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SYNTHESIS OF 5-SUBSTITUTED 2-CHLORO-7-METHYLIMIDAZO[1,2-a]PYRIMIDINE AND THEIR BACTERIAL AND FUNGICIDAL ACTIVITY

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The compounds 2-alkyl (aryl-, heteryl-) substituted and 2,5-disubstituted imidazo[1,2-a]pyrimidines display antibacterial, antiprotozoal, antipyretic [1], diuretic [2], hypotensive [3], and antistrychnine [4] activity. However, the biological properties of 2,5-substituted amino-, R-amino, alkoxy-, aryloxy-imidazo [1,2-a]pyrimidine have not been studied probably because they cannot be prepared by known methods [5]. Alkylation of unsymmetric aminopyridines with halogen carbonyl reagents or condensation of aminoimidazoles with 1,3-dicarbonyl compounds [7] generally give mixtures of isomers which are difficult to separate. We have developed a method for the preparation of 2-chloro-5-H-(hydroxy-, alkoxy-, amino-)-7-methylimidazo-[1,2-a]pyrimidine from 2,5-dichloro-7-methylimidazo[1,2-a]pyrimidine which is free from these disadvantages.

The aim of the present work was to synthesize some 5-substituted 2-chloro-7-methylimidazo[1,2-a]-pyrimidines and to study their biological properties. The starting compound 2,5-dichloro-7-methylimidazo-[1,2-a]pyrimidine (III) was synthesized by reacting 2,3,5,8(1)-tetrahydro-7-methylimidazo [1,2-a]pyrimidine-2,5-dione (I) or 2-amino-4-methyl-6-oxo-1,6-dihydropyrimidine-1-acetic acid (II) [6] with phosphorous oxychloride in an organic solvent (e.g. dimethylaniline). The IR spectrum of compound III shows absorption bands at 725 and 760 cm^{-1} corresponding to the stretching vibrations of the CCl group, and at 1620 cm^{-1} due to the C=N bond. Selective attack by a nucleophilic agent is possible on one or both of the electrophilic centers at C_2 and C_5 which are activated by the chlorine atom in compound III. It should be noted that hydrolysis, alkoxylation, and amination of compound III leads to nucleophilic substitution of the chlorine atom at position 5 of the bicyclic ring. Reduction of III with zinc dust proceeds analogously. Nucleophilic substitution of the chlorine atom in position 5 of the imidazopyrimidine system is explained by the lower electronic population of the pyrimidine ring in comparison with the imidazole ring.

To confirm the structures of the compounds synthesized, we reacted 2-chloro-5-phenylamino-7-methylimidazo[1,2-a]pyrimidine (IX) and thiourea to give 5-phenylamino-7-methylimidazo[1,2-a]pyrimidine-2(3H)-thione (XI) which owing to the presence of active hydrogens in the methylene group at position 3 forms the ilidene derivative XII.

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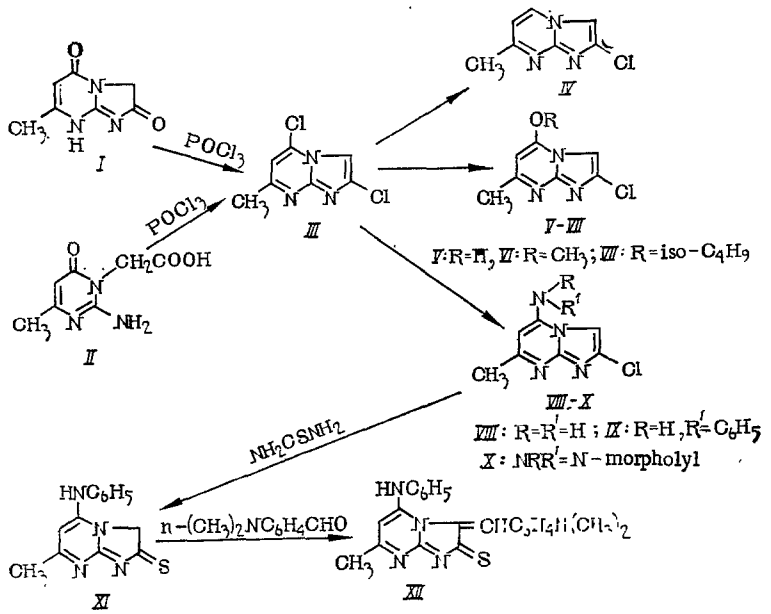

The reaction products III-XII, the characteristics of which are given in Table 1, are white (III-XI) or violet (XII) crystalline substances, readily soluble in organic solvents, and soluble with difficulty in water.

