2. All of the substances except those derived from the butyl ether of ethylene glycol have good solvent power for nitrocotton.

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THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. IV

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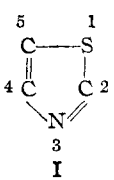
RECEIVED JULY 10, 1930 PUBLISHED SEPTEMBER 5, 1930

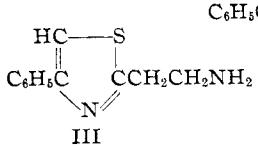
By bridging from carbon to carbon with a thiazole nucleus I in an aliphatic chain compound, it is theoretically possible to introduce structural features which make it practicable to study, from new points of view, the relationship between chemical constitution and physiological and pharmacological action. The thiazole nucleus I is chosen for such heterocyclic constructions because it contains both sulfur and nitrogen in cyclic linkage, and is a heterocycle which does not show high toxic effects when introduced into living organisms. Three distinct positions are available for carbon substitution in the ring (2,4,5), making it possible to obtain by synthesis interesting structural isomers for biological and clinical work. Furthermore, the thiazole cycle is a construction containing a stable molecular configuration with fixed positions for the cyclic double bonds and with no possibility of structural alterations corresponding to lactam $\rightleftharpoons$ lactim or keto $\rightleftharpoons$ enol tautomeric changes. These same considerations apply also to heterocyclic combinations containing oxygen and selenium substituted in place of the thiazole sulfur, which will finally be included in our research program.



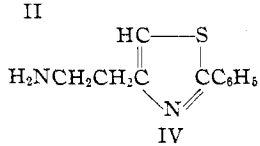
I

The organic constructions which are receiving our attention at present are the bridged thiazole derivatives of bases of the phenylethylamine type, II. It is a well-known fact that nucleus and side-chain substitutions in this base bring about pronounced physiological effects leading to products of therapeutic value. Our program calls for the study of compounds in which the aliphatic part is linked to the benzene nucleus by the thiazole ring, giving heterocyclic amines corresponding in structure to formulas III and IV. In this paper we shall report a practical procedure for preparing the new amine IV. In a later paper we shall describe a practical method for synthesizing the isomeric compound expressed by formula III.

$C_6H_5CH_2CH_2NH_2$ II



III



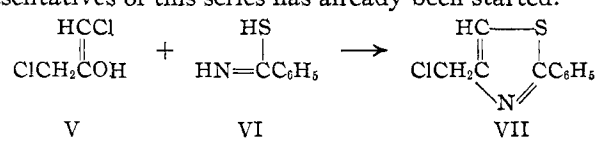
IV

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

All the amines of this type, so far studied biologically, have been shown to be substances of decided pharmacological interest.

The starting points for this research were the halogenated ketone, *sym.*-dichloro-acetone V and thiobenzamide[2] VI. So far as the authors are aware, this halogen compound has been used hitherto for thiazole syntheses only by Suter and Johnson.[3] By interaction with thioamides it makes possible the preparation of interesting chlorine compounds, VII, containing the halogen in an aliphatic side chain or reactive position and useful for fundamental syntheses involving the application of the principle of alkylation.

Our method of operating has been to apply a malonic ester synthesis with the thiazole halide VII, obtaining first the ester VIII. In this operation a small amount of the disubstitution product IX is always formed. These esters are then saponified to form the corresponding malonic acids X and XI, and finally converted to the respective acetates XII and XIV according to fundamental organic technique. The hydrazides XVI and XXI and corresponding azides XVII and XXII are then prepared and the latter transformed into the two ureas represented by formulas XVIII and XXIII. In order to obtain the corresponding amines these ureas are then fused with phthalic anhydride according to the technique of Manske and Ing[4] forming the phthalimide derivatives XIX and XXIV and the latter then converted into the required amines by treatment with hydrazine. In this manner we have prepared successfully the 2-phenylthiazole-4-ethylamine IV (XX in Tables I and II) and the interesting derivative of isopropylamine, namely, di-(2-phenylthiazole-4)-1,3-isopropylamine represented by formula XXV. The various compounds prepared in the course of our work and the fundamental experimental data identifying and characterizing the respective thiazoles synthesized are recorded in the two tables, I and II, respectively. A preliminary pharmacological study of these two amines together with other representatives of this series has already been started.



