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# 1,3,4-THIADIAZOLES—III*

## NUCLEOPHILIC REACTIVITY OF 2-ARYL-5-CHLORO-DERIVATIVES

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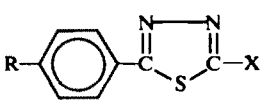
**Abstract**—Some 2-aryl-5-chloro-1,3,4-thiadiazoles (I; X = Cl) were treated with several nucleophilic agents in different solvents. Displacement of chlorine by piperidine was chosen for a kinetic study in ethanol and in benzene, in the temperature range 30–60°. Reactions were first order with respect to both reagents in ethanol, while a third-order term appeared in benzene. Substituents on the Ph ring affected the rate of nucleophilic exchange by a Hammett rho-value of 1·47 at 50° in ethanol. Kinetic results are compared with theoretical expectations and experimental data for this and other classes of thiadiazoles.

ALTHOUGH the chemical behaviour of some 1,3,4-thiadiazole derivatives has been studied,[1–3] this class of heterocycles has not yet been systematically investigated, and little is known of its relationship to other classes, as, for instance, 1,2,4-thiadiazolic compounds.[4] In a study of the nucleophilic attack on 2-aroyl-5-chloro-1,3,4-thiadiazoles,[5] the presence of the CO group proved a complicating factor; therefore it seemed worthwhile studying a simpler system.

The following 2-aryl-5-chloro-1,3,4-thiadiazoles (I; X = Cl) have been chosen



I

a: R = H
b: R = OMe
c: R = Cl
d: R = $NO_2$

in order to study their reactivity towards different nucleophiles, listed in Table 1.

From the reaction of Ia (X = Cl) in ethanol, not only in the presence of sodium ethoxide, but also weaker nucleophiles like cyanide and phenoxide ions (cases Nos. 1, 2 and 3 in Table 1) only the ethoxy derivative was isolated. It has been possible to obtain the phenoxy derivative, in very low yields, in phenol and in aq. dimethylformamide (case No. 4). Thiophenoxide and amines (in Nos. 6, 7 and 8) gave the expected products in good yield. Reactions of Ib, c and d (X = Cl) with piperidine always gave almost quantitative yields.

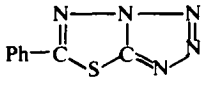
Reaction of 2-chloro-5-phenyl-1,3,4-thiadiazole with sodium azide (No. 9) yielded Ia (X = $N_3$; 38%), isolated in the crystalline state as 6-phenyl-1,3,4-thiadiazolo[3.2-*d*]-

* Part II, Ref. 5.

TABLE 1. REACTIONS OF Ia (X = Cl) IN THE PRESENCE OF NUCLEOPHILIC REAGENTS

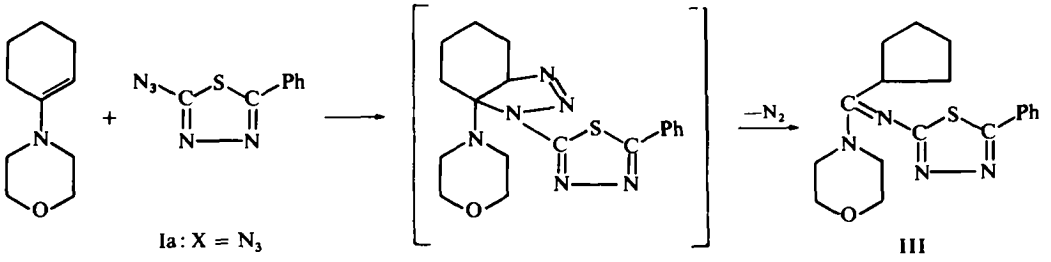
| No. | Nucleophilic reagent | Solvent | Product | Yield |
|---|---|---|---|---|
| 1 | EtONa | ethanol | Ia (X = OEt) | 80% |
| 2 | KCN | ethanol + water (7:1) | Ia (X = OEt) | 86% |
| 3 | PhONa | 97% ethanol | Ia (X = OEt) | — |
| 4 | PhONa | phenol or DMF + water (4:1) | Ia (X = OPh) | scarce |
| 5 | NaOH | ethanol + water (1:1) | Ia (X = OEt)<br>Ia (X = OH) | 47%<br>21% |
| 6 | PhSNa | ethanol | Ia (X = SPh) | 89% |
| 7 | $PhNH_2$ | ethanol | Ia (X = NHPh) | 56% |
| 8 | $C_5H_{11}N$ | ethanol or benzene | Ia (X = $NC_5H_{10}$) | >90% |
| 9 | $NaN_3$ | DMF + water (7:1) | see text | — |