EXPERIMENTAL

Pharmacological

The antimicrobial activity of the compounds against several types of bacteria and fungi was determined using the method of serial dilution in liquid nutrient medium [7]. The minimum bacteriostatic concentrations were: against Staphylococcus aureus (No. 209), 500 μg/ml of compounds III and V; against E. coli (M-17), 250-500 μg/ml of compound VII-IX; against Bacillus pyocyaneus 125-250 μg/ml of compounds III-X; against anthrax 250 μg/ml of compounds III, V, and VII-X, and 500 μg/ml of compound XI. Fungicidal action against the yeast-like fungus Candida albicans is displayed by 5-substituted 2-chloro-7-methylimidazo[1,2-a] pyrimidine at a concentration of 62.5-250 μg/ml. It should be noted that these compounds possess moderate activity against gram-positive and gram-negative microorganisms.

Chemical

IR spectra were taken as mineral oil mulls on a UR-20 spectrophotometer. UV spectra were taken on a SF-4A spectrophotometer.

2,5-Dichloro-7-methylimidazo[1,2-a]pyrimidine (III). A. To a mixture of 20 ml of dimethylaniline and 20 ml of phosphorus oxychloride was added cautiously (evolution of heat) 11.5 g (70 mmole) of compound I. After 10-12 h at room temperature the reaction mixture was poured into 200-250 g of ice, and a 20% sodium hydroxide solution added until the pH was 5.0-6.0. The product III was extracted with chloroform (4 times, 100 ml), the chloroform extracts dried over anhydrous magnesium sulfate, filtered and passed through an aluminum oxide column (400× 40 mm) and eluted with 100 ml of chloroform. The chloroform was evaporated and the residue washed with a small quantity of ether.

B. Compound III was obtained in 41% yield from II using the conditions described in method A.

2-Chloro-7-methylimidazo[1,2-a]pyrimidine (IV). Zinc dust (20 g) was added to a solution of 4.04 g (20 mmole) of compound III in 60 ml of 50% ethanol, and the mixture refluxed for 15 hours. The cooled solution was filtered, the filtrate evaporated to dryness in vacuum and the residue washed with water.

2-Chloro-5-hydroxy-7-methylimidazo[1,2-a]pyrimidine (V). To a solution of 0.8 g (20 mmole) of sodium hydroxide in 20 ml of water was added 2.02 g (10 mmole) of compound III. The mixture was heated for 20-30 min (until III dissolves), cooled, a 10% solution of hydrochloric acid added to bring the solution to pH 4.0-5.0, and the precipitate filtered off and washed with water.

2-Chloro-5-methoxy-7-methylimidazo[1,2-a]pyrimidine (VI). To a solution prepared from 0.23 g (10 mmole) of sodium metal and 15 ml of methanol was added 2.02 g (10 mmole) of compound III and the

