A Study on the Chemical Reactivity of Certain Imidazo[1,2-*c*]pyrimidines (1)

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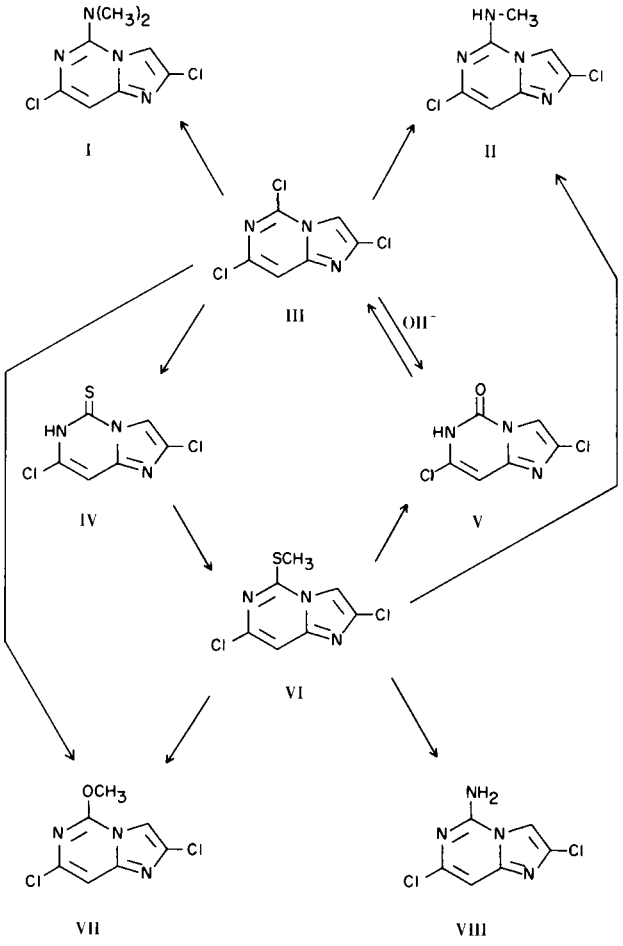
The imidazo[1,2-*c*]pyrimidine ring is a resonance stabilized 10 π electron system and is of interest from the standpoint of chemical reactivity due to the bridgehead nitrogen. The order of susceptibility of the chloro groups of 2,5,7-trichloroimidazo[1,2-*c*]pyrimidine toward nucleophilic displacement was of particular interest. On the basis of previous studies the 5-chloro group will obviously be displaced first. Whether the chloro group residing in the imidazole moiety (C2) or the chloro group residing in the pyrimidine moiety (C7) would be preferentially displaced prompted the present investigation. The results should provide some insight into an approximation of the relative electron distribution in the 5-substituted 2,7-dichloroimidazo[1,2-*c*]pyrimidine derivative being studied by simply establishing which chloro group had been displaced.

The treatment of 2,5,7-trichloroimidazo[1,2-*c*]pyrimidine (III) (2) with aqueous methylamine at reflux temperature afforded a compound which was established by pmr spectroscopy to possess only one methylamino group. Efforts to remove the remaining chloro groups by hydrogenation, which would have proved the site of displacement, were unsuccessful. This prompted us to investigate an alternate proof of structure. Treatment of 2,7-dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI) with methylamine provided a compound which we at first assumed to be a mono chloro, mono methylamine, mono methylthioimidazo[1,2-*c*]pyrimidine. However, pmr spectroscopy revealed only one absorption peak which could be assigned to a methyl group (3). This peak was observed as a sharp doublet at δ 3.05 ($N-CH_3$) and also a broad doublet at δ 8.3 (N–H). There was observed a complete absence of an absorption peak at ~δ 2.5 for the exocyclic methylthio group (4). A more extensive comparison (uv, ir, tlc, etc.) of this compound and II revealed the two compounds to be identical and established that although a chloro group is in general much more susceptible toward nucleophilic displacement than a methylthio group, in this instance the 5-methylthio group had been displaced in preference to the chloro groups at C2 and C7. This same trend was observed when methoxide was used as the nucleophile. Treatment of III and VI with sodium methoxide furnished an identical product (tlc, uv, pmr) which was established

