476. *The Mechanism of* N-*Acylation of* 2-*Mercaptoglyoxalines.*

By J. A. Baker.

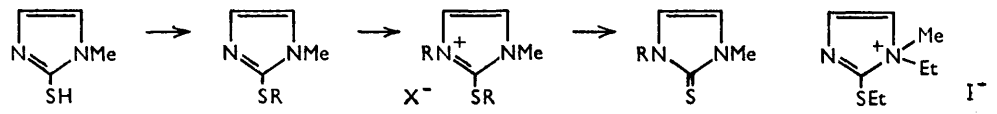
Reaction of 2-ethylthio-1-methylglyoxaline (II; R = Et) with ethyl iodide gives a quaternary salt, which yields 1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = Et) when heated. Evidence is given that *N*-ethoxycarbonylation of 2-mercapto-1-methylglyoxaline (I) in basic media follows a similar route, but the intermediate salt is less stable. Thermal decarboxylation of 1-ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline gives both 2-ethylthio-1-methylglyoxaline and 1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline. 2-Ethoxycarbonylthio-1-methylglyoxaline hydrochloride yields only 2-ethylthio-1-methylglyoxaline.

Earlier confusion concerning the structures of the compounds obtained by the acylation of 2-mercaptoglyoxalines was resolved by Lawson and Morley [1] who showed that acylation in non-basic media gives *S*-acyl and in basic media gives *N*-acyl products. They concluded from spectroscopic evidence that 2-mercaptoglyoxalines exist mainly in the thione form in neutral solution, the thiol–thione equilibrium being altered in favour of the thiol in alkaline solution. In order to explain the anomalous formation of *N*-acylated compounds in aqueous sodium hydroxide, that is, under conditions which would seem to favour *S*-acylation, migration of the acyl group of the first-formed *S*-acyl compound from sulphur to nitrogen was postulated.

2-Mercapto-1-methylglyoxaline (I) with ethyl chloroformate in acetone gives the hydrochloride of 2-ethoxycarbonylthio-1-methylglyoxaline (II; R = CO_2Et). Reaction in pyridine or aqueous sodium hydroxide gives 1-ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = CO_2Et). The latter compound is also formed rapidly when the hydrochloride of the *S*-ethoxycarbonyl compound (II; R = CO_2Et) is treated with pyridine, but when aqueous sodium hydroxide is used the liberated base shows little tendency to rearrange spontaneously. Therefore, spontaneous migration of the ethoxycarbonyl group cannot be part of the reaction mechanism when the acylation is carried out in aqueous sodium hydroxide.

[1] Lawson and Morley, *J.*, 1956, 1103.

2-Mercapto-1-methylglyoxaline (I) with ethyl iodide in non-basic media yields 2-ethylthio-1-methylglyoxaline (II; R = Et) as its hydriodide.[2] If the base is now liberated from its salt, it will react with a second molecule of ethyl iodide to form 1-ethyl-2-ethylthio-3-methylglyoxalinium iodide (IV; R = Et, X = I) [a lower-melting compound is also formed, possibly the unsymmetrical isomer (V)]. This compound loses ethyl iodide



(I) (II) (IV) (III) (V)

at its melting point, but the ethyl group evolved is the one which was attached to sulphur, the product being 1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = Et). This is a neutral compound which forms no picrate. It has strong absorption at 2600 Å, characteristic of the thione group in this environment.[1] With ethyl iodide, the ethiodide (IV; R = Et, X = I) is re-formed.

By analogy, it seemed possible that the formation of a corresponding, but less stable, quaternary compound was an intermediate stage in the rearrangement of the 2-acylthioglyoxalines. In support of this hypothesis it was found that addition of a trace of ethyl chloroformate to an ethereal solution of 2-ethoxycarbonylthio-1-methylglyoxaline (II; R = CO_2Et) caused the rapid formation of the *N*-ethoxycarbonyl compound (III; R = CO_2Et), whereas three weeks were required before an untreated solution showed signs of rearrangement. Rearrangement of the *S*-ethoxycarbonyl compound was also catalysed, but less effectively, by the hydrochlorides of organic bases; pyridine hydrochloride was the most effective of those tried and 2-ethoxycarbonylthio-1-methylglyoxaline hydrochloride the least effective. Free pyridine slightly accelerated the rearrangement. Ammonium chloride was ineffective. The mechanism of this catalysis is not apparent.

