malonic acid VI to form the propionic acid VII are easily accomplished by the usual organic technique and the yield in each operation is excellent. Formation of the hydrazide IX is brought about by refluxing the ester VIII in alcohol with 50% hydrazine hydrate solution. Complete transformation requires about twelve hours of digestion on a steam-bath.

Formation of the Amine XIII from Its Phthalimide.—The phthalimide XII is formed by heating the urea XI with phthalic anhydride at 220–225° as long as carbon dioxide is evolved. The imide is then decomposed by digestion in alcohol with 40% hydrazine hydrate solution and the amine XIII obtained in the form of its hydrochloric acid salt. Conversion of this methoxy compound into the free phenolic amine XIV was brought about by refluxing the base XIII for three hours with 48% hydrobromic acid solution. The amine XIV was obtained as an oil which showed no signs of solidifying on standing and was preserved in the form of its hydrochloric acid salt. Attempts to convert the urea XI directly into the amine XIV by digestion with 48% hydrobromic acid were unsuccessful.

Summary

1. *Sym.*-dichloro-acetone and thioanisamide interact in alcohol solution to form the compound 2-*p*-methoxyphenylthiazole-4-chloromethyl.
2. This halide has been incorporated into malonic ester and the resulting product converted by a standard series of reactions into a bridged thiazole derivative of tyramine, namely, 2-*p*-hydroxyphenylthiazole-4-ethylamine.
3. Eleven new thiazole compounds have been described.

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[Contribution from the Department of Chemistry, Yale University]

THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. VI

By W. S. Hinegardner[1] and T. B. Johnson

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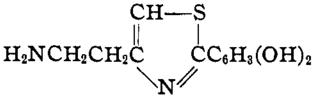
In the development of a practical method for synthesizing a bridged thiazole amine of the adrenaline type we undertook first the preparation of the thiazole amine expressed structurally by formula II. It was important, during the progress of our work, to compare the pharmacological activity of this base with that of 3,4-dihydroxyphenylethylamine I already described by Mannich and Jacobsohn.[2]

$(HO)_2C_6H_3CH_2CH_2NH_2$

I



II

The method of synthesis utilized by us for obtaining this interesting amine is an extension of the technique previously applied for the preparation of the corresponding bridged thiazole derivatives of phenylethylamine

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[1] Metz Research Fellow in Organic Chemistry, 1928–1929.

[2] Mannich and Jacobsohn, *Ber.*, **43**, 189 (1910); also *J. Chem. Soc.*, **97**, 2254, 2257 (1911).

and tyramine. The starting points were vanillin and dichloro-acetone. The vanillin was first methylated according to the procedure of Barger and Silberschmidt,[3] and converted into the oxime of methylvanillin. Veratrol nitrile was then prepared and converted by the action of hydrogen sulfide into 3,4-dimethoxythiobenzamide. When this thioamide and dichloro-acetone were warmed together in alcohol solution, an immediate reaction took place with formation of the primary halide, 2-(3,4-dimethoxyphenylthiazole)-4-chloromethyl, III, in excellent yield.

