Syntheses of Heterocyclic Compounds. Part XII.[1] Halogen-Substituted 3-Arylsydnones

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The reactivity of halogen in the benzene ring and also in the 4-position of the sydnone ring of various arylsydnones towards nucleophiles has been investigated. The course of ring-fission in 4-halogenosydnones induced by primary amines differs from that of secondary amines. The reaction in the latter case provides a preparative route to diamino-acid amides. Several new halogenosydnones are described.

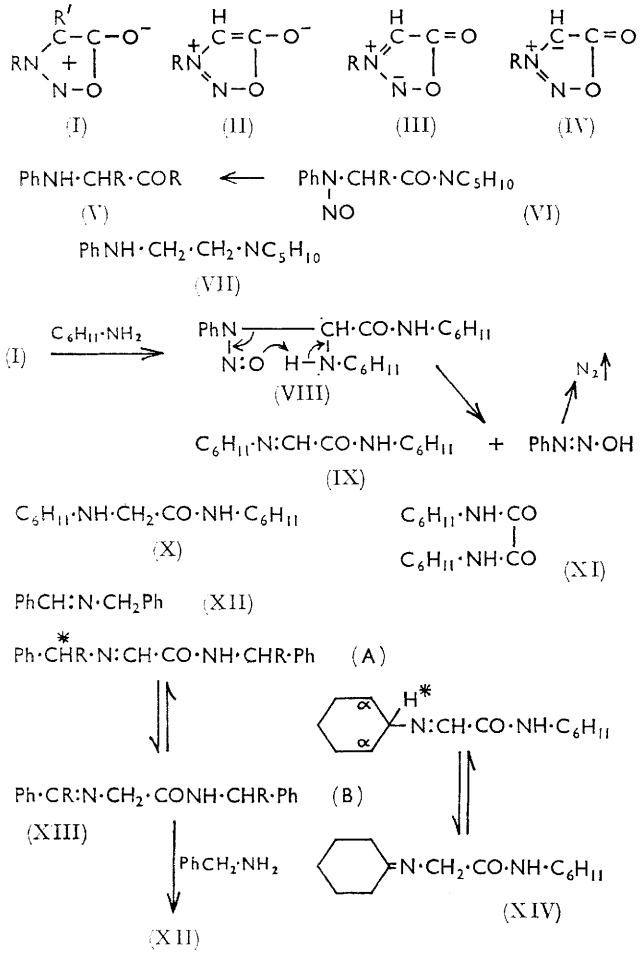
RECENT physical measurements such as the dissociation constant of 3-carboxymethylsydnone,[2] the n.m.r. spectra of a number of sydnones,[3] the Hammett reaction constant (ρ) of *N*-(4-chloro-3-nitrophenyl)sydnone,[4] as well as molecular orbital calculations,[5] indicate that in the mesoionic sydnone system the positive charge is localised mainly on the nitrogen in the 3-position [(II)—(IV)]. The importance of structures (II)—(IV) is also borne out by the behaviour of sydnones in 1,3-dipolar additions [6] and by the lack of reactivity of the benzene ring in 3-phenylsydnone (I; R = Ph, R′ = H) towards electrophilic substitution. Conversely, a halogen substituent, especially fluorine in the 2- or 4-position of the benzene ring (I; R = *o*- or *p*-F·C_6H_4, R′ = H) might be activated nucleophilically by the positively charged nitrogen in (II)—(IV). This situation is somewhat analogous to the activation of fluorine in the *o*- and *p*-fluorobenzenediazonium cation.[7] We found, however, that the fluorine atom in the monofluorophenylsydnones (I; R = *o*-, *m*-, and *p*-F·C_6H_4, R′ = H) was not replaced by aniline, piperidine, or methanolic sodium methoxide, and even the sodium salt of toluene-ω-thiol in boiling cellosolve could not be made to react. We attempted to increase activation of the fluorine by nitration of *p*-fluorophenylsydnone (I; R = *p*-F·C_6H_4, R′ = H) but obtained only *p*-fluorophenol. The chloro-isomer did, however, give the required 4-nitro-compound (I; R = *p*-Cl·C_6H_4, R′ = NO_2), but again the halogen was not replaceable by any of the above reagents in the cold, and warming caused the nitrosydnone to decompose.

