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Synthesis and Mechanism of Formation of 2,3-Dialkyl-1,2,3,4-tetrahydrophthalazine-1,4-diones by Utilizing an O—N Rearrangement of 1-Alkoxy-3-alkyl-3,4-dihydrophthalazin-4-ones

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The reaction of 1-(2′-hydroxyethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (VII) with thionyl chloride in refluxing chloroform results in formation of 2-(2′-chloroethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (III). The mechanism of the reaction has been investigated and is discussed.

Recently, we wished to prepare 2-(2′-chloroethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (III), the starting material for a series of amino-derivatives required for pharmacological testing. The two most direct methods for preparing this compound appeared to be *via* *N*-alkylation of 1-hydroxy-3-methyl-3,4-dihydrophthalazin-4-one (I) (the compound is best represented by this tautomer [1]), or condensation of phthalic anhydride with an *N*-ethyl-*N*′-methylhydrazine appropriately substituted in the ethyl group. The former method proved to be unsuitable since *O*-alkylation prevailed, this being in agreement with previous findings.[2] The latter method, which is successful with simpler hydrazines,[3,4] also worked here. The hydrazine used in the condensation step, *N*-(2-hydroxyethyl)-*N*′-methylhydrazine, was prepared according to a literature method for preparing symmetrically substituted hydrazines.[5] The starting material, *N*-(2-hydroxyethyl)hydrazine, was dibenzoylated with benzoyl chloride in the presence of aqueous sodium hydroxide to give *N*-(2-hydroxyethyl)-*N*,*N*′-dibenzoylhydrazine. This compound was methylated with dimethyl sulphate and alkali, and the benzoyl groups were subsequently removed by hydrolysis with hydrochloric acid giving *N*-(2-hydroxyethyl)-*N*′-methylhydrazine as its dihydrochloride in an overall yield of 36 %. The condensation of the hydrazine dihydrochloride with phthalic anhydride was carried out in aqueous acetate buffer, resulting in a 40 % yield

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of 2-(2′-hydroxyethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (VI). This compound could then be converted to the required compound III by refluxing with thionyl chloride in chloroform. However, the synthetic procedure is rather tedious and the overall yield from *N*-(2-hydroxyethyl)-hydrazine is only *ca.* 10 %.

Fortunately, the synthetic path was simplified and improved by the timely discovery that compound III could be prepared in a two step synthesis involving an O – N rearrangement from the readily available 1-hydroxy-3-methyl-3,4-dihydrophthalazin-4-one (I). The sodium salt of compound I was *O*-alkylated (*cf.* Ref. 2) with 2-chloroethanol in dimethylformamide affording 1-(2′-hydroxyethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (VII) in 70 % yield. On reacting compound VII with thionyl chloride in refluxing chloroform, the product was not the expected 1-(2′-chloroethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (II), but compound III, identical with that obtained in the unambiguous method described above. The yield was 88 % and the structure of the product was confirmed by spectral data (see Table 1). The UV absorption curve of the tetrahydrophthalazinedione system differs from that of the dihydrophthalazinone system [1] and the aromatic protons of the former give two distinct two-proton multiplets in the NMR spectrum whereas those of the latter give a one-proton and a three-proton multiplet.

A similar rearrangement reaction in the aliphatic series is that of imino-2-chloroethyl ethers to *N*-2-chloroethylcarboxamides involving an oxazoline intermediate.[6] More recently, O – N rearrangements of certain *O*-acyl [7] and *O*-alkanesulphonyl [8] derivatives of phthalhydrazide have been reported by Le Berre *et al.*

In order to investigate the mechanism of the rearrangement reaction, we first wished to find if the unrearranged chloro-compound, *i.e.* compound II, was an intermediate. This compound was prepared in good yield by alkylating the sodium salt of compound I with 1-bromo-2-chloroethane in DMF at room temperature for 72 h. Interestingly, when this reaction was carried out at 100° for 1 h, compound II could not be isolated from the reaction mixture. Instead two isomeric compounds were formed, which were separable by fractional crystallization. These compounds gave practically identical mass spectra. The molecular ion appeared at *m/e* 378 and the base peak at *m/e* 203. The minor product (IV) gave a UV spectrum (Table 1) characteristic of a 3,4-dihydrophthalazin-4-one.[1] The intensity of the absorption maxima suggest the presence of two such ring systems, and the NMR spectrum (Table 1) indicates a symmetrical structure. The major product (V) gave a UV spectrum (Table 1) rather more in agreement with a 1,2,3,4-tetrahydrophthalazine-1,4-dione.[1] However, the NMR spectrum (Table 1) indicates an unsymmetrical structure. The designated structures are given in Fig. 1. The similarity of the mass spectra may be attributed to the formation of a common base ion (*m/e* 203). This is formed from compound IV by cleavage of a C – O bond β to a ring, and from compound V by cleavage of the C – O bond β to the ring or the bond attaching the ring nitrogen to the central chain. The structure of this base ion is probably a resonance stabilized oxazolinium ion (VIII in Fig. 2).