TABLE 1. 5-Substituted 2-Chloro-7-methylimidazo[1,2-a]pyrimidines III-XII

Compound	Yield, %	Melting point, °C	UV spectra, λ_{max} (log ε) (in C_2H_5OH)	Found, %				Empirical formula	Calculated, %			
				C	H	Cl	N		C	H	Cl	N
III*	51.11	160—2	234 (4,[illegible]), 288 (4,60), 317 (4,65)	41,8	2,8	34,6	21,1	$C_7H_5Cl_2N_3$	[illegible],6	2,5	35,0	20,8
IV	[illegible]	203—5	228 (4,[illegible]), 314 (3,63), 385 (3,56)	[illegible],8	3,8	21,3	24,7	$C_7H_6Cl_2N_3$	[illegible],1	3,6	21,2	26,0
V	92	274—6	302 (4,[illegible])†	[illegible],7	3,1	19,0	23,2	$C_7H_6ClN_3O$	[illegible],8	3,3	19,3	22,9
VI	83	185—7	—	[illegible],9	3,9	17,9	21,5	$C_8H_8ClN_3O$	[illegible],6	4,1	17,9	21,3
VII	[illegible]	81—[illegible]	—	[illegible],5	6,2	14,6	17,3	$C_{11}H_{14}ClH_3O$	[illegible],1	5,9	14,8	17,5
VIII	[illegible]	[illegible]—0	[illegible] (4,38), 302 (3,78)	[illegible],4	4,1	19,7	30,7	$C_7H_7ClH_4$	[illegible],0	3,9	19,4	30,7
IX	85	[illegible]—2	[illegible] (4,47), 316 (4,31)	[illegible],6	1,8	12,7	20,1	$C_{13}H_{11}ClH_4 \cdot H_2O$	[illegible],4	4,7	12,8	20,2
X	11	[illegible].8—[illegible]0	[illegible] (4,[illegible]), 248 (4,90), 269 (4,39), 323 (4,39)	[illegible],7	5,6	14,3	22,4	$C_{11}H_{13}ClH_4O$	[illegible],3	5,2	14,0	22,2
XI	77	[illegible]—[illegible]	[illegible] (4,[illegible])	—	—	—	21,5	$C_{13}H_{12}N_4$‡	—	—	—	21,9
XII	85	[illegible]—5	[illegible] (4,01), 334 (3,82)	—	—	—	18,4	$C_{22}H_{21}N_5$ **	—	—	—	18,1

*Compounds III-VI were recrystallized from water, VII from 20% methanol, VIII from dioxane, IX from 40% ethanol, X from a mixture of dioxane and water (1 : 3), XI and XII from a mixture of dioxane and water (2 : 1).

†UV spectrum taken in DMFA.

‡Found, %: S 12.8. Calculated, %: S 12.5.

**Found, %: S 8.1. Calculated, %: S 8.3.

reaction mixture heated until neutral. The solvent was evaporated and the residue washed with a small quantity of cold water.

2-Chloro-5-isobutoxy-7-methylimidazo[1,2-a]pyrimidine (VII) was prepared from compound III and isobutanol by the same method.

2-Chloro-5-amino-7-methylimidazo[1,2-a]pyrimidine (VIII). A solution of 2.02 g (10 mmole) of compound III in 15 ml of a 15% alcoholic solution of ammonia was refluxed for 1 h (activated charcoal added during the last 5 min). The charcoal was filtered off and the filtrate diluted with 20 ml of water. The product VIII was filtered off and washed with water.

2-Chloro-5-phenylamino-7-methylimidazo[1,2-a]pyrimidine (IX). To a solution of 1.01 g (5 mmole) of compound III in 15 ml of dioxane was added 0.42 g (5 mmole) of aniline. The mixture was refluxed for 15 min, cooled, diluted with 30 ml of water, and the precipitate filtered off.

2-Chloro-5-morpholino-7-methylimidazo[1,2-a]pyrimidine (X) was prepared by the same method.

5-Phenylamino-7-methylimidazo[1,2-a]pyrimidine-2(3H)-thione (XI). A mixture of 1.3 g (5 mmole) of compound IX and 0.76 g (10 mmole) of thiourea in 30 ml of ethanol was refluxed for 2 h, 0.6 g (15 mmole) of sodium hydroxide in 20 ml of water added and refluxing continued for a further 30 min. The solution was concentrated to one-half of its original volume, cooled, and acetic acid added to pH 6.0-7.0. The precipitate was filtered off and washed with water.

3-p-Dimethylaminobenzylidene-5-phenylamino-7-methyl-2,3-dihydroimidazo[1,2-a]pyrimidine-2-thione (XII). A mixture of 0.52 g (2.5 mmole) of compound XI, 0.54 h (3 mmole) of p-dimethylaminobenzaldehyde and 0.50 g (6 mmole) of anhydrous sodium acetate in 5 ml of glacial acetic acid was refluxed for 30 min, cooled, and 20 ml of ether added. The precipitate was filtered off, washed with water, and dried.

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