Next, we intended to study the anionic mobility of halogen in 4-halogenosydnones. We prepared the 4-iodo- and 4-bromo-compounds (I; R = Ph, R′ = I or Br) by literature methods [8,9] but failed to make the 4-fluoro-isomer by treating the 4-iodo- or 4-bromo-phenylsydnone with potassium fluoride in dimethylformamide or dimethyl sulphoxide and also by using antimony trifluoride in nitromethane. Dehalogenation to give 3-phenylsydnone occurred in the latter case.

We found that 4-iodo- and 4-bromo-phenylsydnone lost the halogen when treated with hydrazine hydrate, and gave a quantitative yield of 3-phenylsydnone (I; R = Ph, R′ = H). This is in disagreement with the claim [9] that iodine is replaced to yield 4-hydrazinosydnone (I; R = Ph, R′ = NH·NH_2).

[1] Part XI, R. Garner and H. Suschitzky, preceding Paper.
[2] F. H. C. Stewart, *Chem. Rev.*, 1964, **64**, 129.
[3] F. H. C. Stewart and N. Danieli, *Chem. and Ind.*, 1963, 1926.
[4] C. Tin-Lok, J. Miller, and F. Stansfield, *J. Chem. Soc.*, 1964, 1213.
[5] C. A. Coulson, "Valence," 2nd edn., Oxford University Press, London, 1961, p. 386.
[6] R. Huisgen, *Angew. Chem.* (*Internat. Edn.*), 1963, **2**, 565.
[7] I. K. Barben and H. Suschitzky, *J. Chem. Soc.*, 1960, 2735; P. Miles and H. Suschitzky, *Tetrahedron*, 1962, **18**, 1369.
[8] K. Nakahara and M. Ohta, *J. Chem. Soc. Japan*, 1956, **77**, 1306.
[9] M. Ohta and H. Kato, *Bull. Chem. Soc. Japan*, 1957, **30**, 210.

Treatment of the 4-bromosydnone (I; R = Ph, R′ = Br) with cold piperidine had no effect, but, on heating, ring-fission and bromine replacement occurred undoubtedly in that order, leading to the diamino-acid amide (V; R = $C_5H_{10}N$). Its structure was established by a study of its infrared and n.m.r. spectra [10] and also by hydrolysis which gave piperidine and aniline.



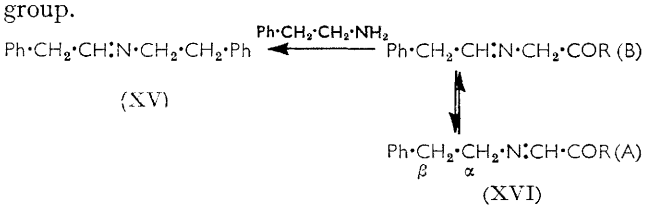
The fact that 3-phenylsydnone is cleaved by hot piperidine to the nitroso-compound (VI; R = H), that the halogen in 4-halogenosydnones does not react with amines, and that piperidine hydrobromide proved a good denitrosating agent suggests that the likely precursor of the amino-acid amide is the nitroso-compound (VI; R = Br) in which the bromine is subsequently replaced by piperidine. We also considered an alternative route, namely elimination of NOBr from the intermediate nitroso-compound (VI; R = Br) followed by addition of piperidine across the resulting azomethine linkage to form the product (V; R = $C_5H_{10}N$). Attempts to induce piperidine addition across the double bond in various Schiff bases failed, however, under the conditions of the reaction.

