[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

SYNTHESIS OF THIAZOLES CONTAINING PHENOL AND CATECHOL GROUPS. II

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Several thiazoles containing the catechol grouping have been described in a recent paper from this Laboratory by Johnson and Gatewood.[2] In all of these combinations the catechol nucleus occupied Position 4 of the thiazole cycle. This series of thiazole-phenol combinations has now been increased by the synthesis of the twelve new derivatives recorded in Table I of this paper. The object has been to obtain for pharmacological study a series of aromatic derivatives containing the phenolic nucleus in both positions, 2 and 4, of the thiazole ring. Especially interesting are the different catechol combinations, which are characterized by their remarkable stability.

The halogenated ketones which have been employed in this research have been chloro-acetocatechol, bromo-acetal and chloro-acetone. By interaction of these halides with the required thioamide combinations all the thiazoles recorded have been synthesized by a general method of preparation. Every one of these new thiazoles has proved to be a crystalline substance of marked stability, and all are sufficiently basic to form characteristic hydrochlorides.

The catechol derivatives of thiazole containing amino groupings thus far examined pharmacologically have shown a lower toxicity than adrenaline when injected into the albino rat intravenously and subcutaneously. Their toxicity appears to increase with the size of the molecule. Also they are rapidly absorbed when administered by the stomach and produce the same pharmacologic action as when injected intravenously or subcutaneously. Their relatively low toxicity and the absence of marked vasoconstricting, pathological lesions in the experimental animals indicate that their blood pressure raising action is not comparable with that of adrenaline. All the thiazoles of this series thus far examined have a definite analgesic and anesthetic action. This action apparently decreases with the size of the molecule. The preliminary pharmacological study of our thiazoles has been carried out in the laboratories of the donors of the Metz Fellowship,[3] and we desire to express here our appreciation of this coöperation.

Experimental Part

The thiazoles described in Table I were all prepared according to the general method by digestion of a thioamide with the required halogenated

[1] Holder of the Metz Research Fellowship 1928–1929.

[2] Johnson and Gatewood, THIS JOURNAL, 51, 1815 (1929).

[3] Metz Research Laboratories in New York City.

ketone combination. The thioanisamide used was prepared according to the method of Rehländer,[4] and the anisonitrile synthesized as described by Hantzsch.[5] Demethylation of aromatic ether constructions to obtain the corresponding free phenols was accomplished by heating the thiazole with a 48% aqueous solution of hydrobromic acid, or by the action of the same reagent on the respective thiazole in glacial acetic acid.

Piperonylthio-amide, $CH_2O_2C_6H_3CSNH_2$.—This was obtained by heating the corresponding nitrile in an alcohol solution of ammonium sulfhydrate at 100°. The yield was 81% and the amide crystallized from alcohol in plates which melted at 180°.

Anal. Calcd. for $C_8H_7O_2NS$: N, 7.73. Found: N, 7.61, 7.64.

3,4-Dihydroxybenzonitrile, $(HO)_2C_6H_3CN$, was prepared from piperonylcyanide and phosphorus pentachloride;[6] yield, 75%.

3,4-Dihydroxythiobenzamide, $(HO)_2C_6H_3CSNH_2$.—This was prepared by addition of hydrogen sulfide to the above nitrile. The reaction takes place by heating in alcohol solution at 100°. The yield of crude thioamide was 80%. The compound crystallizes from hot water in the form of plates which melt at 153–154°. The water solution of the thiazole gives a deep green coloration when mixed with ferric chloride solution.

Anal. Calcd. for $C_7H_7O_2NS$: N, 8.28. Found: N, 8.10, 8.17.

