[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF 4-(3,4-DIHYDROXYPHENYL)-THIAZOLES

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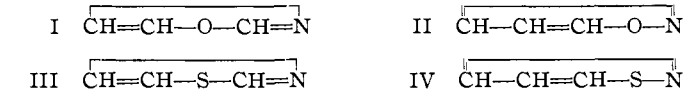
So far as the writers are aware, organic combinations derived from the heterocyclic rings—oxazole, I, isoxazole, II, thiazole, III, and isothiazole, IV, have never been utilized in the practice of general therapeutics, nor



has their pharmacology been systematically investigated. This paper is the first of a proposed series from this Laboratory dealing with such cycles, and in which we shall describe methods of synthesizing new amino derivatives of the sulfur cycle, *thiazole*, represented by Formula III. All of the amines thus far prepared are being examined to determine their pharmacological action. The study of derivatives of the other three cycles included in the above heterocyclic series will be taken up as our investigation progresses.[2]

The basic idea which guided us in the formulation of our program of research was one of determining what influence the incorporation of a thiazole ring, III, or bridging with this cycle, would have on the potency and toxicity of known physiologically active organic substances. To illustrate, by the term "bridging" we mean the introduction of the compound radical—thyazyl,[3] C_3HNS— into the molecule of an amino acid like di-iodotyrosine, for example, leading to the formation of the unknown α-amino acid—*thyazyldi-iodotyrosine*—represented structurally by Formula V. In other words, this would lead to an analog of thyroxine, VI, which may also be viewed as a bridged compound derived from di-iodotyrosine, in which the compound radical, $I_2C_6H_2O$, functions in place of thyazyl in V. If we limit ourselves to thiazole substitutions in positions 2 and 4 of this cycle, only one other isomeric thyazyldi-iodotyrosine is theoretically possible, namely, that represented by Formula VII. The study of practical methods leading to the synthesis of these two acids, V and VII, is now in progress in this Laboratory.

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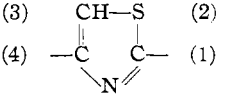
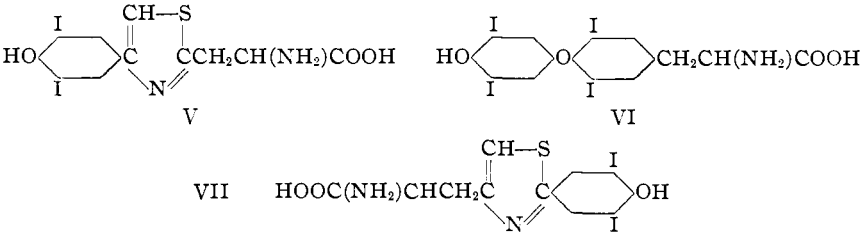
[2] Of the many possible constructions that may be derived from these four cycles, we are not interested, at present, in the different condensed ring systems of which benzoxazoles and benzthiazoles, for example, are representative compounds.