tetrazole (II)* and smaller amounts of 2-amino-5-phenyl-1,3,4-thiadiazole and 2-benzoylamino-5-phenyl-1,3,4-thiadiazole. At present we cannot suggest a mechanism for the formation of the last two products, but obviously they derive from the azido derivative, and the latter product at least requires also the opening of a thiadiazole



II

ring. Ia (X = $N_3$) maintained its open form in carbon tetrachloride solution (IR spectrum) and when reacting with 1-N-morpholino-cyclohexene according to the scheme:



Ia: X = $N_3$ III

characteristic of "activated" azides.[7]

* It should be noted that the analogous 2-aroyl-5-azido-1,3,4-thiadiazoles were isolated in the open azidic form also in the solid state.[5] Though at present there is no direct evidence for the tetrazolic structure II, we assign this structure to our product in the solid state as absorption in the spectral region characteristic for the stretching of azido group is absent. A similar assignment has been done for other compounds showing the same ring-chain tautomerism, for instance:[6]

All reactions confirmed the electron-withdrawing properties of the 1,3,4-thiadiazole ring. Reactions with piperidine were chosen for the study of the kinetics. Piperidino dechlorination in ethanol is suitable for comparison with kinetic results on 1,2,4-thiadiazole derivatives, already known,[4] and for checking the reactivity orders proposed on the basis of theoretical calculations.[8] Nucleophilic reactivity has been foreseen to decrease in the order:

$$(2, 4)_5 > (3, 4) > (2, 4)_3 \quad (*)$$

according to the criterion of localization energy, but in the order:

$$(2, 4)_5 > (2, 4)_3 > (3, 4) \quad (*)$$

on the basis of electron density considerations.

Reactions of 2-aryl-5-chloro-1,3,4-thiadiazoles with piperidine in ethanol resulted of first order with respect to the nucleophile; as an example, data for 2-chloro-5-*p*-methoxyphenyl-1,3,4-thiadiazole are shown in Table 2. With a large excess of

TABLE 2. REACTION ORDER FOR CHLORINE DISPLACEMENT IN Ib (X = Cl) INIT. CONCN. = $10^{-3}$ MOLE $l.^{-1}$) BY PIPERIDINE (INIT. CONCN. = $[C_5H_{11}N]_o$) IN ETHANOL (50·0°)

| $[C_5H_{11}N]_o$ (mole $l.^{-1}$) | 0·0495 | 0·0980 | 0·1945 |
|---|---|---|---|
| $10^4 k$ (l. mole$^{-1}$ sec$^{-1}$) | 2·45 | 2·37 | 2·34 |

piperidine, reactions were strictly pseudo-first order with respect to the thiadiazolic substrates. Second-order rate constants ($k$) were obtained as ratios of pseudo-first order constants to initial piperidine concentration. Kinetic runs were performed at temperatures in the range 30°–60°. Rate constants and activation parameters are gathered in Table 3 ($\Delta E^{\ddagger}$ = Arrhenius activation energy; $A$ = frequency factor (l. mole$^{-1}$ sec$^{-1}$); $\Delta S^{\ddagger}$ = activation entropy).