V VI VII

TABLE I

NOMENCLATURE AND CONSTITUTION (T = THE THIAZOLE NUCLEUS I)

VIII	Diethyl 2-phenylthiazole-4-methyl-malonate	$(C_2H_5OOC)_2CHCH_2TC_6H_5$
IX	Diethyl di-(2-phenylthiazole-4-methyl)-malonate	$(C_2H_5OOC)_2C(CH_2TC_6H_5)_2$
X	2-Phenylthiazole-4-methyl-malonic acid	$(HOOC)_2CHCH_2TC_6H_5$

[2] Gabriel and Heymann, *Ber.*, **23**, 158 (1890).

[3] Suter and Johnson, Paper III, to appear in *Rec. trav. chim* (1930).

[4] Manske and Ing, *J. Chem. Soc.*, **128**, 2348 (1926); Manske, THIS JOURNAL, **51**, 1202 (1929).

TABLE I (*Concluded*)

XI	Di-(2-phenylthiazole-4-methyl)-malonic acid	$(HOOC)_2C(CH_2TC_6H_5)_2$
XII	2-Phenylthiazole-4-β-propionic acid	$HOOCCH_2CH_2TC_6H_5$
XIII	Ethyl 2-phenylthiazole-4-β-propionate	$C_2H_5OOCCH_2CH_2TC_6H_5$
XIV	Ethyl di-(2-phenylthiazole-4-methyl)-acetate	$(C_2H_5OOC)CH(CH_2TC_6H_5)_2$
XV	Di-(2-phenylthiazole-4-methyl)-acetic acid	$HOOCCH(CH_2TC_6H_5)_2$
XVI	2-Phenylthiazole-4-β-propionhydrazide	$H_2NNHCOCH_2CH_2TC_6H_5$
XVII	2-Phenylthiazole-4-β-propionazide	$N_3OCCH_2CH_2TC_6H_5$
XVIII	Di-(2-phenylthiazole-4-ethyl)-*sym.*-urea	$C_6H_5TCH_2CH_2NHCONHCH_2CH_2TC_6H_5$
XIX	2-Phenylthiazole-4-ethyl-phthalimide	$C_6H_4(CO)_2NCH_2CH_2TC_6H_5$
XX	2-Phenylthiazole-4-ethylamine	$H_2NCH_2CH_2TC_6H_5$
XXI	Di-(2-phenylthiazole-4-methyl)-acethydrazide	$H_2NNHCOCH(CH_2TC_6H_5)_2$
XXII	Di-(2-phenylthiazole-4-methyl)-acetazide	$N_3OCCH(CH_2TC_6H_5)_2$
XXIII	Tetra-(2-phenylthiazole-4)-1,3-isopropyl urea	$(C_6H_5TCH_2)_2CHNHCONHCH(CH_2TC_6H_5)_2$
XXIV	Di-(2-phenylthiazole-4)-1,3-isopropyl-phthalimide	$(C_6H_4(CO)_2NCH(CH_2TC_6H_5)_2$
XXV	Di-(2-phenylthiazole-4)-1,3-isopropylamine	$H_2NCH(CH_2TC_6H_5)_2$