[3] The thyazyl radical is represented structurally as

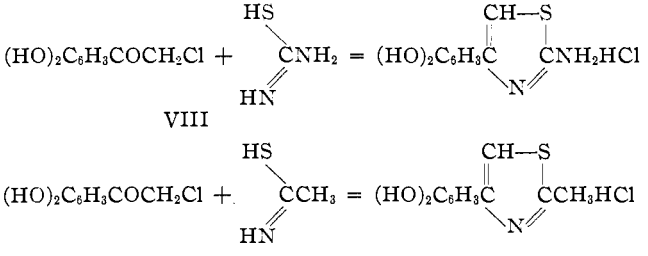




V VI

VII

In order to ascertain the influence of bridging with thyazyl, we first directed our attention to the study of methods of synthesizing thiazoles containing the catechol nucleus, $C_6H_3(OH)_2$. The catechol radical has been little used in drug synthesis except in the production synthetically of adrenaline and related compounds. The reaction which has led successfully to the synthesis of physiologically active thiazole derivatives is one based on the reactivity of an ω-chloroketone toward compounds containing thio-amide groupings. The mechanism of this reaction was first correctly interpreted by Hantzsch.[4] The only halogenated derivative of an aromatic ketone which has been extensively utilized in the development of thiazole chemistry is ω-chloro- or bromo-acetophenone, $C_6H_5COCH_2Br$. The halogenated ketone which served as the starting point of our research was chloro-acetocatechol, VIII, first described by Dzerzgowski,[5] and which served as the starting point for the first successful synthesis of adrenaline.[6] This chloro ketone interacts smoothly with every thio-amide construction that we have thus far examined, leading to the formation of thiazoles containing a catechol group in the 4-position of this cycle. The reactions with thiourea and acet-thioamide, for example, are expressed below



VIII

In the Experimental Part of this paper is given a description of several new aminothiazoles containing the catechol group in the 4-position of the thiazole ring. An unexpected stability has been revealed in the case of the majority of the thiazole amines which we have thus far synthesized. Ordinarily, one expects to meet with organic constructions which easily undergo oxidation when experimenting with catechol derivatives. In our

[4] Hantzsch, *Ann.*, **249**, 1 (1888); **250**, 257 (1890); Traumann, *ibid.*, **249**, 31 (1888).

[5] Dzerzgowski, *J. Russ. Phys.-Chem. Soc.*, **25**, 154, 276 (1893).

[6] Stolz, *Ber.*, **37**, 4149 (1904).

new compounds the bridging with the thiazole cycle has a decidedly stabilizing effect and our new catechol combinations can be preserved without undergoing rapid oxidation changes. Methods for synthesizing thiazole amines containing the cathechol group in the 2-position of this cycle will be described in our next paper.

Experimental Part

Chloro-acetocatechol, $ClCH_2COC_6H_3(OH)_2(3,4)$.—The chloro-acetocatechol used in the various condensation reactions described in this paper was prepared from catechol, chloro-acetic acid and phosphorus oxychloride both by the method of Mannich and Hahn,[7] without the use of a solvent, and the more recent method of Ott[8] in which the reaction is carried out in benzene.

The yields by the first method were improved by warming the mixture very gradually on a water-bath for several hours instead of heating at 100° for one hour and by using more phosphorus halide (1 mole). A sticky mass forms if the solution becomes too hot and the reaction mixture foams vigorously. We also applied Ott's procedure of synthesis but with slight modification in technique.

The following procedure gave the best results and the chloro-acetocatechol may usually be obtained very pure and in a colorless form by only one recrystallization.

Twenty grams of catechol, 20 g. of chloro-acetic acid and 15 g. of phosphorus oxychloride were dissolved in 80 cc. of benzene and the solution was warmed on a water-bath at about 60° for twenty-four hours. At the end of this time the solution was still light colored and contained a heavy deposit of crystalline chloro-acetocatechol. The solution was cooled, the benzene decanted and water then added. The precipitated ketone weighed 15 g. The benzene liquor usually gave a gram or two more when it was evaporated and the residue obtained was triturated with water. After one recrystallization from hot water the ketone melted sharply at 173°.

Preparation of Acetamino-acetonitrile, $CH_3CONHCH_2CN$.—Ten grams of the hydrochloride of amino-acetonitrile[9] was carefully warmed with 50 cc. of freshly distilled acetic anhydride until the solution became clear and effervesced vigorously. After allowing to stand for a few minutes the solution was diluted with benzene and then allowed to evaporate on a hot-plate. The residue solidified and after washing with ether weighed 10 g. The compound is purified by dissolving in chloroform and then precipitating by diluting the solution with ether. It melts at 77°.

Acetamino-acetothioamide, $CH_3CONHCH_2CSNH_2$.—A solution of 20 g. of acetamino-acetonitrile in 75 cc. of absolute alcohol and 25 cc. of concentrated aqueous ammonia was cooled to 10° and saturated with hydrogen sulfide. On allowing the solution to evaporate spontaneously, the thio-amide separated in a crystalline form and was purified by recrystallization from absolute alcohol. The yield was 19 g. and it melted at 123–124°.