Table 1. Spectral data.

Compound	IR ν_{max}(KBr) cm^{-1}	UV λ_{max}(CH_3OH) nm	ε_{max}	NMR τ ($CDCl_3$) Aromatic H	*N*-Methyl H
II	1653	252	3840	1.4 – 1.7 (m, 1H)	6.26 (s, 3H)
	1625	261.5	4050	1.8 – 2.4 (m, 3H)	
	1600	297	5990		
III	1645	297	5700	1.5 – 1.8 (m, 2H)	6.28 (s, 3H)
	1608			2.0 – 2.3 (m, 2H)	
IV [a]	1650	253.5	7400	1.4 – 1.7 (m, 2H)	6.25 (s, 6H)
	1608	263.5	8030	1.8 – 2.4 (m, 6H)	
	1583	301.5	12820		
V	1640	261.5	5770	1.5 – 1.9 (m, 3H)	6.20 (s, 3H)
	1585	298.5	9360	2.0 – 2.4 (m, 5H)	6.25 (s, 3H)
VI	3340	303	4290	1.8 – 2.1 (m, 2H)	6.21 (s, 3H)
	1649			2.2 – 2.5 (m, 2H)	
	1620				
	1604				
VII	3350	252.5	3350	1.4 – 1.7 (m, 1H)	6.31 (s, 3H)
	1635	262	3780	1.9 – 2.4 (m, 3H)	
	1585	297.5	5870		

[a] UV spectrum taken in chloroform solution.

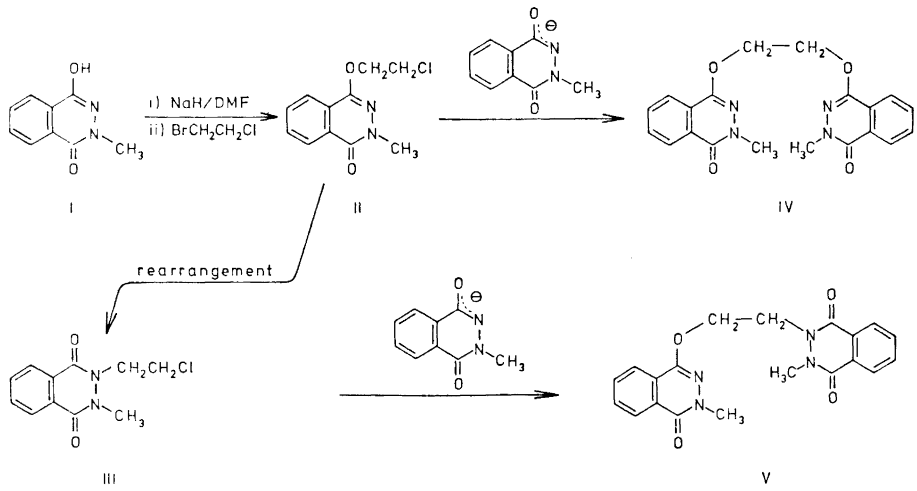

Fig. 1. Formation of compounds IV and V.

The formation of V suggests that the initial product of the alkylation reaction, compound II, can rearrange to compound III which then *O*-alkylates the anion of compound I. This anion may also be alkylated by compound II, in which case compound IV is formed. These reaction paths are illustrated in Fig. 1. The possibility of direct *N*-alkylation may be ruled out on the basis of previous findings.[2]

It was then attempted to isomerize compound II to III. After refluxing compound II in dimethylformamide for 4 h, 85 % of the material had been isomerized. Conversely, refluxing III in dimethylformamide led to the formation of some II. We suggest that this equilibrium, which favours the formation of compound III, proceeds *via* an oxazolinium ion, *i.e.* structure VIII (Fig. 2). It is known that the reaction of 2-hydroxyalkylamides with thionyl chloride leads to the formation of oxazolines.[9,10] From bond energies, it is calculated that III is thermodynamically more stable than II by *ca.* 8 kcal mol^{-1}. Evidence for the stability of ion VIII in the gas phase is provided by the mass spectra of compounds IV and V.