TABLE 3. RATE CONSTANTS (l.MOLE$^{-1}$ SEC$^{-1}$) OF REACTIONS WITH PIPERIDINE IN ETHANOL

| Compound | $10^4 k$ | | | | $\Delta E^{\ddagger}$ (cal/mole) | log $A$ | $\Delta S^{\ddagger}$ (e.u.) (at 50°) |
|---|---|---|---|---|---|---|---|
| | 30·0° | 40·0° | 50·0° | 60·0° | | | |
| Ia (X = Cl) | 1·79 | 3·11 | 5·91 | 10·10 | 11,720 ± 200 | 4·69 ± 0·14 | −39·2 ± 0·6 |
| Ib (X = Cl) | 0·628 | 1·121 | 2·39 | 3·80 | 12,570 ± 420 | 4·86 ± 0·29 | −38·5 ± 1·3 |
| Ic (X = Cl) | — | 6·13 | 11·42 | 18·8 | 11,620 ± 320 | 4·90 ± 0·21 | −38·2 ± 1·0 |
| Id (X = Cl) | — | 44·6 | 80·1 | 132·5 | 11,290 ± 340 | 5·54 ± 0·23 | −35·4 ± 1·1 |

Some runs were carried with excess piperidine in benzene, at 50°, on compounds Ia and d (X = Cl). Reactions were of pseudo-first order with respect to the aryl-chloro-thiadiazole; second-order rate constants ($k$) were obtained as usual. As

* Numbers in parentheses indicate the position of N atoms with respect to S in the thiadiazole ring, and subscripts indicate the reaction center.

shown in Table 4, $k$ values depend linearly from $[C_5H_{11}N]_o$ values; intercept and slope of the equation:

$$k = k_2 + k_3[C_5H_{11}N]_o$$

obtained from least squares regression analysis, are also given in Table 4.

TABLE 4. RATE CONSTANTS OF REACTIONS WITH PIPERIDINE IN BENZENE (50·0°)

| | | | | | | |
|---|---|---|---|---|---|---|
| Compound Ia (X = Cl): | | | | | | |
| $[C_5H_{11}N]_o$ (mole l.$^{-1}$) | 0·101 | 0·193 | 0·338 | 0·484 | 0·628 | 0·966 |
| $10^4 k$ (l. mole$^{-1}$ sec$^{-1}$) | 0·436 | 0·461 | 0·710 | 0·833 | 0·910 | 1·248 |
| $10^4 k_2 = 0·335 \pm 0·023$ l. mole$^{-1}$ sec$^{-1}$; $10^4 k_3 = 0·955 \pm 0·043$ l.$^2$ mole$^{-2}$ sec$^{-1}$ | | | | | | |
| Compound Id (X = Cl) | | | | | | |
| $[C_5H_{11}N]_o$ (mole l.$^{-1}$) | 0·051 | 0·097 | 0·155 | 0·252 | 0·290 | |
| $10^4 k$ (l. mole$^{-1}$ sec$^{-1}$) | 4·59 | 4·83 | 6·01 | 8·01 | 8·23 | |
| $10^4 k_2 = 3·49 \pm 0·18$ l. mole$^{-1}$ sec$^{-1}$; $10^4 k_3 = 16·8 \pm 0·9$ l.$^2$ mole$^{-2}$ sec$^{-1}$ | | | | | | |

As R *para*-substituents are changed in I (X = Cl), the reactivity order in ethanol is (Table 3):

$$OMe < H < Cl \ll NO_2$$

Activation energies decrease as $k$ values increase. Results in benzene (Table 4) are also consistent with the typical order of reactivity of a nucleophilic reaction. A Hammett plot correlates log $k$ values (50°; ethanol) with the common $\sigma_p$ constants,[9] giving (Fig. 1):

$$\rho = 1·47 \pm 0·02$$

Such $\rho$-value is rather low, but it should be considered that it refers to substitution on the phenyl ring and not on the same ring on which attack takes place.

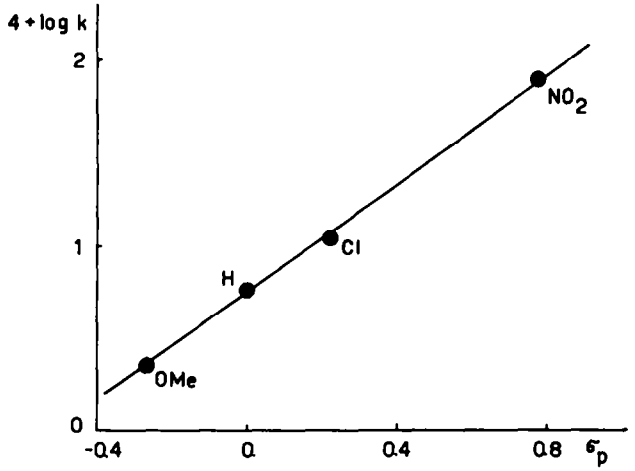
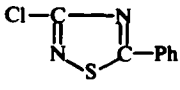
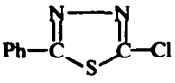



FIG. 1 Hammett plot for reaction of 2-chloro-5-(*para*-substituted)-phenyl-1,3,4-thiadiazoles with piperidine in ethanol at 50°.