REACTION SCHEME



as 2,7-dichloro-5-methoxyimidazo[1,2-*c*]pyrimidine (VII) by pmr spectroscopy (5). Hydrolysis of the 5-methylthio group of VI was accomplished under acidic and basic reaction conditions to furnish 2,7-dichloroimidazo[1,2-*c*]-5-pyrimidone (V). The pmr spectrum of V revealed sharp singlets at δ 6.84 and δ 7.9 which were assigned to the CH protons at C3 and C8 and a low broad singlet at lower field attributable to the proton on the nitrogen at position six. Exposure of III to basic conditions also furnished a compound identical to V prepared from VI. Treatment of V with phosphorus oxychloride converted V back to the

TABLE I

Ultra Violet Spectral Data of Certain Imidazo[1,2-*c*]pyrimidines

No.	Compound	$\lambda_{m\mu}^{max}$ *p*H 1	ϵ	$\lambda_{m\mu}^{max}$ *p*H 11	ϵ
VI	2,7-Dichloro-5-methylthio-imidazo[1,2-*c*]pyrimidine (a)	302	8,900	306	6,700
		287	10,000	286	8,650
		241	21,500	241	20,100
VIII	5-Amino-2,7-dichloro-imidazo[1,2-*c*]pyrimidine	296	12,200	286	12,800
II	2,7-Dichloro-5-methylamino-imidazo[1,2-*c*]pyrimidine	304	13,500	290	15,400
		274	9,100	224	23,400
VII	2,7-Dichloro-5-methoxy imidazo[1,2-*c*]pyrimidine	277	14,400	275	13,300
V	2,7-Dichloroimidazo[1,2-*c*-5-pyrimidone	281	14,300	287	14,300
III	2,5,7-Trichloroimidazo-[1,2-*c*]pyrimidine (a)	228	21,000	205	13,000
		278	8,200	284	10,400
		305 (s)	4,200		
I	2,7-Dichloro-5-dimethylamino-imidazo[1,2-*c*]pyrimidine	308	12,700	298	12,700
		233	21,500	236	17,800
IV	2,7-Dichloroimidazo[1,2-*c*]-pyrimidin-5-thione	317	13,000	321	12,900
		254	11,400	252	20,000

(a) Ethanol spectrum reported in Reference 2.

starting material III. Nucleophilic displacement of the 5-chloro group of III was also effected by thiourea in aqueous ethanol to furnish 2,7-dichloroimidazo[1,2-*c*]-pyrimidin-5-thione (IV). That the 5-chloro group had been preferentially replaced was established unequivocally when methylation of IV furnished a compound identical to VI prepared by a previous method. The preparation of 2,7-dichloro-5-dimethylaminoimidazo[1,2-*c*]pyrimidine (I) was accomplished by treatment of III with 40% aqueous dimethylamine. The treatment of VI with aqueous ammonia in a sealed reaction vessel once again effected a preferential displacement of the 5-methylthio group to furnish 5-amino-2,7-dichloroimidazo[1,2-*c*]pyrimidine (VIII). The pmr spectrum of VIII revealed two sharp singlets at δ 6.85 and δ 8.05 for the protons at C3 and C8 and a low broad singlet at δ 8.15 which was assigned to the exocyclic amino group at C5. Therefore, the nucleophilic displacement of a chloro group at C2 and C7 was not effected even under forcing conditions while there was observed a facile nucleophilic displacement of a chloro group and even a methylthio group at C5.

EXPERIMENTAL (6)

2,7-Dichloro-5-dimethylaminoimidazo[1,2-*c*]pyrimidine (I).