Morpholine and *N*-methylpiperazine gave the analogous amides (V; R = morpholino and 4-methylpiperazinyl). Reduction of the piperidino-amide with lithium aluminium hydride in ether gave the unsymmetrically substituted diamine (VII) and piperidine. The nature of the aminolysis products from the 4-bromosydnone (I; R = Ph, R′ = Br) with primary amines was unexpected. Cyclohexylamine gave the anil (IX) with nitrogen evolution involving the steps (I ⟶ VIII ⟶ IX). We recently adduced evidence [10] for this mechanism by using the *p*-chloro- and *p*-fluorophenylsydnone (I; R = *p*-Cl·C_6H_4 or *p*-F·C_6H_4, R′ = Br) in this reaction. Constitution of the anil was established by reduction to the glycylamide (X) which was identical with the compound obtained from chloroacetyl chloride and cyclohexylamine. A very small quantity of *NN*′-dicyclohexyloxamide (XI), unambiguously prepared from oxalyl chloride and cyclohexylamine, was another product of the aminolysis.

Benzylamine, however, yielded benzylidenebenzylamine (XII) and not as expected by analogy the Schiff base (XIII-A; R = H). Both phenyl groups in the anil (XII) are derived from the amine because 4-bromo-3-*p*-chlorophenylsydnone (I; R = *p*-Cl·C_6H_4, R′ = Br) gave the same product with benzylamine. The different aminolysis result with benzylamine and cyclohexylamine is explicable on the basis of the same mechanism by considering the tautomeric mobility of the respective methyleneazomethines [11] (XIII and XIV; A and B) that could be formed in the reaction. The anil (XIV-A) the main product from cyclohexylamine is evidently more stable than its tautomer (XIV-B) because of conjugation of its azomethine link (–N=C<) with the amide carbonyl, and also, more important, because prototropy of H* in (XIV-A) to give the tautomeric (XIV-B) is foiled by the (+*I*) effect of the α-methylene groups in the cyclohexane ring. On the other hand, conjugation of the azomethine bond with the benzene ring favours the formation of compound (XIII-B; R = H) in the reaction with benzylamine. Subsequently the amine moiety in this Schiff base (XIII-B; R = H) is replaced by benzylamine, leading to the observed product (XII). Such a replacement we found to be feasible by carrying out test experiments (see Experimental section). Exchange of the amine part in the "A-tautomer" (XIV) by the reagent cyclohexylamine would, of course, not alter the nature of the compound. The important role of the (+*I*) effect on the mobility of the triad system (XIII) was further demonstrated by using α-methylbenzylamine in the aminolysis. As expected, the Schiff base (XIII-A; R = Me) was the main product, since the α-methyl group impedes ionisation of the hydrogen (H* in XIII-A; R = Me), thus preventing formation of the tautomer. The outcome of the reaction with phenethylamine was analogous to that of benzylamine, namely production of the anil (XV). This is understandable since proton mobility necessary for converting the initially formed anil (XVI-A; R = NH·CH_2·CH_2Ph) into its tautomer (XVI-B) is

[10] M. Bellas and H. Suschitzky, *Chem. Comm.*, 1965, 136.
[11] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 545.

facilitated by hyperconjugation of the β-methylene group.



EXPERIMENTAL

3-Fluorophenylsydnones.—The appropriate fluoroaniline (1 mol.) was added to an aqueous solution of sodium chloroacetate (1 mol.), and the mixture refluxed for 10 min., cooled, and filtered. The glycine was purified by dissolving it in 4N-sodium hydroxide and extracting the solution with ether. On addition of hydrochloric acid to the aqueous solution the glycine was reprecipitated. Recrystallisation was from a petroleum–ethyl acetate mixture, and details are given in Table 1.

TABLE 1

N-Fluorophenylglycines (R·NH·CH_2·CO_2H)

		Yield	Found (%)			Reqd. (%)	
R	M. p.	(%)	C	H	Formula	C	H
o-F·C_6H_4	127°	20	56·8	4·9	$C_8H_8FNO_2$	56·8	4·8
m-F·C_6H_4	128	35	56·8	4·8	$C_8H_8FNO_2$	56·8	4·8
p-F·C_6H_4	138 *	54	—	—	—	—	—

* Lit.,[12] m. p. 140°.