TABLE I

NEW THIAZOLE COMPOUNDS

No.	Thiazole	Reagents	Yield, %
1	2-(*p*-Methoxyphenyl)-[a]	Bromo-acetal and thioanisamide	..
2	2-(*p*-Hydroxyphenyl)-[b]	Demethylation of 1 with 48% HBr	..
3	2-(*p*-Methoxyphenyl)-4-methyl-[b,c]	Chloro-acetone and thioanisamide	90
4	2-(*p*-Hydroxyphenyl)-4-methyl-	.....	..
5	2-(*p*-Methoxyphenyl)-4-(3,4-dihydroxyphenyl)-[d]	Chloro-acetocatechol and thioanisamide	..
6	2-(*p*-Hydroxyphenyl)-4-(3,4-dihydroxyphenyl)-[e]	.....	..
7	2-(3,4-Dihydroxyphenyl)-4-(3,4-dihydroxyphenyl)-[f]	Chloro-acetocatechol and 3,4-Dihydroxythiobenzamide	80
8	2-(3,4-Dihydroxyphenyl)-	Bromo-acetal and Piperonylthioamide	..
9	2-(3,4-Dihydroxyphenyl)-4-methyl-	Chloro-acetone and Piperonylthioamide	..
10	2-(3,4-Methylene-dihydroxyphenyl)-[g]	Bromo-acetal and 3,4-Dihydroxythiobenzamide	..
11	2-(3,4-Methylene-dihydroxyphenyl)-4-methyl-[h]	Chloro-acetone and 3,4-Dihydroxythiobenzamide	91
12	2-(3,4-Methylene-dihydroxyphenyl)-4-(3,4-dihydroxyphenyl)-[i]	Chloro-acetocatechol and Piperonylthioamide	90

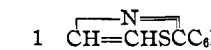
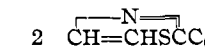
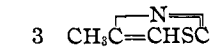
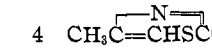
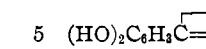
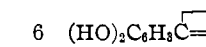
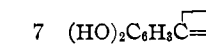
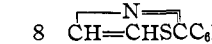
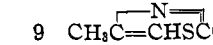
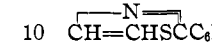
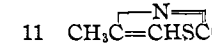
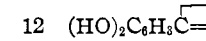
[a] B. p. 156–158° at 6 mm. [b] HCl salt contains one-half molecule of EtOH. [c] B. p. 168° at 7 mm. [d] Contains $2H_2O$ (10.54%). [e] Needles. Contains $2H_2O$ (11.35%). [f] Contains $1H_2O$ (6.1%). [g] Plates. [h] Needles from alcohol. HCl salt contains 1EtOH (4.64%). [i] Contains $2H_2O$, m. p. 135°.

[4] Rehlander, *Ber.*, **27**, 2159 (1894).

[5] Hantzsch, *ibid.*, **24**, 41 (1871).

[6] Ewins, *J. Chem. Soc.*, **95**, 1487 (1909).

TABLE I (*Concluded*)

No.	Formula	Analyses, % N	Analyses, % Cl(HCl)	M. p., °C.	Hydrochloride Yield, %	Hydrochloride M. p., °C.
1		7.24 7.25	15.5 ...	12–15	73 ..	167–169 .....
2		7.82 7.82	14.92 ...	163–165	..	178–180
3		6.86 6.76	12.60 13.42	57[a]	..	130–132
4		7.47 7.36	15.3 ...	220–221[b]	90	250–253
5		4.61 4.66	10.42	154–155	..	106–208
6		4.83 4.84	10.65 ...	212–213	..	.....
7		4.37 4.52	... ...	207	.. ..	....
8		7.39	...	181	..	215–218
9		6.74	...	.....	..	250
10		6.69 6.73	14.23 14.36	84–85	..	216
11		6.25 6.37	11.98 ...	94–95	..	.....
12		4.04 4.10	3.80 3.86	185[c]	..	212–216

[a] From petroleum ether. [b] From alcohol. [c] Anhydrous base.

Summary

1. Twelve new thiazoles containing aromatic groups in Positions 2 or 4 of the thiazole cycle have been synthesized.

2. The object of the work was to obtain aromatic combinations containing phenolic groups and especially the catechol derivatives, and to compare their pharmacological behavior with that of adrenaline.

3. All the compounds thus far studied have exhibited such marked physiological properties that the investigation of this series of compounds will be continued.

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