Anal. Calcd. for $C_4H_8ON_2S$: N, 21.20. Found: N, 21.20, 21.05.

2-Acetaminomethyl-4-(3,4-dihydroxyphenyl)-thiazole. Hydrochloride.—Prepared by interaction of the above thioamide and chloro-acetocatechol in alcohol solution. It is easily purified by crystallization from alcohol and melts at 188–190°.

Anal. Calcd. for $C_{12}H_{13}O_3N_2SCl \cdot C_2H_5OH$: N, 8.08; C_2H_5OH, 13.28. Found: N, 7.72, 7.81; C_2H_5OH, 13.19.

[7] Mannich and Hahn, *Ber.*, **44**, 1548 (1911).

[8] Ott, *ibid.*, 59, 1068 (1926).

[9] Curtius, *ibid.*, **31**, 2490 (1898).

2-Aminomethyl-4-(3,4-dihydroxyphenyl)-thiazole,

$(HO)_2C_6H_3C{=}CHSC(CH_2NH_2){=}N$.—The hydrochloride of this thiazole base was obtained by digesting the above acetyl compound with concentrated hydrochloric acid. The salt was purified by dissolving in 85% alcohol and then precipitating by dilution with ether. It crystallized from hydrochloric acid in prisms melting at 225–230°.

Anal. Calcd. for $C_{10}H_{10}O_2N_2S{\cdot}2HCl$: N, 9.49; Cl, 24.0. Found: N, 9.33; Cl, 24.3.

Acetylmethylamino-acetothio-amide, $CH_3CON(CH_3)CH_2CSNH_2$.—Twenty grams of methylamino-acetonitrile[10] was heated with 30 g. of acetic anhydride in benzene solution for thirty minutes. The solution was then evaporated to remove the solvent, the reaction product dissolved in cold saturated alcoholic ammonia, and the resulting solution saturated with hydrogen sulfide. We obtained 16 g. of thio-amide which crystallized from hot water in prismatic crystals melting at 156–157°. The compound is soluble in hot water or in alcohol and insoluble in ether.

Anal. Calcd. for $C_5H_{10}ON_2S$: N, 19.17. Found: N, 19.28, 19.21.

2-α-Acetamino-isopropyl-4-(3,4-dihydroxyphenyl)-thiazole,

$(HO)_2C_6H_3C{=}CHSC(C(CH_3)_2NHCOCH_3){=}N$.—α-Amino-*iso*butyronitrile was first prepared according to the method of Biltz and Slotta.[11] This was then acetylated[12] according to Hellsing's directions and from the acetyl compound was prepared the thio-amide by saturation in alcoholic ammonia solution with hydrogen sulfide. From 20 g. of the acetylated nitrile we obtained 14 g. of the thio-amide melting at 185–186°. Hellsing reports a melting point of 162°.

Five grams of this thio-amide and 5.6 g. of chloro-acetocatechol in 20 cc. of absolute alcohol were heated at the temperature of a boiling water-bath for thirty minutes. After cooling the hydrochloride of the thiazole was precipitated from this solution by dilution with ether. The yield was 8.0 g. It was purified by reprecipitation from alcohol and melted at 188–189°.

Anal. Calcd. for $C_{14}H_{16}O_3N_2S{\cdot}HCl$: C, 51.1; H, 5.2; N, 8.5. Found: C, 51.2; H, 5.3; N, 8.3.

This salt is readily hydrolyzed by the action of cold water giving the free acetylthiazole. The latter was purified by crystallization from dilute alcohol. It separated in the form of prismatic crystals and melted at 198–200°.

Anal. Calcd. for $C_{14}H_{16}O_3N_2S{\cdot}2H_2O$: N, 8.54; H_2O, 10.97. Found: N, 8.73, 8.51; H_2O, 10.78.

