diluted with ice and ether. The ethereal layer was shaken with sodium carbonate, which extracted benzoic acid, then dried and evaporated. The residue when distilled with steam yielded 0.61 g. of pure benzophenone.

Summary

When tetraphenyl propenone reacts with phenyl magnesium bromide, the principal product is a diphenyl derivative which is formed by 1,4-addition to the system $-CO-C_6H_5$.

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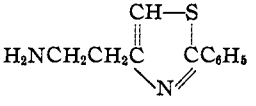
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. V

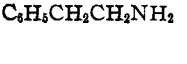
BY W. S. HINEGARDNER[1] AND T. B. JOHNSON

RECEIVED AUGUST 8, 1930 PUBLISHED OCTOBER 6, 1930

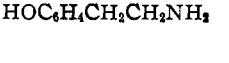
In Paper IV of this series, Hinegardner and Johnson[2] have described the synthesis of 2-phenylthiazole-4-ethylamine, expressed structurally by formula I. This is a representative of a new type of aliphatic amines in which the thiazole nucleus has been substituted for a methylene *radical* in γ-phenylpropylamine. It is a bridged thiazole compound of pharmacological interest and is only one of a series of compounds of its type which may be prepared by our method of synthesis. In this paper we describe a series of intermediate compounds which have been prepared in the develop-



I



II



III

ment of a practical synthesis of 2-*p*-hydroxyphenylthiazole-4-ethylamine, XIV. This latter amine bears the same relationship to tyramine III as the thiazole amine I does to phenylethylamine II. It is a very potent substance biologically and its pharmacological activity is being investigated.

The starting points for our research were *sym.*-dichloro-acetone and the thioamide of anisic acid. These interact smoothly when warmed together in alcoholic solution, giving an excellent yield of the primary halide IV. Utilizing then the same technique as was described in our previous paper[2] for the preparation of the amine I, the various transformations recorded in Table I have been carried through successfully, leading up to the desired amine, XIV. The experimental data establishing the constitution and chemical identity of these various thiazoles are recorded in Table II.

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

[2] Hinegardner and Johnson, THIS JOURNAL, **52**, 3724 (1930).

TABLE I

NOMENCLATURE AND CONSTITUTION

IV	2-*p*-Methoxyphenylthiazole-4-chloromethyl	$ClCH_2T^aC_6H_4OCH_3$
V	Diethyl-2-*p*-methoxyphenylthiazole-4-methyl malonate	$(C_2H_5OOC)_2CHCH_2TC_6H_4OCH_3$
VI	2-*p*-Methoxyphenylthiazole-4-methyl malonic acid	$(HOOC)_2CHCH_2TC_6H_4OCH_3$
VII	2-*p*-Methoxyphenylthiazole-4-β-propionic acid	$HOOCCH_2CH_2TC_6H_4OCH_3$
VIII	Ethyl-2-*p*-methoxyphenylthiazole-4-β-propionate	$C_2H_5OOCCH_2CH_2TC_6H_4OCH_3$
IX	2-*p*-Methoxyphenylthiazole-4-β-propionhydrazide	$H_2NNHCOCH_2CH_2TC_6H_4OCH_3$
X	2-*p*-Methoxyphenylthiazole-4-β-propionazide	$N_3COCH_2CH_2TC_6H_4OCH_3$
XI	Di-(2-*p*-methoxyphenylthiazole-4-ethyl)-*sym.*-urea	$CH_3OC_6H_4TCH_2CH_2NHCONHCH_2CH_2TC_6H_4OCH_3$
XII	2-*p*-Methoxyphenylthiazole-4-ethyl phthalimide	$C_6H_4(CO_2)NCH_2CH_2TC_6H_4OCH_3$
XIII	2-*p*-Methoxyphenylthiazole-4-ethylamine	$NH_2CH_2CH_2TC_6H_4OCH_3$
XIV	2-*p*-Hydroxyphenylthiazole-4-ethylamine	$H_2NCH_2CH_2TC_6H_4OH$

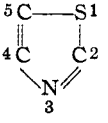
[a] T = Thiazole nucleus, 

TABLE II

EXPERIMENTAL DATA

Serial no.	Solvent	Yield, %	M. p., °C.	B. p., °C.	Crystal form	Nitrogen, % Calcd.	Found
IV	Pet. ether	72	55–56	185–188 (3–4 mm.)	Prisms	5.84	5.85 5.77
V	.....	51.7	.....	235–239 (3–4 mm.)	.....	3.85	3.78
VI[a]	Dil. alc.	85	97	.....	Prisms	4.56	4.48
VII	Alcohol	..	126–127	.....	Needles	5.32	5.28
VIII	Alcohol	95	53–54	.....	.....	4.81	4.90
IX	Dil. alc.	95	158–159	.....	Needles	15.17	15.20
X	.....	94	78–79	.....	.....		
XI	Water	97.4	173–174	.....	Prisms or plates	11.35	11.30
XII	Alcohol	88	120–121	.....	Needles	7.69	7.63
XIII	.....	85	.....	292–293 (3–4 mm.)	.....	11.96	12.08
XIV	.....	..	Hydrochloride, 218–222	.....	.....	Chlorine, 24.19	Chlorine, 23.85

[a] This acid crystallizes with two molecules of water.

Experimental Part

Thioanisamide was prepared according to the following series of reactions: anisic aldehyde ⟶ anisaldoxime ⟶ anisic nitrile (81%) ⟶ thioanisamide (88.8%). The reaction of this thioamide with dichloro-acetone is easily brought about by warming in alcohol solution, and the product of reaction IV can be purified by crystallization or distillation.

Preparation of the Malonate, V.—In the preparation of this ester we were not troubled with the formation of a disubstitution derivative of the malonic ester when the chloride IV was used as was observed in the first synthesis applied by Hinegardner and Johnson.[2] For this reason the yield of our primary malonic ester V was better than that in our previous work. Saponification of the ester and decarboxylation of the resulting

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.

NEW HAVEN, CONNECTICUT

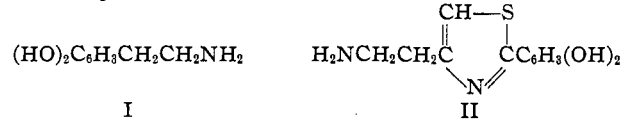
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. VI

BY W. S. HINEGARDNER[1] AND T. B. JOHNSON

RECEIVED AUGUST 8, 1930 PUBLISHED OCTOBER 6, 1930

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]



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

[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).