From the above phenylglycines the *N*-nitroso-compounds (Table 2) were prepared by Eade and Earl's method [13] and obtained as needles (from ethanol).

TABLE 2

N-Nitroso-*N*-phenylglycines, R·N(NO)·CH_2·CO_2H

		Yield	Found (%)			Reqd. (%)	
R	M. p.	(%)	C	H	Formula	C	H
o-F·C_6H_4	88°	70	48·5	3·8	$C_8H_7FN_2O_3$	48·5	3·6
m-F·C_6H_4	102	79	48·4	3·6	$C_8H_7FN_2O_3$	48·5	3·6
p-F·C_6H_4	96	76	48·9	4·0	$C_8H_7FN_2O_3$	48·5	3·6

The *N*-nitroso-compounds (1 g.) listed in Table 2 were dissolved in acetic anhydride (3 ml.) and the solution kept for 3 days at room temperature in the dark. Addition of water precipitated the crude *fluorophenylsydnones* which crystallised from aqueous ethanol (Table 3).

TABLE 3

Fluorophenylsydnones (I; R′ = H)

		Yield	Found (%)			Reqd. (%)	
R	M. p.	(%)	C	H	Formula	C	H
o-F·C_6H_4	109°	57	53·7	3·0	$C_8H_5FN_2O_3$	53·4	2·8
m-F·C_6H_4	131	50	53·6	2·7	$C_8H_5FN_2O_3$	53·4	2·8
p-F·C_6H_4	154	70	53·0	2·4	$C_8H_5FN_2O_3$	53·4	2·8

No ionic fluorine could be detected after prolonged treatment of the above sydnones with warm piperidine, aniline, methanolic sodium methoxide, or a solution of the sodium salt of toluene-ω-thiol in cellosolve.

When *p*-fluorophenylsydnone was nitrated as described for the *p*-chloro-isomer (below) the only product isolated was a red oil which on treatment with hot 2N-hydrochloric acid gave *p*-fluorophenol, identified by its infrared spectrum.

[12] N. B. Tien, Ng. Ph. Buu-Hoï, and Ng. O. Xuong, *J. Org. Chem.*, 1958, **23**, 186.

[13] R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 1946, 591.

3-(p-Chlorophenyl)-4-nitrosydnone.—*p*-Chlorophenylsydnone [14] (2 g.) in sulphuric aid (40 ml.) was nitrated at 0° by dropwise addition of nitric acid (4 ml.) during 10 min. with stirring. The reaction was then allowed to proceed for 20 min. at −5°, and the mixture finally poured on to ice. The crude product was filtered off, washed on the filter (water), and dried in a vacuum-desiccator. Chromatography on a silica column with benzene as eluent gave a yellow oil which solidified on contact with petroleum. Recrystallisation from this solvent yielded the *nitro-compound* (8%), m. p. 98° (decomp.) (Found: C, 40·1; H, 1·7; N, 17·4. $C_8H_4ClN_3O_4$ requires C, 39·8; H, 1·7; N, 17·4%). Its infrared spectrum showed strong bands at 1800 (sydnone carbonyl) and at 1520 and 1320 $cm.^{-1}$ (aromatic NO_2). The nitro-compound did not react with cold methanolic sodium methoxide and decomposed when warmed in this reagent.

Attempted Preparation of 4-Fluoro-3-phenylsydnone.—(*a*) 4-Bromo- or 4-iodo-3-phenylsydnone (0·5 g.), prepared by the method of Ohta and his co-workers,[8,9] was heated in dimethyl sulphoxide or dimethylformamide (10 ml.) containing dry, finely powdered potassium fluoride (1 g.) for 10 hr. at 125°. Only starting material was recovered.

(*b*) 4-Iodo-3-phenylsydnone (0·4 g.) was refluxed in redistilled nitromethane (20 ml.) in presence of antimony trifluoride (0·5 g.) for 12 hr. Separation of the reaction mixture after removal of solvent by thin-layer chromatography on silica gel with benzene gave starting material and 3-phenylsydnone only. When the experiment was carried out without antimony trifluoride deiodination did not occur.

