Heterocyclic Syntheses with Isothiocyanatoformic Esters and their Derivatives

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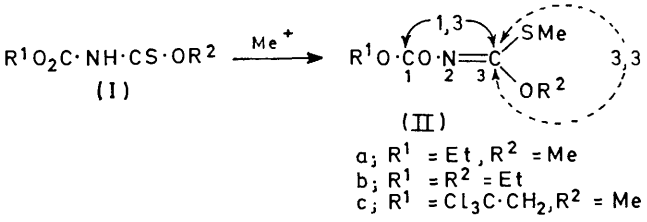
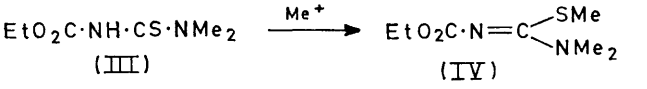
With difunctional nucleophiles, *N*-[alkoxy(methylthio)methylene]carbamates undergo cyclisation either in the 1,3- or in the 3,3-sense. The former type of reaction (reagents in parentheses) gives 1,2,4-triazol-5-ones (hydrazine), 1,2,4-oxadiazol-5-ones (hydroxylamine), and 1,3,5-triazin-2-ones (guanidines). 3,3-Cyclisation (diamines) provides a novel and mild route to cyclic guanidines.

THE readily accessible carbamates [*e.g.* (I) and (III)] derived from the addition of alcohols and amines to isothiocyanatoformic esters have been known for many years.[1] Despite their potential as intermediates for heterocyclic synthesis, little work of this type has been

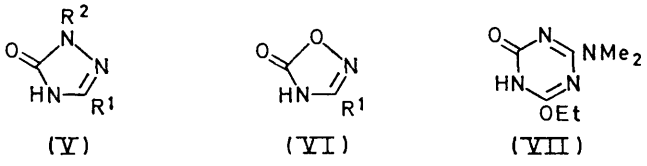


(I) (II)

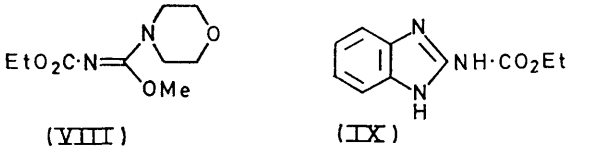
a; R^1 = Et, R^2 = Me
b; R^1 = R^2 = Et
c; R^1 = $Cl_3C{\cdot}CH_2$, R^2 = Me



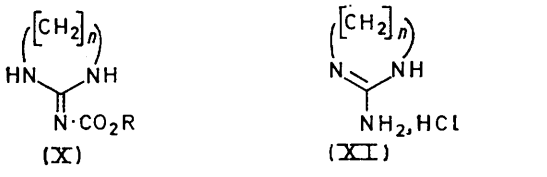
(III) (IV)



(V) (VI) (VII)



(VIII) (IX)



(X) (XI)

reported. In the light of our present work many of the structures assigned previously [2] to products are clearly incorrect.

Rather than isolate the unstable isothiocyanatoformic esters,[3] we found it more convenient to generate them *in situ*. In order to enhance the reactivity of the esters (I) and (III) to nucleophilic attack at C-3 they were converted into their *S*-methyl derivatives (II) and (IV). Thus (IIa) reacted with morpholine exclusively at C-3 under mild conditions to give the morpholinomethylenecarbamate (VIII).

With difunctional nucleophiles the esters (II), following initial attack at C-3, undergo cyclisation either in the 1,3- or in the 3,3-sense. The 1,3-cyclisations with hydrazine, hydroxylamine, and guanidines give alkoxy-triazolones (V; R^1 = OMe), -oxadiazolones (VI; R^1 = OMe) and -triazinones (VII), respectively. This method for 3-alkoxy-1,2,4-oxadiazol-5-ones is simpler than a recently [4] described synthesis. The preparation of the phenyltriazolone (V; R^1 = OMe, R^2 = Ph) confirms Katritzky's assignment [5] of this structure to the product obtained from phenylurazole and diazomethane.

The dimethylaminomethylenecarbamate (IV) also underwent 1,3-cyclisation reactions with the same reagents to give the dimethylamino-heterocycles (V and VI; R^1 = NMe_2).

