184. 1 : 4-*Oxazines. Part I. Synthesis of Hydroxy*-1 : 4-*oxazines.*

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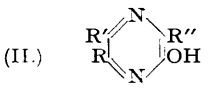
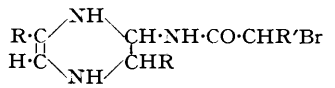
A simple method for the synthesis of 1 : 4-oxazine derivatives is described in which an α-bromoacyl derivative (VII) of ethyl α-amino-β-ketobutyrate is treated with ammonia or sodium ethoxide. In this way, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R′ = Et) and ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R′ = Et) have been prepared. The esters can be hydrolysed to the corresponding acids (VIII; R′ = H) which when heated lose carbon dioxide to yield the hydroxy-1 : 4-oxazines (IX).

Treatment of an α-bromoacyl derivative (I) of an α-amino-ketone of the type NH_2·CHR·COR′ (in which R is not hydrogen) with ammonia gives a hydroxypyrazine (II) (Tota and Elderfield, *J. Org. Chem.*, 1942, **7**, 317; Newbold and Spring, *J.*, 1947, 373). Similar treatment of an α-bromoacyl derivative (III) of an aminomethyl ketone, however, gives a 2-acylamidopyrazine (VI) (Newbold, Spring, and Sweeny, *J.*, 1948, 1855; 1949, 300). The mechanism proposed for the latter reaction involves the self-condensation of the aminomethyl ketone derivative (III) to give a tetrahydropyrazine (IV) which is converted by an intramolecular reductive dehalogenation into a dihydropyrazine such as (V), oxidation of which gives the aromatic pyrazine (VI). This mechanism is in accord with the observation that this type of reaction only takes place with aminomethyl ketone derivatives and that it requires the presence of a halogen substituent in the acyl group. Furthermore, in one instance the dihydropyrazine intermediate was sufficiently stable to allow its isolation.

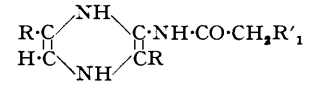
(I.) R′·CO·CHR·NH·CO·CHR″Br

R·CO·CH_2·NH·CO·CHR′Br (III.)

(II.) 



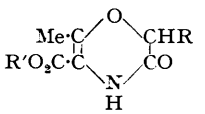
(IV.)

(V.) 

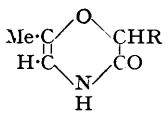
(VI.)

Me·CO·CH(CO_2Et)·NH·CO·CHRBr

(VII.)



(VIII.)



(IX.)

Since Tota and Elderfield's direct method could not be applied to the synthesis of 3 : 5-disubstituted 2-hydroxypyrazines, an examination was made of the action of ammonia on an α-bromoacyl derivative of type (I) in which R is a group capable of elimination after ring-closure is complete; the object of this approach was to enforce 2-hydroxypyrazine formation and exclude 2-acylamidopyrazine formation by temporary protection of the methylene group essential for the latter reaction. The present paper records our experience with α-bromoacyl derivatives (VII) of ethyl α-amino-β-ketobutyrate (ethyl α-aminoacetoacetate).

Acylation of this ester with α-bromopropionyl chloride in the presence of *N*-methylmorpholine gives ethyl α-(α-bromopropionamido)-β-ketobutyrate (VII; R = Me). Treatment of the last compound with liquid ammonia at room temperature gives neither a hydroxypyrazine nor an acylamidopyrazine but a 1 : 4-oxazine derivative, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R′ = Et) by simple elimination of the elements of hydrogen bromide. This 1 : 4-oxazine derivative is more conveniently obtained by treatment of (VII; R = Me) with sodium ethoxide. Cautious alkaline hydrolysis of ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate gives the corresponding 1 : 4-oxazine-3-carboxylic acid (VIII; R = Me, R′ = H) which when heated yields 3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine (IX; R = Me).

In a similar manner treatment of ethyl α-bromoacetamido-β-ketobutyrate (VII; R = H) with ammonia or, better, sodium ethoxide yields ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R′ = Et), hydrolysed to 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (VIII; R = R′ = H) from which 5-hydroxy-2-methyl-1 : 4-oxazine (IX; R = H) is obtained by the action of heat.

Although tetrahydro-1 : 4-oxazines (morpholines) are well known, as are compounds such as

phenoxazine containing the 1 : 4-oxazine system as part of a fused aromatic ring system, as far as we are aware simple 1 : 4-oxazine derivatives have not previously been described; Hill and Powell (*J. Amer. Chem. Soc.*, 1945, **67**, 1462) have suggested that a dehydration product from a benzoyl derivative of 3 : 4-dihydroxyphenacylaminoethanol is a dihydro-1 : 4-oxazine, and Cook and Cox (*J.*, 1949, 2347; cf. Chadwick and Pacsu, *J. Amer. Chem. Soc.*, 1943, **65**, 392) have described a series of 2 : 5-diketomorpholines.