TABLE II

EXPERIMENTAL DATA

Number	Solvent	Yield, %	M. p., °C.	B. p., °C.	Crystal form	Nitrogen, % Calcd.	Found	
VII	Petroleum ether	81	31	155–156 (4 mm.)	Prisms	6.68	6.81	6.70
VIII[a]	Petroleum ether	54.1	30–31	218–222 (4–5 mm.)	Prisms	4.24	4.21	4.18
IX	Alcohol	34.7	116		Needles	5.53	5.49	5.51
X	Dil. alc.	98	141–142		Prisms	5.06	5.04	5.00
XI	Dil. alc. or acetone	85	156–157		Prisms	6.22	6.18	
XII	Alcohol	80	83–84		Needles	6.01	6.06	
XIII	Alcohol	86.6	42–43	170–171 (3–4 mm.)	Prisms	5.36	5.35	
XIV	Alcohol	80	61.5–62[b]	272° at (2–3 mm.)	Needles	6.45	6.55	
XV	Alcohol	80	127–128		Needles	6.89	6.81	
XVI	Alcohol	80	142–143		Prisms	17.01	17.3	17.4
XVII		90	72		Needles			
XVIII	Alcohol	85	176–177		Plates	12.90	12.84	
XIX	Alcohol	87	113–114			8.38	8.24	8.34
XX[c]		76		146–147 (2–3 mm.)		13.72	13.71	13.67
XXI		75	Hydrochloride 235–238		Prisms			
XXII	Water	80	80					
XXIII	Alcohol	70	182–183		Prisms	10.76	10.57	10.62
XXIV	Alcohol	80	158–159		Plates	8.28	8.24	8.22
XXV	Alcohol	75	Hydrochloride 235–238		Needles	Cl, 21.89	Cl, 21.94	

[a] By using the sodium salt of diethylmalonate in 50% excess and by carrying on the synthesis at the temperature of boiling alcohol, the yield of the thiazole VIII was easily raised to 70% of the calcd. and with very little formation of the thiazole IX.

[b] Hydrochloride 91–92°.

[6] The monohydrochloride of this amine crystallizes as rhombic plates melting at 171–172° (calcd. Cl, 14.73. Found Cl, 14.77). The dihydrochloride crystalhzes in needles and melts at 206–209°. (Calcd. Cl, 25.59. Found Cl, 25.41, 25.48.)

Experimental Part

2-Phenyl-4-chloromethyl Thiazole, VII.—This halide was prepared according to the method of Suter and Johnson.[3]

Diethyl-2-phenylthiazole-4-methyl Malonate, VIII.—For the preparation of this ester the usual technique applicable for a malonic ester synthesis was employed. By using 50% more than the calculated quantity of diethyl sodium malonate, the yield of monosubstituted ester VIII was raised to the maximum of 70%. The balance of the reaction product is the disubstituted ester IX, which is obtained in the form of a crystalline solid. This deposits from the crude ester reaction product on cooling at a low temperature. Both esters were carried through the same series of reactions and converted into the corresponding amines XX and XXV.

Saponification of these two esters with alcoholic potassium hydroxide led smoothly to the formation of the corresponding malonic acids. The latter on heating above their respective melting points are converted into the acetic acids XII and XV.

Preparation of the Hydrazides, XVI and XXI.—These are formed in excellent yields by digesting the esters XIII and XIV in alcohol with a slight excess of 40% hydrazine hydrate solution. The reaction requires for completion twenty to thirty hours of heating and the hydrazides are obtained in crystalline form without difficulty.

The hydrazides are converted into their corresponding azides by diazotization in glacial acetic acid solution. The latter were obtained in a crystalline condition and both compounds exploded with violence when heated above their respective melting points.

Summary

1. Using thiobenzamide and 2-phenylthiazole-4-chloromethyl thiazole as starting points in our synthetic research, twenty-four new thiazoles have been prepared.

2. The final products of the series of reactions recorded in this paper are the bridged thiazole amines—2-phenylthiazole-4-ethylamine and di-(2-phenylthiazole-4)-1,3-isopropylamine. Both of these bases are physiologically active substances.

3. Our work on thiazole amines is being continued.

NEW HAVEN, CONNECTICUT