2-α-Amino-isopropyl-4-(3,4-dihydroxyphenyl)-thiazole,

$(HO)_2C_6H_3C{=}CHSC(C(CH_3)_2NH_2){=}N$.—Eight grams of the above hydrochloride of the acetylthiazole was digested with 50 cc. of strong hydrochloric acid for one hour. The hydrochloride of the aminothiazole began to separate from the solution almost immediately. We obtained 6 g. of the salt, which was purified by precipitating from alcohol solution with ether and recrystallization from hydrochloric acid. It melted with decomposition at 210–215°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2S{\cdot}HCl{\cdot}H_2O$: N, 8.21; H_2O, 5.28. Found: N, 8.30, 8.50; H_2O, 5.17.

[10] Heimrod, *Ber.*, **47**, 347 (1914).

[11] Biltz and Slotta, *J. prakt. Chem.*, **113**, 241 (1926).

[12] Hellsing *Ber.*, **37**, 1924 (1904).

The thiazoles recorded in Table I were also prepared in the course of our research.

TABLE I

INCIDENTAL THIAZOLE COMPOUNDS

No.	Thiazole	Formula
1	2-Acetylmethylaminomethyl-4-(3,4-dihydroxyphenyl)-hydrochloride	$(HO)_2C_6H_3\overline{C{=}CHSC(CH_2N(CH_3)COCH_3){=}N}\cdot HCl$
2	2-Methylaminomethyl-4-(3,4-dihydroxyphenyl)-	$(HO)_2C_6H_3\overline{C{=}CHSC(CH_2NHCH_3){=}N}\cdot C_2H_5OH$
3	2-Mercapto-4-(3,4-dihydroxyphenyl)-	$(HO)_2C_6H_3\overline{C{=}CHSC(SH){=}N}\cdot H_2O$[a]
4	2-Phenyl-4-(3,4-dihydroxyphenyl)-	$(HO)_2C_6H_3\overline{C{=}CHSC(C_6H_5){=}N}$
5	2-Amino-4-(3,4-dihydroxyphenyl)-hydrochloride	$(HO)_2C_6H_3\overline{C{=}CHSC(NH_2){=}N}$[b]
6	2-Methylamino-4-(3,4-dihydroxyphenyl)-hydrochloride	$(HO)_2C_6H_3\overline{C{=}CHSC(NHCH_3){=}N}\cdot HCl$

[a] From ammonium dithiocarbamate and chloro-acetocatechol.

[b] From thiourea and chloro-acetocatechol.

No.	Formula	M. p., °C.	Nitrogen analyses Calcd., %	Found, %	
1	$C_{13}H_{15}O_3N_2SCl$	186–188	8.90	8.85	9.11
2	$C_{11}H_{12}O_2N_2S\cdot C_2H_5OH$	128–130[a]	9.93	9.92	10.01
3	$C_9H_7O_2NS_2\cdot H_2O$[b]	250	5.76	5.76	5.72
4	$C_{15}H_{11}O_2NS$	164–165	4.86	4.56	4.69
5	$C_9H_9N_2SCl\cdot H_2O$[c]	230–235	10.7	10.6	
6	$C_{10}H_{11}O_2N_2SCl$[d]	275–280	10.8	10.5	

[a] Hydrochloride m. p., 220–225°. [b] H_2O, calcd.: 7.41. Found: 7.37. [c] Calcd.: C, 41.1; H, 4.2. Found: C, 41.6; H, 4.3. [d] Calcd.: C, 46.4; H, 4.3. Found: C, 46.8; H, 4.3.

Summary

1. The halogenated ketone ω-chloro-acetocatechol, $ClCH_2COC_6H_3(OH)_2$, has been shown to interact smoothly with organic compounds containing thio-amide groupings.

2. These condensations lead to the formation of new thiazoles containing the catechol group in position 4 of the thiazole cycle.

3. In this paper we have given methods for preparing several new aminothiazoles. All of these compounds thus far examined have been found to be physiologically active.

4. They are characterized by their stability in the air, notwithstanding the presence of a catechol grouping in their respective molecules.

5. This research on thiazoles is being continued in this Laboratory. It will include a study of the pharmacology of our new synthetic compounds.

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