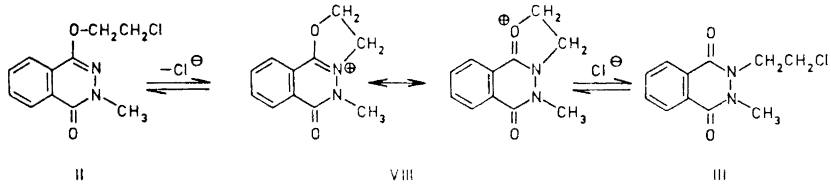

Fig. 2. Isomerization of compound II *via* an oxazolinium ion (VIII).

However, refluxing compound II in chloroform gave no isomerization product. This suggests that II is not an intermediate in the formation of III from VII with thionyl chloride in refluxing chloroform. In order to verify this, we followed the reaction by means of TLC on silica with ethyl acetate as moving phase. After only 10 min, the spot due to compound VII (R_F 0.42) had disappeared completely, and only one spot was observable (in UV), which was due to compound III (R_F 0.58). A spot due to the unrearranged chloride (II) (R_F 0.73) could not be detected. The reaction of compound VI with thionyl chloride in refluxing chloroform was followed in the same way. After only 2 min, the reaction was complete. The product was compound III, no other spot being observable. The rapidity of these two reactions suggests participation of a neighbouring group, and the reaction mechanisms outlined in Fig. 3 are proposed.

Here also, it is suggested that the oxazolinium ion VIII is an intermediate. It can be formed from the chlorosulphite of alcohol VII by the nucleophilic attack of the 2-nitrogen on the 2′-carbon and from the chlorosulphite of alcohol VI by the nucleophilic attack of the oxygen of the 1-carbonyl group on the 2′-carbon. The intermediacy of a chlorosulphite in the formation of oxazolines from 2-hydroxyalkylamides and thionyl chloride has been advocated previously.[10] The S_Ni mechanism,[11] which would lead to the formation of the chloro-

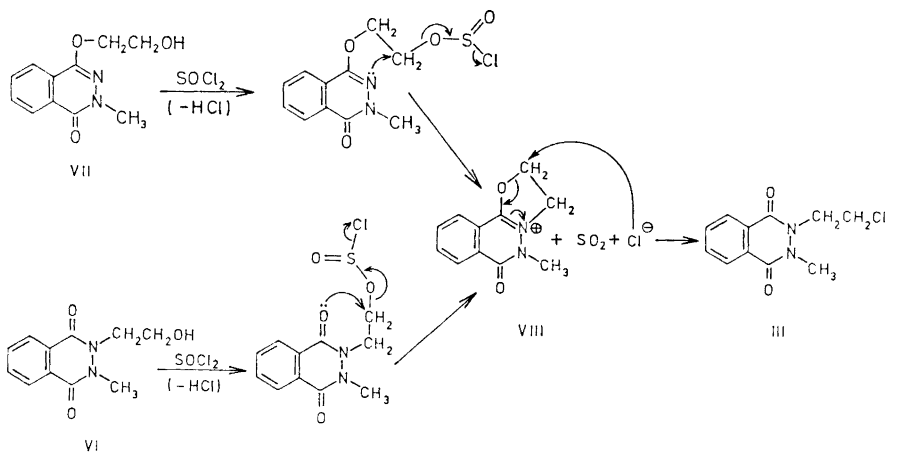

Fig. 3. Proposed mechanism of formation of compound III from compounds VI and VII.

compound II from the chlorosulphite of alcohol VII, is apparently completely suppressed. The reason for the exclusive product of the nucleophilic attack of the chloride ion on the oxazolinium ion VIII being compound III is probably that the activation energy from VIII to the transition state for formation of II is prohibitively high under the reaction conditions.