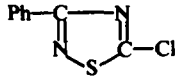
Three isomeric chloro-phenyl-thiadiazoles can be compared as to their reactivity with piperidine at 30·0° in ethanol. Rate constants (l. mole$^{-1}$ sec$^{-1}$) are as follows:



$10^4 k$ = 0·028 (ref. 4)



$10^4 k$ = 1·79



$10^4 k$ = 198 (ref. 4)

The experimental order of reactivity, with the symbols used before, is then:

$$(2, 4)_5 > (3, 4) > (2, 4)_3.$$

Nucleophilic displacement of chlorine seems particularly favoured when a thia-group is in the α-position to the reaction center. The two compounds above, having this characteristic, can be compared in order to judge the sensitivity of the reaction to substitution and aza-activation of the heterocyclic ring; in fact, they can be considered as aza- and phenyl-disubstituted 2-chlorothiazoles, differing only in the position of substitution. As a good approximation, consistent with their different reactivity, and with kinetic results on 2-chloro-benzothiazole derivatives,[10] it can be assumed that electronic effects are transmitted through N but not through S atoms in the ring. In this case position 4 is *meta*, and position 5 is *para*, with respect to the reaction center, that is one can look at 5-chloro-3-phenyl-1,2,4-thiadiazole and 2-chloro-5-phenyl-1,3,4-thiadiazole as *m*-Ph, *p*-aza and *m*-aza, *p*-Ph substituted 2-chloro-thiazoles, respectively. The Hammett relation has been applied to the reaction of these compounds with piperidine in ethanol at 30°, using the principle of additivity of $\sigma$ constants:

$$\rho' = [\log k_{(24)_5} - \log k_{(34)}]/[\sigma_m(\text{Ph}) + \sigma_p(\text{—N=}) - \sigma_m(\text{—N=}) - \sigma_p(\text{Ph})]$$

Using the following $\sigma$-values:

$\sigma_m(\text{Ph}) = 0{\cdot}06$;[9] $\sigma_p(\text{Ph}) = -0{\cdot}01$;[9] $\sigma_m(\text{—N=}) = 0{\cdot}63$;[11–13] $\sigma_p(\text{—N=}) = 0{\cdot}94$.[11,12]

$\rho'$ is equal to 5·4. This value should be taken cautiously, as it derives from two rate constants only; nevertheless, it suggests a high sensitivity to activation on the heterocyclic ring, comparable to that of nucleophilic aromatic displacements to substituents on the benzene ring ($\rho$ values often around 5). The large difference between our $\rho$ and $\rho'$ values (1·47 and 5·4, respectively) indicates that the transmission of electronic effects from the Ph ring to the site of attack is markedly less efficient than transmission from positions on the heterocyclic ring. It is noteworthy that the effect of substituents, carried by the benzene ring of 2-chlorobenzothiazole, on the reaction with diethylamine at 25° in methanol, is expressed by a $\rho$-value of 3·4,[14] that is intermediate between our $\rho$ and $\rho'$ values. Besides differences in reaction conditions, two main

factors seem to play a role in determining the gap between the $\rho$ value for benzothiazoles and the low $\rho$-value found for the phenyl-thiadiazolic system: first, a benzene ring condensed with the heterocycle is more efficient than one bound at one position only; secondly, in thiadiazole derivatives activation by aza- and thia- groups determines an incipient saturation effect, not present in thiazolic compounds.