With 1,2- (aromatic and aliphatic) and 1,3- (aliphatic) diamines, the esters (II) underwent 3,3-cyclisation reactions providing a C-1 unit in the formation of the benzimidazole (IX) and the ethoxycarbonylguanidines (X; R = Et). The occurrence of the latter reaction led us to consider its potential as a route from diamines to cyclic guanidines. A similar route *via* dimethyl *N*-tosyliminodithiocarbonimidate gives *N*-tosylguanidines; the tosyl group can be removed with liquid hydrogen fluoride.[6] Our method, in which alkoxycarbonyl groups are used for protection, offered the possibility of avoiding this hazardous reagent. However, difficulty was experienced in the attempted hydrolysis of the carbamate groups and attention was directed towards the readily removed trichloroethoxycarbonyl group.[7] In a single-step reaction trichloroethyl chloroformate was converted into the methylenecarbamate (IIc). The reaction of this reagent with ethylene- and trimethylene-diamines occurred under very mild

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conditions (0°; MeOH) giving *ca.* 80% yields of the guanidine esters (X; R = $Cl_3C{\cdot}CH_2$, $n = 2$ or 3). Zinc dust (0°) reduction of these gave, in turn, good yields of the guanidine hydrochlorides (XI; $n = 2$ or 3), the overall route providing exceptionally mild conditions for the conversion of diamines into cyclic guanidines.

EXPERIMENTAL

N.m.r. data refer to solutions in deuteriochloroform with tetramethylsilane as an internal standard, recorded with a Perkin-Elmer R10 instrument. I.r. spectra were determined for Nujol mulls. Unless otherwise stated, light petroleum refers to the fraction b.p. 60—80°. No attempt was made to optimise reaction conditions; the yields given are, for the most part, those obtained in single experiments.

Ethyl Methoxy(thiocarbonyl)carbamate (Ia).—To a stirred and cooled solution of potassium isothiocyanate (291·5 g, 3 mol) in anhydrous acetone (1·5 l), ethyl chloroformate (325·5 g, 3 mol) was added dropwise during 1 h. The mixture was stirred for a further 2 h; methanol (96 g, 3 mol) was then added and the whole was kept overnight. The oil obtained by filtration and evaporation was dissolved in ether–light petroleum (1 : 1) and treated with charcoal. On cooling the solution to −35°, the product (230 g, 48%) separated as a pale yellow powder, m.p. 59—61°. A sample sublimed at 50° and 0·01 mmHg gave white prisms, m.p. 66° (lit.,[1] 65—66°).

Ethyl Ethoxy(thiocarbonyl)carbamate (Ib).—Prepared as above but using ethanol, the product (49%) had m.p. 44—45° (lit.,[2] 46°).

Ethyl N-[*Methoxy(methylthio)methylene*]*carbamate* (IIa).—To a stirred solution of potassium carbonate (191 g; anhydrous) in water (2·25 l) was added the crude ethyl methoxy(thiocarbonyl)carbamate (225 g, 1·38 mol). After 15 min stirring the solution was filtered and dimethyl sulphate (174 g, 1·38 mol) was added dropwise to the filtrate with vigorous stirring during 45 min. The mixture was then stirred for 1 h, and extracted with light petroleum (600 ml). After drying ($MgSO_4$), the solution was cooled to −40°; the *product* separated as a pale cream powder (150 g, 61%), m.p. 34—36°. Recrystallisation from light petroleum gave needles, m.p. 35—36° (Found: C, 40·8; H, 6·25; N, 7·9. $C_6H_{11}NO_3S$ requires C, 40·65; H, 6·25; N, 7·9%), $\nu_{max.}$ 1680s, 1550s, 1285s, 1195s, 1070s, and 805m cm^{-1}, τ 5·95 (2H, q, J 7 Hz), 6·15 (3H, s), 7·7 (3H, s), and 8·75 (3H, t, J 7 Hz).

Ethyl N-[*Ethoxy(methylthio)methylene*]*carbamate* (IIb).—Prepared analogously from ethyl ethoxy(thiocarbonyl)carbamate, the *product* (71%) had m.p. 38—39° (light petroleum) (Found: C, 43·85; H, 7·0; N, 7·5. $C_7H_{13}NO_3S$ requires C, 44·1; H, 6·85; N, 7·35%).