The course of the reaction between ammonia and an α-(α-bromoacylamido)-ketone (I) is controlled by the nature of the substituent R; if this is a hydrogen atom, reaction proceeds to give a 2-acylamidopyrazine (VI). When R is an alkyl or aryl group, the reaction leads to a hydroxypyrazine (II) and, where R is the carbethoxy-group, it gives a 1 : 4-oxazine derivative. The formation of a 1 : 4-oxazine derivative is dependent upon a high degree of enolisation induced in the carbonyl group of the compounds (VII) by the neighbouring carbethoxyl group, a view supported by the observation that 3-(α-bromopropionamido)butan-2-one, which on treatment with ammonia gives 3-hydroxy-2 : 5 : 6-trimethylpyrazine (Newbold and Spring, *loc. cit.*), on reaction with sodium ethoxide gives 3-(α-ethoxypropionamido)butan-2-one and not 5-hydroxy-2 : 3 : 6-trimethyl-1 : 4-oxazine. Similarly, treatment of either α-bromopropionamidoacetone or ω-(α-bromopropionamido)acetophenone with sodium ethoxide in each case leads to simple replacement of halogen by an ethoxy-group to give α-ethoxypropionamidoacetone and ω-(α-ethoxypropionamido)acetophenone, respectively. In each case the yield of ethoxy-derivative is high and in neither case is the formation of a 1 : 4-oxazine observed.

Experimental.

Ethyl α-(α-Bromopropionamido)-β-ketobutyrate.—A stirred suspension of ethyl α-amino-β-ketobutyrate hydrochloride (10·0 g.) in dry chloroform (150 c.c.), to which was added a solution of α-bromopropionyl chloride (11·0 g.) in dry chloroform (50 c.c.), was cooled to 0° and treated with *N*-methylmorpholine (13·0 g.) in dry chloroform (25 c.c.) added dropwise during 30 minutes; the reaction mixture was stirred for 1 hour at 0°, then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4), and the chloroform removed under reduced pressure. The residue, which solidified, was crystallised from light petroleum (b. p. 40—60°), from which *ethyl α-(α-bromopropionamido)-β-ketobutyrate* (13·0 g., 84%) separated as needles, m. p. 70° (Found: C, 38·5; H, 5·0; N, 5·0. $C_9H_{14}O_4NBr$ requires C, 38·6; H, 5·0; N, 5·0%).

Ethyl α-Bromoacetamido-β-ketobutyrate.—The method described above being used, ethyl α-amino-β-ketobutyrate hydrochloride (13·5 g.) was treated with bromoacetyl chloride (15·0 g.) in the presence of *N*-methylmorpholine (20·0 g.) to give *ethyl α-bromoacetamido-β-ketobutyrate* (16·5 g., 83%), which separated from light petroleum (b. p. 80—100°) as needles, m. p. 99° (Found: C, 36·2; H, 4·5; N, 5·1. $C_8H_{12}O_4NBr$ requires C, 36·1; H, 4·5; N, 5·3%). Both acylamidoketobutyrates are insoluble in water, readily soluble in the common organic solvents, and give a claret-red colour with aqueous ethanolic ferric chloride solution.

Ethyl 5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate.—(*a*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (10·0 g.) in liquid ammonia (100 c.c.) containing ammonium iodide (0·5 g.) was kept in an autoclave at 15° for 16 hours. After removal of the ammonia, the residue was extracted (Soxhlet) with light petroleum (b. p. 60—80°). Concentration of the extract gave *ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate* (4·3 g., 61%) as needles, m. p. 96° (Found: C, 54·1, 54·3; H, 6·5, 6·8; N, 7·3, 6·8. $C_9H_{13}O_4N$ requires C, 54·3; H, 6·5; N, 7·0%). Light absorption (ethanol): Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5600).

(*b*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (0·80 g.) in ethanol (2 c.c.) was added to a solution of sodium ethoxide, from sodium (0·07 g.) and ethanol (2 c.c.). After being kept overnight at 15° the solvent was removed under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60—80°; 3 × 10 c.c.). Ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (0·4 g.) separated on cooling as needles, m. p. 96° alone or mixed with the specimen described under (*a*).

Ethyl 5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate.—(*a*) Ethyl α-bromoacetamido-β-ketobutyrate (5·1 g.) was treated with liquid ammonia as described above. Removal of the ammonia gave a gummy residue which was extracted with light petroleum (b. p. 80—100°; 6 × 25 c.c.); concentration of the extract under reduced pressure gave *ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate* (0·5 g., 14%) as needles, m. p. 112° (Found: C, 51·6; H, 5·9; N, 7·85. $C_8H_{11}O_4N$ requires C, 51·9; H, 5·9; N, 7·6%). Light absorption (ethanol): Maxima at 2300 A. (ε = 6800) and 2800 A. (ε = 5400).