When running kinetics in benzene as solvent, besides the second-order term (rate constant $k_2$), a third-order term appeared in the kinetic equation (rate constant $k_3$). Similar effects have been observed in many cases of nucleophilic aromatic substitution,[15] and even in substitution at a saturated carbon,[16] when the nucleophilic agent was a primary or secondary amine. The third-order term should correspond to a reaction route in which the rate determining transition state contains two molecules of amine. In some $S_NAr$ reactions, when the third-order term was highly important, as seen by high values of the $(k_3/k_2)$ ratio, and strong acceleration by bases other than the reagent was demonstrated, the phenomenon was explained within the intermediate complex mechanism, as base catalysis of the second step of the process, this step being rate-controlling.[17] In cases where $(k_3/k_2)$ ratios have small values, and the reaction has been carried out in aprotic solvents, where amine molecules are likely to be extensively associated through hydrogen bonds, it is probable that the higher-order term expresses the intervention in the displacement of associated amine molecules, in competition with the non-associated ones.[16,18]

The latter could well be also our case, since the solvent was benzene and $(k_3/k_2)$ ratios (from Table 4) have low values: 2·85 l. mole$^{-1}$ for Ia (X = Cl) and 4·81 l. mole$^{-1}$ for Id (X = Cl). As a consequence, certainly in ethanol and very probably in benzene too, the mechanism of the substitution is either a one-step displacement or a two-step displacement, the first step being rate determining.

The change of solvent from ethanol to benzene has marked kinetic consequences, that can be evaluated by comparing $k$ constants in EtOH with $k_2$ constants in benzene, that is the pure second-order rate constants. Both for R = H and for R = $NO_2$, nucleophilic substitution of chlorine by piperidine is faster in ethanol than in benzene, by factors of 17·6 and 22·9, respectively (at 50°). A solvent effect of this nature is expected for a process between neutral molecules giving rise to a polar transition state. Its order of magnitude is the same as that found in many aromatic nucleophilic substitutions.

## EXPERIMENTAL

*Materials and reactions*

*2-Amino-5-aryl-1,3,4-thiadiazoles.* Compounds Ia, c, d (X = $NH_2$) were prepared by dehydration of the corresponding aroylthiosemicarbazides with conc $H_2SO_4$.[19] For Ib (X = $NH_2$), 99% phosphoric acid was employed.[20] M.ps of Ia, b, d (X = $NH_2$) were as in lit.[2] Ic (X = $NH_2$) melted at 215–216° from dioxan. (Found: C, 45·85; H, 2·90; N, 19·08; $C_8H_6ClN_3S$ requires: C, 45·39; H, 2·86; N, 19·85%).

*2-Aryl-5-chloro-1,3,4-thiadiazoles.* Compounds Ia, c, d (X = $NH_2$) were ground with a large excess (about 5:1 moles) of $NaNO_2$[2] and the mixture was introduced, in small portions and with stirring, into a large excess of conc HCl, containing some Cu powder, at about −5°. The reaction mixture was allowed to reach room temp and heated to 50° until the evolution of gas ceased. Crystals precipitated on dilution and neutralization with NaOH.

For Ia (X = Cl): yield, 70%; m.p. 86–88° (from EtOH) (lit. 88°[3]). UV (EtOH): $\lambda_{max}$ = 276 nm ($\varepsilon$ = 9900).

For Ic (X = Cl): yield, 89%; m.p. 126° from dioxan–water. (Found: C, 41·80; H, 1·90; N, 12·71; $C_8H_4Cl_2N_2S$ requires: C, 41·57; H, 1·75; N, 12·12%); UV (EtOH): $\lambda_{max}$ = 283 nm ($\varepsilon$ = 18,000).

For Id (X = Cl); yield 54%; m.p. 213° (from dioxan). (Found: C, 40·05; H, 1·78; N, 17·3; $C_8H_4ClN_3O_2S$ requires: C, 39·76; H, 1·67; N, 17·30%); UV (EtOH): $\lambda_{max}$ = 295 nm ($\varepsilon$ = 20,400).