When the reaction of compound VII with thionyl chloride was carried out in the presence of an equimolar amount of pyridine at 0°C, only 20 % of the rearranged chloro-compound III was formed. The main product was chloro-compound II (yield 60 %). Here nucleophilic chloride ion is present in the reaction mixture [11] and attacks the 2'-carbon of the chlorosulphite competing successfully with the nucleophilic attack of the neighbouring nitrogen atom. When the reaction was carried out in refluxing chloroform in the presence of a catalytic amount of dimethylformamide, the main product (over 80 %) was chloro-compound III. However, thin layer chromatography revealed that some chloro-compound II was formed. Here, the chloride ion concentration of the reaction solution is lower, but there is still some S_N2 attack on the 2'-carbon of the chlorosulphite intermediate by chloride ion from the dimethylformamide-thionyl chloride adduct.[12] Thus a clean rearrangement reaction is observed only when alcohol VII is reacted with thionyl chloride in the absence of pyridine or dimethylformamide as catalyst.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Unicam SP 200 spectrophotometer and UV spectra on a Beckman DK-2A instrument. NMR spectra were measured on a Varian A-60 spectrometer operating at 60 Mc/s with TMS as internal standard. Mass spectra were recorded on an LKB 9000 mass spectrometer operating at 70 eV. Microanalyses were carried out by Dr. A. Bernhardt, Elbach, West Germany, or at our analytical laboratories.

N,N′-*Dibenzoyl*-N-*(2-hydroxyethyl)hydrazine.* A solution of sodium hydroxide (44.0 g 1.10 mol) in 120 ml water and benzoyl chloride (147.6 g, 1.05 mol) were added simultaneously from separate dropping funnels to an ice-cold stirred solution of 2-hydroxyethylhydrazine (38.05 g, 0.50 mol) in 100 ml water, the aqueous alkali being added at a slightly faster rate. When addition was complete, after 1.5 h, the reaction mixture was stirred for a further 2 h. When necessary, 2 N sodium hydroxide was added to maintain alkalinity in the aqueous phase. The reaction mixture was then saturated with carbon dioxide, and extracted with ethyl acetate. The organic phase was washed with aqueous sodium bicarbonate and water, then dried over magnesium sulphate. Removal of the solvent left a viscous syrup, which began to crystallize after standing some time under ethyl acetate. The crystals (79.7 g, m.p. 106 – 110°) were recrystallized from ethyl acetate giving 65.4 g, m.p. 109 – 111°. A further recrystallization from ethyl acetate gave 52.0 g, m.p. 110 – 111.5°. Yield 37 %. (Found: N 9.68. Calc.: N 9.85.) IR (KBr): ν_{OH} 3450 (s), ν_{NH} 3320 (s), $\nu_{C=O}$ 1660 (s, sh), 1530 (s) cm^{-1}. NMR ($CDCl_3$): τ 6.21 (broad s, 4H), 5.59 (broad s, 1H, removed with D_2O), 2.3 – 3.0 (m, 10H), 0.06 (broad s, 1H, removed with D_2O).

N,N′-*Dibenzoyl*-N-*(2-hydroxyethyl)*-N′-*methylhydrazine.* A solution of sodium hydroxide (4.20 g, 0.105 mol) in 10 ml water and dimethyl sulphate (13.20 g, 0.105 mol) were added simultaneously from separate dropping funnels to a stirred solution of *N,N′*-dibenzoyl-*N*-(2-hydroxymethyl)hydrazine (25.85 g, 0.091 mol) in a minimum amount of ethanol. A quarter of the total amounts of each were added, and after 1 h, a further quarter was added, and so on. When addition was complete, 250 ml water was added to the stirred mixture. The oily product was extracted with chloroform, dried over sodium sulphate and the solvent removed, leaving 26.8 g viscous oil, which could not be induced to crystallize. IR (liquid film): ν_{OH} 3450 (s), $\nu_{C=O}$ 1660 (s, sh) cm^{-1}. NMR ($CDCl_3$): τ 6.88 (s, 3H), 5.8 – 6.5 (m, 5H, 1H removed with D_2O), 2.3 – 3.1 (m, 10H).