Bromination of Sydnones.—In a modification of Ohta and Kato's [15] procedure, to a well-stirred suspension of 3-*p*-chlorophenylsydnone (3·5 g.) in chloroform (8 ml.) and ether (150 ml.) containing sodium hydrogen carbonate (10 g.), bromine (1·5 ml.) was slowly added. The mixture was refluxed for 0·5 hr., the solvent finally driven off, and the residue neutralised with dilute hydrochloric acid. Recrystallisation from methanol gave *4-bromo-3-p-chlorophenylsydnone* (3·0 g.) as needles, m. p. 122° (Found: C, 34·9; H, 1·8. $C_8H_4BrClN_2O_2$ requires C, 34·9; H, 1·5%). *4-Bromo-3-p-fluorophenylsydnone* prepared as above had m. p. 105° (Found: C, 37·4; H, 1·8. $C_8H_4BrFN_2O_2$ requires C, 37·1; H, 1·6%).

Reactions of 4-Bromo-3-phenylsydnone.—(*a*) *With hydrazine.* The 4-bromo- or 4-iodo-compound (1 g.) gave, on reflux in hydrazine hydrate (10 ml.) for 1 hr., a nearly quantitative yield of 3-phenylsydnone.

(*b*) *With secondary amines.* In a typical experiment the sydnone (1 g.) was refluxed in piperidine (10 ml.) for 2 hr. and the reaction mixture poured into water, to give (*N-phenyl-α-piperidinoglycyl*)*piperidine* (1 g.) (V; R = $C_5H_{10}N$), m. p. 128°, as needles (from ethyl acetate–petroleum) (Found: C, 71·3; H, 9·0. $C_{18}H_{27}N_3O$ requires C, 71·7; H, 9·0%). On hydrolysis (2N-sodium hydroxide) the reaction mixture when extracted with ether yielded piperidine (identified as picrate, m. p. 145°) by driving off the solvent. Steam-distillation of the hydrolysate followed by ether extraction of the steam distillate gave, on addition of a picric acid solution in benzene to the extract, the picrate of aniline. Reduction of the glycylpiperidine (V; R = $C_5H_{10}N$) (1·5 g.) with lithium aluminium

[14] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 1949, 307.

[15] M. Ohta and H. Kato, *J. Chem. Soc. Japan*, 1957, **78**, 1653.

hydride (0·4 g.) in boiling ether (150 ml.) for 4 hr. gave, after the usual working-up procedure, an oil which smelt strongly of piperidine. The oil was purified by thin-layer chromatography on silica with a mixture of benzene (70%) and chloroform, yielding 1-anilino-2-piperidinoethane (0·35 g.) which gave a *picrate*, m. p. 145° (Found: C, 52·6; H, 5·3. $C_{16}H_{23}N_5O_7$ requires C, 52·6, H, 5·4%), and a di-hydrochloride, m. p. 176° (lit.,[16] 178—179°) (Found: C, 56·2; H, 8·3. Calc. for $C_{13}H_{22}Cl_2N_2$: C, 56·4; H, 8·0%).

With morpholine and the sydnone (1 g.) the (N-*phenylglycyl*)*morpholine* (V; R = morpholino), m. p. 150°, was obtained (1 g.) (Found: C, 62·3; H, 7·4. $C_{16}H_{12}N_3O_3$ requires C, 62·0; H, 7·6%). Its infrared spectrum had peaks at 3300 (NH) and 1640 cm.$^{-1}$ (tertiary amide). Its hydrolysis (2N-sodium hydroxide) gave mainly aniline.

From *N*-methylpiperazine the *piperazinyl-amide* was obtained, m. p. 135° (Found: C, 65·8; H, 8·8. $C_{18}H_{29}N_5O$ requires C, 65·3; H, 8·8%).