11·5 g Ib (X = $NH_2$) were dissolved, with gentle heating, in a mixture of 50 ml conc HCl and 230 ml glacial AcOH. A saturated aqueous soln of 4·5 g $NaNO_2$ was added dropwise, with stirring, at a temp between 0 and −3°. A small quantity of Cu powder was added and the mixture allowed to reach room temp; after 3 hr it was heated at 50–55° for ½ hr. Ib (X = Cl) precipitated on dilution, yield: 94%, m.p. 98° from EtOH. (Found: C, 47·59; H, 3·14; N, 12·04; $C_9H_7ClN_2OS$ requires: C, 47·68; H, 3·11; N, 12·35%); UV (EtOH): $\lambda_{max}$ = 302 nm (ε = 20,500).

2-*Ethoxy*-5-*phenyl*-1,3,4-*thiadiazole* (Ia; X = OEt). Compound Ia (2 g; X = Cl) in 24 ml EtOH was treated with NaOEt (0·77 g) in 5 ml EtOH and refluxed for 5 hr. The solvent was evaporated (red. press.) and the residue treated with water and extracted with ether. After removal of the solvent 1·68 g were obtained. m.p. 66–68° from EtOH. (Found: C, 58·22; H, 4·83; N, 13·61; $C_{10}H_{10}N_2OS$ requires: C, 58·25; H, 4·89; N, 13·58%).

*Reaction between* Ia (X = Cl) *and* NaOH. Compound Ia (0·5 g; X = Cl), in 10 ml EtOH was refluxed for 5 hr with NaOH (0·5 g) in 10 ml water, and EtOH removed (red. press.). The ppt was filtered off, washed with water and dried *in vacuo*; it was recognized as Ia (X = OEt; 0·3 g). From the filtrate, after acidification with HCl, filtration, washing and drying, 0·1 g Ia (X = OH) (in the form of 2-phenyl-1,3,4-thiadiazolin-5-one, as recognized by IR spectrum) were obtained.[21]

*Reaction between* Ia (X = Cl) *and* KCN. Compound Ia (0·5 g; X = Cl) and KCN (0·3 g) in 10 ml EtOH and 1·5 ml water were refluxed for 22 hr. EtOH was removed (red. press.) and the residue, after filtration, washing and drying, gave 0·47 g Ia (X = OEt).

*Reaction between* Ia (X = Cl) *and* PhONA. Compound Ia (2 g; X = Cl) in 24 ml EtOH was treated with phenol (1·05 g) and NaOH (0·5 g) in 6 ml EtOH and 1 ml water. The soln was refluxed for 6 hr and the solvent evaporated (red. press.) The residue was treated with a 5% NaOH aq and extracted with ether. The ether layer gave a solid recognized as Ia (X = OEt).

2-*Phenoxy*-5-*phenyl*-1,3,4-*thiadiazole* (Ia; X = OPh). Phenol (1·05 g) and NaOH (0·5 g) in 4 ml N,N-dimethylformamide (DMF) and 4 ml water were added to Ia (2 g; X = Cl) in 13 ml DMF. The mixture was heated on a steam bath for 4 hr, cooled, diluted with a large amount of 5% NaOH aq, and extracted with ether. From the extract, an oil was recovered which at ca. −30° yielded a solid, m.p. 57–59° from EtOH. (Found: C, 66·44; H, 3·75; N, 11·2; $C_{14}H_{10}N_2OS$ requires: C, 66·13; H, 3·96; N, 11·02%).

2-*Phenyl*-5-*phenylthio*-1,3,4-*thiadiazole* (Ia; X = SPh). To a warm soln of Ia (3·1 g; X = Cl) in 50 ml EtOH, a soln of NaSPh (obtained from 1·74 g thiophenol, 0·364 g Na and 20 ml EtOH) was added under $N_2$. The soln was refluxed for 5 hr and left at room temp overnight. After evaporation of the solvent (red. press.) the residue was treated with water and extracted with ether. The extract yielded 3·8 g of a solid, m.p. 88–90° from EtOH. (Found: C, 62·13; H, 3·83; N, 10·5: $C_{14}H_{10}N_2S_2$ requires: C, 62·22; H, 3·73; N, 10·37%).