N-*(2-Hydroxyethyl)*-N′-*methylhydrazine dihydrochloride.* The crude *N,N′*-dibenzoyl-*N*-(2-hydroxyethyl)-*N′*-methylhydrazine (26.8 g) was stirred at 100° with 134 g concentrated hydrochloric acid for 2 h. The solution was then cooled, and the precipitated benzoic acid removed by filtration and washed with water. The filtrate and washings were combined and concentrated under reduced pressure. The residue (14.62 g) crystallized, but was very hygroscopic and could not be recrystallized. (Yield of crude product based on *N,N′*-dibenzoyl-*N*-(2-hydroxyethyl)-hydrazine, 98.5 %.) NMR (D_2O): τ 7.12 (s, 3H), 6.6 – 6.9 (m, 2H, one half of A_2B_2 system), 6.0 – 6.3 (m, 2H, other half of A_2B_2 system).

2-(2′-Hydroxyethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (VI). Phthalic anhydride (0.91 g, 6.1 mmol) was added to a solution of *N*-(2-hydroxyethyl)-*N′*-methylhydrazine dihydrochloride (1.00 g, 6.1 mmol) and sodium acetate trihydrate (0.83 g, 6.1 mmol) in 11 ml 40 % aqueous acetic acid. The mixture was heated under reflux under argon for 4 h. After evaporation of the solution to dryness, the residue was triturated several times with boiling isopropyl ether until no more dissolved. On cooling the isopropyl ether solution, 644 mg crystalline product was obtained. Recrystallization from isopropyl ether gave 542 mg, m.p. 124 – 126°. Yield 40 %. (Found: C 60.13; H 5.53; N 12.85. Calc. for $C_{11}H_{12}N_2O_3$: C 59.99; H 5.49; N 12.72.)

1-(2′-Hydroxyethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (VII). 1-Hydroxy-3-methyl-3,4-dihydrophthalazin-4-one [1] (I) (26.5 g, 0.150 mol) was added portionwise to a stirred suspension of sodium hydride (4.32 g, 0.180 mol) in 180 ml dry dimethylformamide under argon. When evolution of gas had ceased, 2-chloroethanol (16.9 g, 0.210 mol) in 100 ml dry dimethylformamide was added during 30 min. The mixture was heated under reflux for 1.5 h. Most of the solvent was removed under reduced pressure, then 200 ml water added. The mixture was extracted with chloroform, the chloroform solution dried over magnesium sulphate and the solvent removed, leaving a residue which was recrystallized from methanol affording 23.2 g, m.p. 147 – 148°. Yield 70 %. (Found: C 60.06; H 5.56; N 12.85. Calc. for $C_{11}H_{12}N_2O_3$: C 59.99; H 5.49; N 12.72.)

2-(2′-Chloroethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (III). Method A (from compound VI). Compound VI (0.44 g, 0.002 mol) was heated under reflux with thionyl chloride (0.71 g, 0.006 mol) in 10 ml dry chloroform for 16 h. The solvent was removed under reduced pressure, the last traces of thionyl chloride being removed azeotropically with benzene. The residue was recrystallized from methanol giving 0.36 g, m.p. 118 – 119.5°. Yield 75 %. (Found: C 55.40; H 4.75; Cl 14.92; N 11.89. Calc. for $C_{11}H_{11}ClN_2O_2$: C 55.35; H 4.65; Cl 14.85; N 11.74.)

Method B (from compound VII). Compound VII (5.28 g, 0.024 mol) was heated under reflux with thionyl chloride (8.54 g, 0.072 mol) in 60 ml dry chloroform for 24 h. After removal of the solvent *in vacuo*, the last traces of thionyl chloride being removed azeotropically with benzene, the residue was recrystallized from methanol, giving 4.99 g, m.p. 118.5 – 120°C. Yield 88 %. A mixed m.p. with the product from method A showed no depression.

1-(2'-Chloroethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (II). 1-Hydroxy-3-methyl-3,4-dihydrophthalazin-4-one [1] (I) (13.2 g, 0.075 mol) was added portionwise to a stirred suspension of sodium hydride (2.16 g, 0.090 mol) in 150 ml dry dimethylformamide under argon. When evolution of gas was complete, this suspension was added to a stirred solution of 1-bromo-2-chloroethane (75 g, 0.525 mol) in 60 ml dry dimethylformamide under argon during 30 min, the mixture being cooled in an ice-bath. The mixture was then stirred for 72 h at room temperature. Most of the solvent and excess 1-bromo-2-chloroethane were removed under reduced pressure, 200 ml water added and the mixture extracted with chloroform. The chloroform solution was dried over magnesium sulphate, the solvent removed and the residue recrystallized from methanol giving 12.8 g, m.p. 109 – 110°. Yield 71 %. (Found: C 55.61; H 4.59; Cl 15.04; N 11.62. Calc. for $C_{11}H_{11}ClN_2O_2$: C 55.35; H 4.65; Cl 14.86; N 11.74.)