(*c*) *With primary amines.* 4-Bromo-3-phenylsydnone (1·0 g.) and cyclohexylamine (12 ml.) were heated on a water-bath for 6 hr., during which time a slow evolution of nitrogen was observed. The mixture was poured into water and the precipitate filtered off. It was dried, and extracted with hot petroleum (b. p. 40—60°), leaving a residue of *NN'*-dicyclohexyloxamide (0·08 g.), m. p. 269° (lit.,[17] 273°), identical with a sample prepared from oxalyl chloride and cyclohexylamine (Found: C, 66·5; H, 9·5. Calc. for $C_{14}H_{24}N_2O_2$: C, 66·6; H, 9·6%). Evaporation of the petroleum gave the cyclohexylamine *Schiff base* (IX) (0·4 g.), m. p. 114° (Found: C, 71·5; H, 10·3; N, 11·6. $C_{14}H_{24}N_2O$ requires C, 71·2; H, 10·3; N, 11·8%). Reduction of the anil as ethanol solution over palladium–charcoal with hydrogen at n.t.p. gave *NN'*-dicyclohexylglycinamide (X) as a syrup identical with a specimen prepared from chloroacetyl chloride and cyclohexylamine (infrared spectrum). It was characterised as its *picrate*, m. p. 203° (Found: C, 51·7; H, 6·6. $C_{20}H_{29}N_5O_8$ requires C, 51·4; H, 6·3%).

Other amines under similar conditions reacted as follows. Benzylamine gave benzylidenebenzylamine, b. p. 130°/1·5 mm. (0·7 g.), n_D^{20} 1·596 (lit.,[18] 1·601) when heated with the sydnone (0·9 g.). The reaction mixture from α-methylbenzylamine was chromatographed on alumina and eluted with a benzene–chloroform mixture (80 : 20), to give the *anil* (XIII-A; R = Me), m. p. 116° (Found: C, 77·2; H, 7·0. $C_{18}H_{20}N_2O$ requires C, 77·2; H, 7·2%). Its infrared spectrum showed bands at 1680 (amide >CO), 1650 (anil >C=N), and 3320 cm.$^{-1}$ (>NH). Phenethylamine yielded a small quantity of *NN'*-phenethyloxamide, m. p. 180° (lit.,[19] 186°), identical (mixed m. p. and spectrum) with a sample prepared from oxalyl chloride and phenethylamine, and mainly the unstable *phenethylidenephenethylamine* (XV), m. p. 32°, whose *picrate* had m. p. 142° (Found: C, 58·1; H, 5·0. $C_{22}H_{20}N_4O_7$ requires C, 58·4; H, 4·5%).

Reactions of Other 4-Bromosydnones.—Cyclohexylamine (20 ml.) and 4-bromo-3-*p*-chlorophenylsydnone (3 g.), when treated as above, gave the Schiff base (IX). In addition, chlorobenzene was obtained by steam-distillation of the acidified reaction mixture, and extraction of the distillate with ether. With benzylamine the result was as for its reaction with 4-bromo-3-phenylsydnone (see above).

4-Bromo-3-*p*-fluorophenylsydnone and cyclohexylamine again yielded the Schiff base (IX) and ionic fluorine was detected in the reaction mixture.[10]

3-Phenylsydnone and Piperidine.—Phenylsydnone (1 g.) and piperidine (10 ml.) were refluxed for 3 hr., and the mixture poured on to ice. Recrystallisation of the precipitate from aqueous ethanol gave (*N-nitroso*-N-*phenylglycyl*)*piperidine*, m. p. 80° (1 g.), as pale yellow needles (Found: C, 63·0; H, 6·9. $C_{13}H_{17}N_3O_2$ requires C, 63·1; H, 6·9%).

Reaction of Schiff Bases with Amines.—On refluxing benzylideneaniline in excess of piperidine for 1 hr., a quantitative yield of phenyldipiperidinomethane, m. p. 80° was obtained. Benzylamine and the Schiff base gave, under similar conditions, benzylidenebenzylamine.

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