2-*Anilino*-5-*phenyl*-1,3,4-*thiadiazole* (Ia; X = NHPh). Compound Ia (1·2 g; X = Cl) and aniline (1·2 g) in 12 ml EtOH were refluxed for 56 hr and left at room temp for 40 hr. The solvent was evaporated (red. press.) and the residue treated with very dilute HCl; 1·2 g were obtained, m.p. 195–197° from EtOH; lit: 199°.[3] (Found: C, 66·34; H, 4·57; N, 16·8; Calc. for $C_{14}H_{11}N_3S$: C, 66·39; H, 4·38; N, 16·59%).

2-*Phenyl*-5-*piperidino*-1,3,4-*thiadiazole* (Ia; X = $NC_5H_{10}$). Compound Ia (2 g; X = Cl) and piperidine (1·7 g) in 24 ml EtOH were refluxed for 1 hr, cooled and diluted with water: 2·05 g precipitated, m.p. 90–92° from EtOH–water. (Found: C, 63·61; H, 6·25; N, 17·15; $C_{13}H_{15}N_3S$ requires: C, 63·61; H, 6·16; N, 17·13%); UV (EtOH): $\lambda_{max}$ = 318 nm (ε = 17,100).

2-p-*Methoxyphenyl*-5-*piperidino*-1,3,4-*thiadiazole* (Ib; X = $NC_5H_{10}$). Compound Ib (2 g; X = Cl), piperidine (1·6 g) and 46 ml EtOH were refluxed for 1·5 hr, cooled, diluted with water and extracted with ether. From the ether layer 2·05 g were obtained, m.p. 102° from EtOH. (Found: C, 61·34; H, 6·00; N, 15·15; $C_{14}H_{17}N_3OS$ requires: C, 61·08; H, 6·22; N, 15·26%); UV (EtOH): $\lambda_{max}$ = 319 nm (ε = 21,100).

2-p-*Chlorophenyl*-5-*piperidino*-1,3,4-*thiadiazole* (Ic; X = $NC_5H_{10}$). Compound Ic (1·5 g; X = Cl), piperidine (1·3 g) and 43 ml EtOH were refluxed for 1·5 hr. On cooling, 1·1 g precipitated, m.p. 149° from EtOH. (Found: C, 56·17; H, 5·11; N, 15·32; $C_{13}H_{14}ClN_3S$ requires: C, 55·80; H, 5·04; N, 15·02%); UV (EtOH): $\lambda_{max}$ = 324 nm (ε = 19,300). More product was obtained on dilution of the mother liquor.

2-p-*Nitrophenyl*-5-*piperidino*-1,3,4-*thiadiazole* (Id; X = $NC_5H_{10}$). Compound Id (2 g; X = Cl), piperidine (1·55 g) and 45 ml EtOH were refluxed for ½ hr. On cooling and dilution with water 2·1 g were obtained, m.p. 206–209° from dioxan. (Found: C, 53·69; H, 4·84; N, 19·20; $C_{13}H_{14}N_4O_2S$ requires: C, 53·79; H, 4·86; N, 19·30%); UV (EtOH): $\lambda_{max}$ = 261 and 370 nm (ε = 11,500 and 18,300).

*Reactions between* Ia (X = Cl) *and* $NaN_3$.

(1) Compound Ia (3 g; X = Cl) and $NaN_3$ (1·5 g) in 34 ml DMF and 5 ml water were heated on a steam

bath for 3 hr. On cooling and dilution with water, 1·17 g precipitated, m.p. 112–114°; (Found: C, 47·45; H, 2·70; N, 34·95. Calc. for $C_8H_5N_5S$: C, 47·29; H, 2·48; N, 34·48%). The product in the solid state (Nujol mull) showed no absorption bands in the region 2500–1600 $cm^{-1}$; therefore the structure of 6-phenyl-1,3,4-thiadiazolo[3.2-*d*]-tetrazole (II) was attributed to it (lit. m.p. 103–104°[22]). The mother liquor was acidified and extracted with ether. Evaporation of the ether gave an oil which, when treated with EtOH and kept 2 days in refrigerator, yielded a solid, m.p. 153–155°, not identified.

(2) As in (1), but heating for 30 hr, only 0·36 g II were obtained. From the mother liquor, on further dilution with water, a solid precipitated which was identified as Ia (X = $NH_2$). From the filtrate, on acidification and extraction with ether, an oil was obtained that after some days gave a solid, m.p. 127–130°, not identified.