(*b*) Ethyl α-bromoacetamido-β-ketobutyrate (4·1 g.) in dry ethanol (25 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·4 g.) and ethanol (5 c.c.), at 15° and kept at this temperature for 16 hours. Evaporation of the ethanol under reduced pressure and extraction (Soxhlet) of the residue with light petroleum (b. p. 60—80°) gave ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (1·55 g., 54·5%) as needles, m. p. 112° either alone or when mixed with the specimen prepared by method (*a*).

5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic Acid.—A suspension of ethyl 5-hydroxy-2 : 6-dimethyloxazine-3-carboxylate (3·0 g.) in aqueous sodium hydroxide (150 c.c.; 0·1N.) was shaken at 15°. After 16 hours, when dissolution was complete, the mixture was acidified to pH 4·0 with hydrochloric acid and evaporated under reduced pressure to half-bulk. After cooling to 5° the crystalline solid was separated, washed with ethanol, and dried in air (2·15 g., 83%). *5-Hydroxy-2 : 6-dimethyl-1 : 4-3-carboxylic acid* separates from methanol as prisms, m. p. 214° (decomp.) (Found: C, 49·6; H, 5·6; N,

8·5%; equiv., 172. $C_7H_9O_4N$ requires C, 49·1; H, 5·3; N, 8·2%; equiv., 171). Light absorption (ethanol): Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5900).

5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid was similarly obtained from its ethyl ester in 64% yield. It crystallised from methanol as prisms, m. p. 226° (decomp.) (Found: C, 46·1; H, 4·3; N, 9·4%; equiv., 161. $C_6H_7O_4N$ requires C, 45·9; H, 4·5; N, 8·9%; equiv., 157). Light absorption (ethanol): Maxima at 2260 A. (ε = 6900) and 2800 A. (ε = 5800).

3-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine.—5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic acid (200 mg.) was heated to 235° at atmospheric pressure for 15 minutes, effervescence then having ceased. Sublimation of the residue at 120°/1 mm. gave *3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine* as plates, m. p. 73° (40 mg.) (Found: C, 56·8; H, 7·15; N, 10·9. $C_6H_9O_2N$ requires C, 56·7; H, 7·1; N, 11·0%). Light absorption (ethanol): Maximum at 2680 A. (ε = 3800). The compound, which is extremely hygroscopic, is soluble in the cold in the common solvents with the exception of light petroleum.

5-Hydroxy-2-methyl-1 : 4-oxazine.—5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (100 mg.) was kept at 250° for 15 minutes at atmospheric pressure. The product was distilled at 120°/3 mm. to give a colourless oil, which solidified. Sublimation at 80°/0·5 mm. gave *5-hydroxy-2-methyl-1 : 4-oxazine* (20 mg.) as hygroscopic prisms, m. p. 54—55° (Found: C, 52·95; H, 6·4; N, 12·3. $C_5H_7O_2N$ requires C, 53·2; H, 6·2; N, 12·4%). Light absorption (ethanol): Maximum at 2680 A. (ε = 4300).

3-(α-Ethoxypropionamido)butan-2-one.—A solution of 3-(α-bromopropionamido)butan-2-one (1·5 g.) in dry ethanol (15 c.c.) was added to a cold solution of sodium ethoxide, from sodium (0·2 g.) and ethanol (5 c.c.), and kept at 15° for 36 hours. The red solution was separated from sodium bromide and evaporated to dryness under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 80—100°; 3 × 5 c.c.). Removal of the solvent from the extract gave an oil which solidified on cooling. Sublimation at 70°/0·1 mm. followed by crystallisation from light petroleum (b. p. 60—80°) gave *3-(α-ethoxypropionamido)butan-2-one* (0·66 g.) as prisms, m. p. 45° (Found: C, 57·3; H, 9·0; N, 7·4. $C_9H_{17}O_3N$ requires C, 57·7; H, 9·1; N, 7·5%).

α-Ethoxypropionamidoacetone.—α-Bromopropionamidoacetone (0·8 g.) in dry ethanol (10 c.c.) was added to a solution of sodium ethoxide, from sodium (0·11 g.) and ethanol (5 c.c.), and the solution left overnight at 15°. The reaction mixture, filtered from sodium bromide, was evaporated under reduced pressure to give a gum. Sublimation at 60°/0·5 mm. gave *α-ethoxypropionamidoacetone* (0·2 g.) as hygroscopic needles, m. p. 65° (Found: C, 55·4; H, 8·7; N, 8·3. $C_9H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%).

ω-(α-Ethoxypropionamido)acetophenone.—ω-(α-Bromopropionamido)acetophenone (2·5 g.) in dry ethanol (15 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·3 g.) and ethanol (5 c.c.). After 36 hours at 15° the ethanol was removed under reduced pressure and the residue extracted with boiling light petroleum (b. p. 100—120°; 10 × 10 c.c.). Concentration of the extract gave *ω-(α-ethoxypropionamido)acetophenone* (270 mg.) as needles, m. p. 89° (Found: C, 66·5; H, 7·4; N, 6·3. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 6·0%).

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