Trichloroethyl N-[*Methoxy(methylthio)methylene*]*carbamate* (IIc).—To a cooled and stirred solution of potassium isothiocyanate (5·72 g, 0·059 mol) in anhydrous acetone (100 ml), trichloroethyl chloroformate (12·5 g, 0·059 mol) was added dropwise during 20 min. The mixture was kept at 20° during the addition and for 2 h afterwards, with stirring. Methanol (1·9 g, 0·059 mol) was then added, and the mixture was stirred for 3 h. Anhydrous potassium carbonate (8·14 g, 0·059 mol) was then added, followed, dropwise, by dimethyl sulphate (7·43 g, 0·059 mol), with vigorous stirring. The exothermic reaction was controlled at 30° by water-bath cooling. The mixture was stirred overnight; filtration and evaporation then gave a pale yellow oil. A solution of this in chloroform (50 ml) was washed [H_2O (50 ml)], dried ($MgSO_4$), and evaporated, finally at 0·1 mmHg and 60° for 45 min. The residual oil was taken up in a mixture of n-hexane (150 ml) and ether (150 ml) and treated with charcoal. The solution was cooled to −60° and the *product* separated as prisms (7·2 g, 44%), m.p. 34—35° (Found: C, 25·3; H, 2·7; N, 4·9. $C_6H_8Cl_3NO_3S$ requires: C, 25·65; H, 2·85; N, 5·0%).

Ethyl 4,4-*Dimethyl*-3-*thioallophanate* (III).—Prepared in an analogous manner to ethyl methoxy(thiocarbonyl)carbamate by addition of dimethylamine (1 equiv.) to ethyl isothiocyanatoformate prepared *in situ*, the *product* (46%) crystallised from ether at −60°; m.p. 67—68° (Found: C, 40·65; H, 6·7; N, 15·6. $C_6H_{12}N_2O_2S$ requires C, 40·9; H, 6·2; N, 15·9%).

Ethyl N-[*Dimethylamino*(*methylthio*)*methylene*]*carbamate* (IV).—A mixture of ethyl 4,4-dimethyl-3-thioallophonate (7·5 g), anhydrous potassium carbonate (11·8 g), and methyl iodide (6·7 g) in acetone (75 ml) was heated under reflux for 2·5 h, cooled, filtered, and evaporated. The residual oil was taken up in ether (60 ml) and the solution was filtered to remove potassium iodide. Removal of the ether and distillation of the residual oil gave the *product* (7·1 g, 88%), b.p. 90—93° at 0·04 mmHg, n_D^{23} 1·5280 (Found: C, 44·5; H, 7·5; N, 14·45. $C_7H_{14}N_2O_2S$ requires C, 44·2; H, 7·35; N, 14·75%).

3-*Methoxy*-1,2,4-*triazol*-5(4H)-*one* (V; R^1 = OMe, R^2 = H).—A solution of ethyl *N*-[methoxy(methylthio)methylene]carbamate (30 g, 0·17 mol) in ethanol (150 ml) was treated with hydrazine hydrate (8·5 g, 0·17 mol). After the mildly exothermic reaction, the mixture was heated under reflux for 2 h. On cooling the *product* separated and crystallised from ethanol as prisms (10·6 g, 56%), m.p. 219—220° (decomp.) (Found: C, 31·0; H, 4·35; N, 36·3. $C_3H_5N_3O_2$ requires C, 31·3; H, 4·35; N, 36·5%), $\nu_{max.}$ *ca.* 3100s,br and 1725s cm^{-1}.

3-*Methoxy*-1-*phenyl*-1,2,4-*triazol*-5(4H)-*one* (V; R^1 = OMe, R^2 = Ph).—Prepared similarly from ethyl *N*-[methoxy(methylthio)methylene]carbamate and phenylhydrazine, the *product* (49%) crystallised from ethanol as prisms, m.p. 197—198° (lit.,[5] 197°).