(3) In another reaction, carried out as in (1), II was isolated only in a 17·7% yield. From the mother liquor, on further dilution, precipitated Ia (X = NHCOPh), m.p. 226–229° from benzene; lit. 235°,[23] IR spectrum identical with that of an authentic specimen; correct elemental analysis. On acidification of the filtrate, a solid, m.p. 120–130°, not identified, was obtained.

*Reaction between* II *and* 1-N-*morpholino-cyclohexane*

Compound II (2 g) in 61 ml $CHCl_3$ and 1-morpholino-cyclohexene (1·64 g) in 23 ml $CHCl_3$ were refluxed for 10 hr. One mole $N_2$ per mole reactants was evolved. The solvent was distilled and the residue crystallized from dioxane–pet. ether (b.p. 60–120°). 2·2 g. N-(*5-phenyl-1,3,4-thiadiazol-2-yl)cyclopentane-carboxyimidyl-4-morpholine* III were obtained, m.p. 127–129°. (Found: C, 62·84; H, 6·51; N, 16·20; $C_{18}H_{22}N_4OS$ requires: C, 63·14; H, 6·48; N, 16·36%).

*Hydrolysis of* III

(a) Compound III (1 g) was refluxed for 3 hr with 65 ml 10% $H_2SO_4$. After cooling, filtering and washing with water 0·6 g *2-cyclopentan-carboxyamino-5-phenyl-1,3,4-thiadiazole* were obtained, m.p. 226–227° from dioxan. (Found: C, 61·58; H, 5·69; N, 15·0; $C_{14}H_{15}N_3OS$ requires: C, 61·53; H, 5·53; N, 15·38%).

(b) The product (0·25 g) obtained in (a) in 30 ml AcOH and 3·5 ml 48% HBr were refluxed, with stirring, for 4 hr. Solvents were removed *in vacuo*, and the residue, washed with a 20% soln of NaOH and with water, gave Ia (X = $NH_2$) in good yield.

*Kinetics*

Commercial abs EtOH was treated with Mg and distilled; "analytical grade" benzene was purified twice by a standard treatment with $AlCl_3$, dried on Na and distilled.

Runs were carried with concentrations of thiadiazolic compounds from $3 \cdot 10^{-4}$ to $4 \cdot 10^{-3}$ mole $l.^{-1}$ and piperidine concentrations from 0·015 to 0·20 mole $l.^{-1}$ in EtOH, and from 0·10 to 1·0 mole $l.^{-1}$ in benzene. Reagents were weighed and dissolved; aliquots of the soln, as soon as prepared, were poured into separate flasks, that were introduced in a thermostat, accurate to ±0·1°. The content of each flask, withdrawn at the desired time, was quickly diluted with EtOH, by a standard procedure, in order to quench the reaction and reach the concentration range (ca. $5 \cdot 10^{-5}$ mole $l.^{-1}$ of total thiadiazoles) for spectrophotometric analyses. The latter were performed on the best wavelength for analysis of piperidino-derivatives I (X = $NC_5H_{10}$), that is 320 nm (Ia), 340 nm (Ib), 325 nm (Ic) or 370 nm (Id).

Absorbances ($D_t$) were read on a Perkin–Elmer Infracord 137 apparatus. Most reactions were kinetically followed during 1 to 2 half-lives. "Infinity" samples, taken at about 20 half-lives, were used for measurement of the absorbance at "infinite time" ($D_\infty$). Pseudo first-order rate constants ($k'$) were obtained from linear plots of $-\ln(D_\infty - D_t)$ vs. time, by the least squares procedure. Second-order rate constants ($k$) were derived as ratios of $k'$-values to the initial piperidine concentration, corrected for solvent thermal expansion. Arrhenius activation energy ($\Delta E^\ddagger$), frequency factor ($A$) and activation entropy ($\Delta S^\ddagger$) were computed by standard methods. Probable errors were evaluated for each quantity.[24] On the average, rate constants $k$ had probable errors around 1·7%, and in no case larger than 4%.

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