1,2-Bis-(3'-methyl-3',4'-dihydrophthalazin-4'-on-1'-yloxy)ethane (IV) and 1-(3'-methyl-3',4'-dihydrophthalazin-4'-on-1'-yloxy)-2-(3'-methyl-1',2',3',4'-tetrahydrophthalazine-1',4'-dion-2'-yl)ethane (V). 1-Hydroxy-3-methyl-3,4-dihydrophthalazin-4-one [1] (I) (4.41 g, 0.025 mol) was added portionwise to a stirred suspension of sodium hydride (0.72 g, 0.03 mol) in 50 ml dry dimethylformamide. When evolution of hydrogen had ceased, the suspension was added to a stirred solution of 1-bromo-2-chloroethane (5.0 g, 0.035 mol) in 20 ml dry dimethylformamide under argon during 30 min. The reaction mixture was heated up to 100° during 1 h, kept at this temperature for 1 h, then allowed to cool to room temperature. Next day, the solvent was removed under reduced pressure and 50 ml water added. The mixture was extracted with chloroform and the organic phase dried over magnesium sulphate. On allowing a warm methylene chloride solution of the residue to cool, 0.3 g crystalline material was obtained which was recrystallized from 1,2-dichloroethane, giving compound IV (0.18 g, m.p. 259.5 – 261°). MS: M^+, *m/e* 378 (6 %), 203 (100 %), 162 (4 %), 133 (4 %), 130 (11 %), 104 (12 %), 76 (6 %). (Found: C 63.30; H 4.91; N 14.72. Calc. for $C_{20}H_{18}N_4O_4$: C 63.47; H 4.71; N 14.80.) The filtrate from the methylene chloride solution was evaporated and recrystallized twice from methanol giving compound V (0.86 g, m.p. 220 – 220.5°). MS: M^+, *m/e* 378 (6 %), 203 (100 %), 162 (5 %), 130 (8 %), 104 (12 %), 76 (8 %). (Found: C 63.46; H 4.91; N 14.69. Calc. for $C_{20}H_{18}N_4O_4$: C 63.47; H 4.79; N 14.80.)

Isomerization experiments

The reactions of chloro-compounds II and III in refluxing dimethylformamide (bath temperature 170°) and that of chloro-compound II in refluxing chloroform were followed by means of thin layer chromatography (Merck Kieselgel F_{254}, 20 × 20 cm plates) with ethyl acetate as moving phase. 10 µl samples were removed at various intervals (5, 15, 30 min, 1, 2, 4, 6 h) and diluted with 0.8 ml ether, then 10 µl of each solution chromatographed. The plates were observed under a short-wave ultraviolet lamp.

1-(2'-Chloroethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (II) in refluxing DMF. 500 mg of compound II were dissolved in 6 ml DMF and heated under reflux for 6 h. A spot corresponding to compound III (R_F 0.60) appeared within 5 min. After 2 h, the ratio of the intensities of the spot at R_F 0.60 to that of starting compound II (R_F 0.73) appeared to remain constant. However, a third spot, having the same R_F value as hydroxy-compound VI appeared after 30 min and increased in intensity.

After 6 h, the DMF was removed under reduced pressure and the residue chromatographed on 20 g Merck 0.05 – 0.20 mm Kieselgel using isopropyl ether-isopropanol (4:1) as eluent. Three compounds were isolated: compound II (40 mg, m.p. 105 – 107°), compound III (190 mg, m.p. 117 – 118°), and compound VI (45 mg, m.p. 124 – 126°). None of the compounds gave a depression in m.p. on admixture with authentic specimens. The formation of compound VI may be ascribed to the presence of moisture in the solvent.

2-(2'-Chloroethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (III) in refluxing DMF. 240 mg of compound III were dissolved in 3 ml DMF and heated under reflux for 8 h. A spot corresponding to compound II (R_F 0.73) appeared within 5 min. The ratio of the intensity of the new spot to that of the starting material (R_F 0.60) appeared to remain constant after 2 h, the starting material giving the more intense spot. After 30 min, a third spot having the same R_F value as compound VI appeared.