3-*Methoxy*-1,2,4-*oxadiazol*-5(4H)-*one* (VI; R^1 = OMe).—A mixture of ethyl *N*-[methoxy(methylthio)methylene]carbamate (9 g), hydroxylamine hydrochloride (3·9 g), and anhydrous sodium acetate (4·6 g) in ethanol (54 ml) and water (21 ml) was heated under reflux for 1·5 h. Most of the ethanol was removed under reduced pressure, and the resultant aqueous solution was continuously extracted with chloroform for 24 h. Evaporation of the extract, and crystallisation of the residue from ethanol–light petroleum gave the *product* as needles (2·5 g, 42%), m.p. 151—152° (Found: C, 31·4; H, 3·45; N, 24·3. $C_3H_4N_2O_3$ requires C, 31·05; H, 3·45; N, 24·15%), $\nu_{max.}$ 3100s,br, 1815s, and 1635s cm^{-1}.

4-*Dimethylamino*-6-*ethoxy*-1,3,5-*triazin*-2(1H)-*one* (VII; R^1 = Et).—To a solution of sodium (0·61 g, 0·026 g atom) in anhydrous ethanol (50 ml) was added *NN*-dimethylguanidine hydrochloride (3·23 g, 0·026 mol), and the mixture was heated under reflux for 30 min. Ethyl *N*-[ethoxy(methylthio)methylene]carbamate (5·0 g, 0·026 mol) was then added and the mixture was heated under reflux for 22 h. After removal of the ethanol, water (75 ml) was added and the pH of the solution adjusted to 6—7 with

acetic acid. The *product* (3·2 g, 67%) was separated and washed with water, and crystallised from ethanol as plates, m.p. 213—214° (re-solidifies and re-melts *ca.* 230°; see later) (Found: C, 45·65; H, 6·55; N, 30·35. $C_7H_{12}N_4O_2$ requires C, 45·65; H, 6·5; N, 30·45%), τ −2·1br (1H), 5·57 (2H, q, *J* 7 Hz), 6·83 (6H, s), and 8·65 (3H, t, *J* 7 Hz).

Thermal Rearrangement of 4-Dimethylamino-6-ethoxy-1,3,5-triazin-2-one.—The triazinone (0·5 g) was heated in an oil-bath. The compound melted at 213°, re-solidified at 220°, and re-melted at 230°. After allowing the material to cool, crystallisation (EtOH) gave needles (0·42 g), m.p. 233—235° (Found: C, 45·55; H, 6·1; N, 30·65. Calc. for $C_7H_{12}N_4O_2$: C, 45·65; H, 6·5; N, 30·45%), τ −0·85br (1H), 6·13 (2H, q, *J* 7 Hz), 6·84 (6H, s), and 8·81 (3H, t, *J* 7 Hz). The n.m.r. spectrum indicates that the ethyl group migrates to one of the ring N atoms.

3-Dimethylamino-1,2,4-triazol-5(4H)-one (V; R^1 = NMe_2, R^2 = H).—Like the analogous 3-methoxytriazolinone the compound was prepared by heating equimolecular proportions of hydrazine hydrate and ethyl *N*-[dimethylamino(methylthio)methylene]carbamate in ethanol. The *product* (28%) had m.p. 262—263° (from ethanol) (Found: C, 37·45; H, 6·25; N, 43·75. $C_4H_8N_4O$ requires C, 37·55; H, 6·25; N, 43·75%).

3-Dimethylamino-1,2,4-oxadiazol-5(4H)-one (VI; R^1 = NMe_2).—Prepared by heating an excess of hydroxylamine with ethyl *N*-[dimethylamino(methylthio)methylene]carbamate in ethanol, the *product* (71%) had m.p. 198—200° (decomp) (from ethanol) (Found: C, 37·1; H, 5·55; N, 32·35. $C_4H_7N_3O_2$ requires C, 37·2; H, 5·45; N, 32·5%).

Ethyl Benzimidazol-2-ylcarbamate (IX).—A mixture of ethyl *N*-[ethoxy(methylthio)methylene]carbamate (5·0 g) and *o*-phenylenediamine (2·83 g) in toluene (30 ml) was heated under reflux for 6 h. After the mixture had cooled, the product was separated and crystallised from dimethylformamide as needles (3·9 g, 72%), m.p. 320—325° (lit.,[8] 320°) (Found: C, 58·35; H, 5·35; N, 21·0. Calc. for $C_{10}H_{11}N_3O_2$: C, 58·55; H, 5·35; N, 20·5%).

