylic acid], m.p. 144–145°; *anal.* Calcd. for $C_{30}H_{28}O_8N_2S_2$: N, 4.60; S, 10.5. Found: N, 4.68; S, 10.6. Hydrolysis with potash in ethanol yielded the corresponding dihydroxy acid, m.p. 240–242°; *Anal.* Calcd. for $C_{12}H_{12}O_6N_2S_2$: C, 41.9; H, 3.51; N, 8.23. Found: C, 42.0; H, 3.95; N, 8.35, which on oxidation with $Na_2Cr_2O_7$ gave 2,2′-succinylbis-(4-thiazolecarboxylic acid), m.p. 284–286° (dec.); λ_{max}^{Nujol} 5.84 sh, 5.90; *anal.* Found: C, 42.5; H, 2.90, identical in all respects with the diketo acid V derived from thiostreptoic acid.

The sulfur content of the antibiotic (9.4%) considered in conjunction with the four sulfur-containing fragments isolated so far require for thiostrepton a minimum molecular weight of 1700.[15]

(13) P. Brookes, A. T. Fuller and J. Walker, *J. Chem. Soc.* 689 (1957).

(14) J. F. Olin and T. B. Johnson, *Rec. Trav. Chim.*, **50**, 72 (1931).

(15) Ether extraction of acid hydrolysates (1 *N* HCl, 24 hours, at 105°) furnished a yellow volatile crystalline compound. *Anal.* $C_{12}H_9O_4N$: C, 62.6; H, 4.3; N, 6.14; λ_{max} 265 mμ (ε, 25,000), 375 mμ (ε, 2,000). An additional fragment from the same hydrolysate contains alanine acylated by the yellow chromophore.

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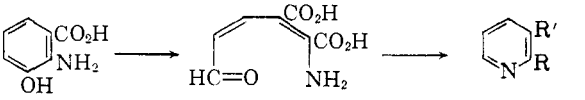
RECEIVED JULY 28, 1960

CONVERSION OF 3-AMINOCATECHOLS TO 6-HYDROXYPICOLINIC ACIDS[1]

Sir:

In the enzymatic conversion of 3-hydroxyanthranilic acid (I) to quinolinic (III, R = R′ = CO_2H), nicotinic (III, R = H, R′ = CO_2H) and picolinic acid (III, R = CO_2H, R′ = H), α-amino-β-carboxymuconic acid semialdehyde (II), an established intermediate produced by a ring cleavage, undergoes decarboxylation and/or intramolecular cyclization.[2] Chemical conversions of benzene derivatives to pyridine derivatives by cleavage of the carbocyclic ring and recyclization have not been developed.[3]



I II III

We wish to report a new and general method for the chemical conversion of 3-aminocatechols (IV) to 6-hydroxypicolinic acids (VII). Unstable 3-aminocatechol (IVa),[4] 3,4-dihydroxyanthranilic acid (IVb),[5] m.p. 175° (dec.), unstable 2,3-diamino-4,5-dihydroxytoluene (IVc),[6] 1,2-dihydroxy-3-aminonaphthalene (IVd), m.p. 164° (dec.), and unstable 1,2-dihydroxy-3-amino-4-anilinonaphthalene (IVe)[7] are transformed respectively to 6-hydroxypicolinic acid (VIIa), m.p. 261–263°, 6-hydroxyquinolinic acid (VIIb), m.p. 253–254.5°, 3-amino-4-methyl-6-hydroxypicolinic acid (VIIc), m.p. 285–288° (dec.), isocarbostyril-3-carboxylic acid (VIId), m.p. 318–320° and 4-anilinoisocarbostyril-3-carboxylic acid (VIIe), m.p. 250–256° (dec.).[8]

Silver oxide in anhydrous ethyl acetate oxidizes each dihydroxyamine (IV) to a blue-black unstable aminoquinone (V).[9] In an extension of the application of the Baeyer–Villiger reaction to *o*-quinones,[10] each aminoquinone, after separation from inorganic material, is oxidized without isolation from solvent with a peroxy organic acid apparently to an unisolated derivative of muconic acid anhydride (VI). On treatment of the anhydride with water a substituted muconic acid presumably is formed. Hydrolysis of monocyclic muconic acid anhydrides in the presence of strong ultraviolet light gives only intractable tars. Apparently *cis-cis* muconic acid derivatives are produced initially and isomerize to *trans–trans* modifications.[11] In the absence of

(1) Financial assistance from National Institutes of Health Grants Nos. H-2295 and CY-2895 is gratefully acknowledged.

(2) H. S. Mason, "Mechanisms of Oxygen Metabolism" in "Advances in Enzymology," Vol. 19, Interscience Publishers, Inc., New York, N. Y., 1957, p. 92.

(3) Ozonolysis of a substituted aminomethylcatechol ether and then cyclization accounts for the construction of ring III as a pyridone in the synthesis of strychnine (R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daenker and K. Scheinker, THIS JOURNAL **76**, 4749 (1954)). Pyridine is reported to be one of the products from benzene and active nitrogen (P. M. Aronovich, N. K. Bel'skii, and B. M. Mikhailov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 696 (1956), *C.A.* **51**, 1893 (1957)).

(4) Identified as its hydrochloride, m.p. 196–202° (dec.).

(5) At one time this compound was considered to be an enzymatic intermediate in the conversion of I to III (K. Makino, F. Itoh and K. Nishi, *Nature*, **167**, 115 (1951)).

(6) Isolated as its dihydrobromide salt, m.p. 162–176° (dec.).

(7) Identified as its hydrochloride salt, m.p. 211–213° (dec.).

(8) Satisfactory analytical data have been obtained for all compounds and/or their derivatives reported in this Communication.

(9) Through condensation with *o*-phenylenediamine each aminoquinone is transformed into the corresponding derivative of 1-aminophenazine which was analyzed. Aminoquinones, tautomeric hydroxyquinone-monoimines and imino dihydroquinones are regarded as equivalent structures for the present purpose.

(10) P. Karrer, R. Schwyzer and A. Neuwirth, *Helv. Chim. Acta*, 31, 1210 (1948).

(11) In boiling water exposed to an ultraviolet lamp, *cis,cis*-muconic acid is changed quantitatively to the *trans,trans*-isomer (J. A. Elvidge, R. P. Linstead, B. H. Orkin, P. Sims, H. Baer and D. B. Pattison, *J. Chem. Soc.* 2228 (1950)).