2,5,7-Trichloroimidazo[1,2-*c*]pyrimidine (III, 2.5 g.) was suspended in 40% aqueous dimethylamine (50 ml.) and the suspension heated at reflux temperature with stirring for 2 hours. Methanol (25 ml.) was added to effect a clear solution which was then heated until a precipitate began to form. The reaction mixture was allowed to cool at room temperature for several hours and the solid was collected to yield 1.8 g. of product which could be precipitated from methanol-water, m.p. 103-105°.

Anal. Calcd. for $C_8H_8Cl_2N_4$: C, 41.60; H, 3.49; N, 24.20. Found: C, 41.58; H, 3.70; N, 24.25.

2,7-Dichloro-5-methylaminoimidazo[1,2-*c*]pyrimidine (II).

Method 1.

2,7-Dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI, 1 g.) was dissolved in methanol (100 ml.) and to this solution was added 10 ml. of liquified methylamine in one portion. The reaction mixture was heated at reflux temperature for 5 hours (after 1 hour a solid began to separate from solution). The mixture was allowed to stand at room temperature for 2 hours and the solid collected by filtration. The solid was reprecipitated from methanol with water to yield 0.5 g. of white crystals, m.p. 282-284° dec.

Anal. Calcd. for $C_7H_6Cl_2N_4$: C, 38.70; H, 2.80; N, 25.80. Found: C, 38.60; H, 2.68; N, 25.83.

Method 2.

2,7-Dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI, 1 g.) was suspended in 40% aqueous methylamine (50 ml.) and this mixture then heated at reflux temperature for 30 minutes to afford a solid (0.57 g.) which proved to be identical to the material prepared by method 1 (uv spectra and tlc).

Method 3.

Five hundred milligrams of 2,5,7-trichloroimidazo[1,2-*c*]pyrimidine (III) was suspended in 40% aqueous methylamine (25 ml.) and the reaction mixture heated at reflux temperature for 2.5 hours. The solid was collected by filtration and recrystallized from a methanol-water mixture to yield 0.27 g. of crystals identical to those obtained by method 1 and method 2, m.p. 279-281° dec. The mixture melting point showed no depression and the uv spectra was in agreement with that of the product from method 1.

2,5,7-Trichloroimidazo[1,2-*c*]pyrimidine (III).

2,7-Dichloroimidazo[1,2-*c*]-5-pyrimidone (V, 1.5 g.) was suspended in phosphorus oxychloride (40 ml.) and the suspension heated at reflux temperature for eight hours. The solution was poured onto ice with stirring and the solid which had separated was collected by filtration, dried, and dissolved in ethyl ether (200 ml.). The ether solution was washed with water (2 x 50 ml.), and the ethereal solution dried over sodium sulfate. The solution was evaporated to dryness *in vacuo* and the solid residue recrystallized from cyclohexane to afford 0.55 g. of III, m.p. 123-124.5°. Thin layer chromatography showed this product to be identical to an authentic sample of 2,5,7-trichloroimidazo[1,2-*c*]pyrimidine (2).

2,7-Dichloroimidazo[1,2-*c*]pyrimidine-5-thione (IV).

Two g. of III were suspended in 50% aqueous ethanol (30 ml.) containing thiourea (2 g.) and the suspension heated at reflux temperature for 2 hours. The mixture was then allowed to stand at room temperature for 2 hours and the solid which had separated was collected by filtration to yield 1.04 g. of IV. The product was precipitated from ethanol with water for analysis, m.p. 228-230°.

Anal. Calcd. for $C_6H_3Cl_2N_3S$: C, 32.80; H, 1.37; N, 19.10. Found: C, 32.79; H, 1.52; N, 18.81.

2,7-Dichloroimidazo[1,2-*c*]-5-pyrimidone (V).

Method 1.