1-(2'-Chloroethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (II) in refluxing chloroform. A solution of 55 mg of compound II in 1.5 ml chloroform was heated under reflux for 24 h. Only one spot, that due to the starting material (R_F 0.72) was observed, no other spot appearing.

Reaction of 1-(2'-hydroxyethoxy)-3-methyl-3,4-dihydrophthalazin-4-one (VII) with thionyl chloride in the presence of catalysts

Pyridine as catalyst. Compound VII (6.0 g, 0.027 mol) was mixed with dry pyridine (2.15 g, 0.027 mol) and 25 ml dry ether added. Thionyl chloride (6.4 g, 0.054 mol) was then added dropwise to the stirred mixture which was cooled in an ice-bath. The mixture was allowed to stand overnight, then heated under reflux for 30 min. After cooling, water was added and the precipitate removed by filtration, washed with water and dried. The filtrate was extracted with ether and the ether phase dried over $MgSO_4$ and the solvent removed. The residue was combined with the dried precipitate and 1 g of this material was chromatographed on 50 g Kieselgel (Merck, 0.05 – 0.20 mm). Elution was performed using isopropyl ether. Two compounds were obtained, the first eluted (0.60 g) having m.p. 107 – 110° being identical with compound II, and the second (0.19 g, m.p. 111 – 115°) being identical with compound III.

DMF as catalyst. Compound VII (11.0 g, 0.050 mol) was dissolved in 85 ml dry chloroform and 0.8 ml dry DMF was added. Then thionyl chloride (17.8 g, 0.150 mol) was added dropwise to the stirred solution which was subsequently heated under reflux for 7 h. The solvent and excess thionyl chloride were removed under reduced pressure, the last traces of the latter being removed azeotropically with benzene. The residue was recrystallized from methanol affording 9.70 g, m.p. 116 – 118°. This material was identical with 2-(2'-chloroethyl)-3-methyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (III). Yield 82 %.

Investigation of the course of the reactions of compounds VI and VII with thionyl chloride

General procedure. The compounds were heated under reflux with thionyl chloride in dry chloroform for 4 h at a bath temperature of 70 – 72°. Samples (10 µl) were removed at various intervals (2, 5, 10, 15, 30 min, 1, 2, 4 h), immediately shaken with 1 ml water and the mixture was extracted with 0.4 ml ether. 10 µl of each ether phase was applied to a TLC plate (Merck Kieselgel F_{254}, 20 × 20 cm) and the chromatograms developed using ethyl acetate as the moving phase. The plates were observed under a short-wave ultraviolet lamp.

Reaction of compound VI with thionyl chloride in chloroform. Compound VI (55 mg, 0.25 mmol) and thionyl chloride (90 mg, 0.75 mmol) were heated under reflux in 1 ml chloroform. Within only 2 min, the reaction was complete, the product having the same R_F value as compound III (0.61). No other spots were observed after this time.

Reaction of compound VII with thionyl chloride in chloroform. Compound VII (220 mg, 1.0 mmol) and thionyl chloride (360 mg, 3.0 mmol) were heated under reflux in 3 ml chloroform. After 5 min, 4 spots were observable, R_F 0.34, 0.42 (identical with compound VII), 0.58 (identical with compound III) and 0.68. After 10 min, only one spot was observable, R_F 0.58. A spot corresponding to chloro-compound II (R_F 0.73) was never observed.

Reaction of compound VII with thionyl chloride in chloroform with DMF as catalyst. Compound VII (220 mg, 1.0 mmol), thionyl chloride (357 mg, 3.0 mmol) and 0.02 ml dry

DMF were heated under reflux in 3 ml chloroform. After 5 min, 4 spots were observable, R_F 0.35, 0.40 (identical with compound VII), 0.55 (identical with compound III) and 0.67. After 10 min, there were still 4 spots, those with R_F 0.35 and 0.40 being less intense, and that at R_F 0.55 being more intense than in the previous sample. The fourth spot, R_F 0.70, was less intense than that at R_F 0.55. It had the same R_F value as compound II. The spot at R_F 0.67 was no longer observable. After 15 min, only 2 spots were observable, R_F 0.55 and 0.70. Their intensities relative to each other in subsequent samples remained unchanged, the spot at R_F 0.55 being more intense.

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