Ethyl N-[Methoxy(morpholino)methylene]carbamate (VIII).—A mixture of ethyl *N*-[methoxy(methylthio)methylene]-carbamate (3·54 g, 0·02 mol) and morpholine (1·74 g, 0·02 mol) in ether (25 ml) was kept at room temperature for 3 days, during which time there was a steady evolution of methanethiol. Evaporation, and distillation of the residual oil gave the *product* (3·5 g, 81%) as an oil, b.p. 110—114° at 0·01 mmHg, n_D^{23} 1·4962 (Found: C, 49·6; H, 7·35; N, 12·45. $C_9H_{16}N_2O_4$ requires C, 50·0; H, 7·4; N, 12·95%).

Ethyl Hexahydropyrimidin-2-ylidenecarbamate (X; R = Et, *n* = 3).—To a solution of 1,3-diaminopropane (1·1 g, 0·015 mol) in anhydrous ethanol (5 ml) was added ethyl *N*-[ethoxy(methylthio)methylene]carbamate (2·9 g, 0·015 mol), and the mixture was kept overnight. The *product* (1·1 g, 43%) was separated and crystallised from ethanol; m.p. 188—189° (Found: C, 48·9; H, 7·6; N, 24·9. $C_7H_{13}N_3O_2$ requires C, 49·1; H, 7·65; N, 24·5%), $\nu_{max.}$ 3250m, 3115m, 1630s, br, and 1575s cm^{-1}, τ 0·75br (2H), 6·0 (2H, q, *J* 7 Hz), 6·68 (4H, t, *J* 6 Hz), *ca.* 8·1 (2H, m), and 8·8 (3H, t, *J* 7 Hz).

Trichloroethyl Hexahydropyrimidin-2-ylidenecarbamate (X; R = $Cl_3C{\cdot}CH_2$, *n* = 3).—To a stirred solution of 1,3-diaminopropane (110 mg, 0·0015 mol) in methanol (10 ml) maintained at 0°, trichloroethyl *N*-[methoxy(methylthio)-methylene]carbamate (420 mg, 0·0015 mol) was added in portions during 1 h. The mixture was then kept at 0° for 2 days; the solid was separated, dried, and crystallised from dimethylformamide to give the *product* (343 mg, 83%) as white needles, m.p. 200—201° (Found: C, 30·9; H, 3·6; N, 15·6. $C_7H_{10}Cl_3N_3O_2$ requires C, 30·6; H, 3·65; N, 15·3%).

Trichloroethyl Imidazolidin-2-ylidenecarbamate (X; R = $Cl_3C{\cdot}CH_2$, *n* = 2).—Prepared as above from 1,2-diaminoethane, the *product* (84%) had m.p. 203° (from dimethylformamide) (Found: C, 27·35; H, 3·45; N, 15·85. $C_6H_8Cl_3N_3O_2$ requires C, 27·65; H, 3·1; N, 16·15%).

2-Amino-3,4,5,6-tetrahydropyrimidine Hydrochloride (XI; *n* = 3).—A stirred suspension of zinc dust (4 g) in acetic acid (10 ml) and water (10 ml) maintained at 0°, was treated with trichloroethyl hexahydropyrimidin-2-ylidenecarbamate (1 g) in portions during 45 min. The mixture was then stirred and kept at 0° for a further 1 h. The excess of zinc dust was separated and washed with water (30 ml), and the combined filtrate and washings were saturated with hydrogen sulphide. The precipitated zinc sulphide was removed by centrifugation and concentrated hydrochloric acid (3 ml) was added to the clear solution, which was then evaporated. Crystallisation of the residue from methanol–ether gave needles (486 mg, 98%), m.p. 154—156° (lit.,[9] 152—157°; lit.,[6] 127—129·5°) (Found: C, 35·6; H, 7·35; N, 30·85. Calc. for $C_4H_{10}ClN_3$: C, 35·4; H, 7·45; N, 31·0%).

2-Aminoimidazolidine Hydrochloride (XI; *n* = 2).—Prepared similarly by reduction of trichloroethyl imidazolidin-2-ylidenecarbamate with zinc, the product (83%) had m.p. 118° (from methanol–ether) (lit.,[6] 118—121°).

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