Table I

Nomenclature and Constitution

III	2-(3,4-Dimethoxyphenylthiazole)-4-chloromethyl	$ClCH_2TC_6H_3(OCH_3)_2$
IV	Diethyl 2-(3,4-dimethoxyphenylthiazole)-4-methyl malonate	$(C_2H_5OOC)_2CHCH_2TC_6H_3(OCH_3)_2$
V	2-(3,4-Dimethoxyphenylthiazole-4-methyl)-malonic acid	$(HOOC)_2CHCH_2TC_6H_3(OCH_3)_2$
VI	2-(3,4-Dimethoxyphenylthiazole)-4-β-propionic acid	$HOOCCH_2CH_2TC_6H_3(OCH_3)_2$
VII	Ethyl 2-(3,4-dimethoxyphenylthiazole)-4-β-propionate	$C_2H_5OOCCH_2CH_2TC_6H_3(OCH_3)_2$
VIII	2-(3,4-Dimethoxyphenylthiazole)-4 β-propionhydrazide	$H_2NNHCOCH_2CH_2TC_6H_3(OCH_3)_2$
IX	2-(3,4-Dimethoxyphenylthiazole)-4-β-propionazide	$N_3COCH_2CH_2TC_6H_3(OCH_3)_2$
X	Di-2-(3,4-dimethoxyphenylthiazole)-4-ethyl-*sym.*-urea	$(CH_3O)_2C_6H_3TCH_2CH_2NHCONHCH_2CH_2TC_6H_3(OCH_3)_2$
XI	2-(3,4-Dimethoxyphenylthiazole)-4-ethyl phthalimide	$C_6H_4(CO)_2NCH_2CH_2TC_6H_3(OCH_3)_2$
XII	2-(3,4-Dimethoxyphenylthiazole)-4-ethylamine	$NH_2CH_2CH_2TC_6H_3(OCH_3)_2$
XIII	2-(3,4-Dioxyphenylthiazole)-4-ethylamine	$NH_2CH_2CH_2TC_6H_3(OH)_2$

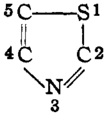
T = Thiazole nucleus 

Table II

Experimental Data

Serial no.	Solvent	Yield, %	M. p., °C.	B. p., °C.	Crystal form	Nitrogen, % Calcd.	Nitrogen, % Found
III	Benzene, ligroin	74	89–90	.....	Prisms	5.19	5.30 5.22
IV	.....	53	.....	251–255 (2–3 mm.)	.....	3.56	3.63
V[a]	Alcohol	80	141	.....	Prisms	4.15	4.10
VI	Alcohol	80	94	.....	Needles	4.78	4.74
VII	Alcohol	81	69	220–223 (3 mm.)	Needles	4.36	4.39
VIII	Alcohol	94	162	.....	Needles	14.0	13.8
IX	.....	90	77–78	.....	.....	..	...
X	Alcohol, water	90	165–166	.....	Plates	10.11	10.00
XI	Alcohol	72	143–144	.....	Needles	7.11	7.03
XII	Alcohol	52	Di-hydro-chloride 225–227 55	210–212 (4 mm.)	..... Cl,	10.6 21.03	10.5 20.75

[a] This acid crystallizes with one molecule of water.

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[3] Barger and Silberschmidt, *J. Chem. Soc.*, 133, 2924 (1928).

The different steps of the synthetic process leading up to the amine construction XIII are shown in Table I. The yields in each step are very favorable, and the intermediate compounds can be easily obtained in a high degree of purity.

The conversion of the dimethyl ether represented by formula XII into the amine XIII has not, thus far, been accomplished successfully. Demethylation of this thiazole by the action of hydriodic and hydrobromic acids leads to the formation of the base XIII, but this has not been obtained thus far in a state of purity. For this reason no constants for this compound are reported. The study of this interesting compound and several of its derivatives is being continued. The experimental data characterizing the different thiazoles prepared are recorded in Table II.

Experimental Part

3,4-Dimethoxythiobenzamide $(CH_3O)_2C_6H_3CSNH_2$.—This was prepared by heating veratrol nitrile with an alcohol solution of hydrogen sulfide in an iron bomb at 100° and was easily obtained in a yield of 90% of the theoretical. The amide crystallizes from alcohol in the form of prisms or needles melting at 183°. It is difficultly soluble in alcohol, acetone and benzene and practically insoluble in water. Alcohol is the best solvent for crystallization.

Anal. Calcd. for $C_9H_{11}O_2NS$: N, 7.10. Found: N, 7.08, 7.02.