Five g. of 2,7-dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI) were suspended in a mixture of ethanol (50 ml.) and 2 *N* sodium hydroxide (50 ml.) and this mixture heated at reflux temperature for 22 hours. The resulting solution was evaporated to dryness *in vacuo* and the residue dissolved in hot water (250 ml.), filtered, and the *p*H of the solution adjusted to 5 with acetic acid. The solid was collected by filtration to yield 3.4 g. of V, m.p. 285-286° dec.

Anal. Calcd. for $C_6H_3Cl_3N_3O$: C, 35.32; H, 1.48; N, 20.60. Found: C, 35.60; H, 1.71; N, 20.40.

Method 2.

2,7-Dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI) (0.5 g.) was suspended in a mixture of 38% aqueous hydrochloric acid (12.5 ml.) and ethanol (12.5 ml.) and the suspension then heated at reflux temperature for 20 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue reprecipitated from dilute aqueous sodium hydroxide with dilute aqueous hydrochloric acid to yield 0.1 g. of product, m.p. 284-285° dec. This product was found to be identical to the compound prepared by method 1 (uv spectra and mixed m.p.).

Method 3.

Five hundred milligrams of III were dissolved in a mixture of 2 *N* sodium hydroxide (12.5 ml.) and ethanol (12.5 ml.) and the mixture heated at reflux temperature for 4 hours. The resulting solution was evaporated to dryness *in vacuo* and the residue precipitated from hot water with acetic acid to yield 0.25 g. of solid identical (by uv and mixed m.p.) to that obtained above, m.p. 285-286°.

2,7-Dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI).

Two hundred mg. of 2,7-dichloroimidazo[1,2-*c*]pyrimidine-5-thione (IV) were dissolved in 10 ml. of 1 *N* sodium hydroxide. To this solution was added methyl iodide (0.1 ml.) and the mixture then stirred at room temperature for 1 hour. The solid which had formed was collected by filtration and washed with water, yield 180 mg. Thin layer chromatography on SilicAR-7 GF in four solvent systems showed this material to be identical to an authentic sample (2) of 2,7-dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine.

2,7-Dichloro-5-methoxyimidazo[1,2-*c*]pyrimidine (VII).

Method 1.

Five hundred milligrams of 2,5,7-trichloroimidazo[1,2-*c*]pyrimidine (III) were dissolved in methanol (50 ml.) containing 0.15 g. of sodium methoxide. This solution was heated at reflux temperature for 8 hours and then evaporated to dryness *in vacuo*. The residue was recrystallized from a methanol-water mixture to yield 0.3 g. of crystalline solid, m.p. 133°.

Anal. Calcd. for $C_7H_5Cl_2N_3O$: C, 38.60; H, 2.31; N, 19.30. Found: C, 38.79; H, 2.53; N, 18.99.

Method 2.

One g. of 2,7-dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI) was dissolved in methanol (30 ml.) containing 0.13 g. of sodium methoxide. This solution was heated at reflux temperature for 5 hours, filtered and 25 ml. of water then added to the filtrate. The solution was allowed to stand at room temperature for 2 hours and the needles collected by filtration. The product was recrystallized from a methanol-water mixture to yield 0.54 g. of product, m.p. 134-135°. This product was shown to be identical to that prepared by method 1 (comparison of uv spectra and mixture melting point).

5-Amino-2,7-dichloroimidazo[1,2-*c*]pyrimidine (VIII).

A suspension of 2,7-dichloro-5-methylthioimidazo[1,2-*c*]pyrimidine (VI, 5.0 g.) in a mixture of 100 ml. of aqueous ammonia (28%) and 100 ml. of ethanol was placed in a sealed reaction vessel and heated to 100° for 4 hours. The solid which had separated from solution after the reaction vessel had cooled to room temperature was collected by filtration to yield 3.04 g. of yellow needles. Recrystallization from 2-propanol furnished a white solid, m.p. dec. >250°.

Anal. Calcd. for $C_6H_4Cl_2N_4$: C, 35.50; H, 1.99; N, 27.60. Found: C, 35.33; H, 1.96; N, 27.64.

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