Preparation of the Hydrazide, VIII.—This is easily obtained by heating the propionate VII in alcohol solution with the required amount of 40% hydrazine hydrate solution for twelve to fifteen hours. Conversion to the corresponding azide is accomplished by diazotization in acetic acid solution. This compound is a very unstable compound when heated above its melting point. By warming the azide in dilute acetic acid solution, almost the theoretical yield of the urea X is obtained. The following steps of the synthesis leading up to the amine XII from this urea do not present any experimental difficulties.

Demethylation of the Amine, XII.—Thus far, conversion of this compound into the hydroxyl compound XIII has not been accomplished successfully. Refluxing with hydriodic and hydrobromic acids leads to complete demethylation, but the base formed is very susceptible to oxidation and the solutions take on a very dark color during the digestion process. Neutralization of the hydrobromic acid solution by potassium hydroxide causes separation of the amine as an oil, which dissolves immediately when the solution is made alkaline. The base was extracted with ether and dried over sodium sulfate. On evaporating the solvent, a brown resinous substance was obtained which could not be distilled without decomposition and also showed no signs of crystallization. Further attempts are being made to purify this base and separate it if possible in the form of its hydrochloride.

Summary

1. 3,4-Dimethoxythiobenzamide has been prepared. This interacts smoothly with dichloro-acetone to form 2-(3,4-dimethoxyphenylthiazole)-4-chloromethyl.

2. This chlorothiazole compound has been transformed by a series of standardized reactions into the new bridged thiazole amine 2-(3,4-di-

methoxyphenylthiazole)-4-ethylamine. The further study of this base is being continued with the object of developing a practical synthesis of the bridged thiazole derivative of 3,4-dihydroxyphenylethylamine represented by formula II in this paper.

3. Ten new thiazole derivatives have been described.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

STUDIES ON THE POLYMETHYLBENZENES. IV. THE PREPARATION AND PHYSICAL PROPERTIES OF PURE PSEUDOCUMENE[1]

BY LEE IRVIN SMITH AND AXEL P. LUND

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The work reported in this paper is a continuation of a research which has for one of its immediate purposes the separation of the isomeric liquid hydrocarbons which result from the methylation of xylene by the method of Friedel and Crafts.[2] In the previous papers reports were made on the pure tetramethylbenzenes, and on penta- and hexamethylbenzenes. This paper deals with pseudocumene (1,2,4-trimethylbenzene), and reports the preparation and purification, together with the freezing point, refractive index and vapor pressure curve of a very pure sample.

Pseudocumene has been obtained from petroleum,[3] but the commercial source is coal tar.[4] However, pseudocumene obtained in this way is always contaminated with mesitylene, and it is very doubtful whether a specimen of the pure hydrocarbon has ever been obtained from any of these sources.

Synthetic pseudocumene has been made in several ways, but the yields were always low and, in addition, most of the methods are open to the objection that isomeric by-products might result. Thus Jacobsen[5] reports that if phorone is heated with phosphorus pentoxide or zinc chloride, some pseudocumene results, but if concd. sulfuric acid be used, only mesitylene results. The decomposition of camphor by zinc chloride is reported to give pseudocumene[6] but these syntheses do not give pure products, nor good enough yields for purposes of preparation.

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[1] Abstracted from a thesis by Axel P. Lund, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science.

[2] Smith and co-workers, I, THIS JOURNAL, **51**, 2994 (1929); II, **51**, 3001 (1929); III, **52**, 1998 (1930); also **48**, 1413 (1926).

[3] Engler, *Ber.*, **18**, 2234 (1885); Markownikow, *Ann.*, **234**, 97 (1886).

[4] Jacobsen, *Ber.*, **9**, 256 (1876); *Ann.*, **184**, 179 (1877); Schultz and Herzfeld, *Ber.*, **42**, 3602 (1909).

[5] Jacobsen, *ibid.*, **10**, 855 (1877).

[6] R. Fittig, Köbrich and Jilke, *Ann.*, **145**, 140 (1868); Reuter, *Ber.*, **16**, 626 (1883).