The quaternary compound (IV; R = CO_2Et, X = Cl) is apparently re-formed in the presence of excess of ethyl chloroformate. When the resulting solution is warmed, decarboxylation takes place until all the ethyl chloroformate has decomposed, the 1-ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = CO_2Et) being recovered.

It is concluded that the first product of the reaction of 2-mercaptoglyoxalines with ethyl chloroformate is an *S*-ethoxycarbonyl compound in basic and non-basic media. In non-basic media, this exists as a hydrochloride which resists further attack by the reagent. In basic media, the free base is formed, which reacts with more ethyl chloroformate to form a quaternary compound. This is unstable and splits off the ethoxycarbonyl group from the sulphur atom as ethyl chloroformate, giving an *N*-ethoxycarbonyl compound as the final product.

Rearrangement of an ethoxycarbonyl group from sulphur to nitrogen is also known for thioureas. Dixon and his co-workers [3] isolated an unstable bicarbonate as an intermediate product in this rearrangement when sodium hydrogen carbonate was used to liberate the free base.

It has been reported that 1-ethoxycarbonyl-[1] and 4-ethoxycarbonyl-2-mercaptoglyoxalines [4] give 2-ethylthioglyoxalines when heated. When 1-ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = CO_2Et) was heated above its melting point the major product was 2-ethylthio-1-methylglyoxaline (II; R = Et), but some 1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = Et) was also formed. The hydrochloride of 2-ethoxycarbonylthio-1-methylglyoxaline (II; R = CO_2Et) also gave 2-ethylthio-1-methylglyoxaline when heated but no *N*-ethyl derivative was obtained.

[2] Marckwald, *Ber.*, 1892, **25**, 2354.
[3] Dixon *et al.*, *J.*, 1920, **117**, 80, 720.
[4] Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 1084.

Experimental

2-Ethoxycarbonylthio-1-methylglyoxaline Hydrochloride.—Ethyl chloroformate (12 g., 0·11 mol.) was added dropwise with stirring to 2-mercapto-1-methylglyoxaline (11·4 g., 0·1 mol.) in acetone (50 ml.) under reflux during 10 min. and heating continued for a further 10 min. Cooling and seeding afforded *2-ethoxycarbonylthio-1-methylglyoxaline hydrochloride* as deliquescent prisms (12·5 g., 56%), m. p. 88—89° (decomp.). It may be recrystallised from acetone but with low recovery (Found: C, 38·2; H, 4·9; N, 12·3; S, 14·1. $C_7H_{11}O_2N_2SCl$ requires C, 37·8; H, 5·0; N, 12·6; S, 14·4%), $\lambda_{max.}$ 242 mμ (ε 8850) in H_2O. The picrate had m. p. 94—95° (decomp.) (from ethanol), Lawson and Morley [1] giving m. p. 94—96° (decomp.).

Stability of 2-Ethoxycarbonylthio-1-methylglyoxaline.—2N-Sodium hydroxide (4 ml.) was added to 2-ethoxycarbonylthio-1-methylglyoxaline hydrochloride (1 g.) in water (5 ml.) and the oil which separated extracted with ether. The dried ($MgSO_4$) ethereal solution was kept at room temperature for 17 hr. Hydrogen chloride was then passed in until precipitation was complete. The oily precipitate was extracted with water. Addition of aqueous picric acid gave 2-ethoxycarbonylthio-1-methylglyoxaline picrate (540 mg., 30%), m. p. and mixed m. p. 94—95° (decomp.).

2-Ethylthio-1-methylglyoxaline (II; R = Et).—This *compound* was prepared by Marckwald's method [2] as a colourless oil, b. p. 115—116°/18 mm. (Found: C, 50·9; H, 7·3; N, 19·6. $C_6H_{10}N_2S$ requires C, 50·7; H, 7·1; N, 19·7%), $\lambda_{max.}$ 221 (ε 6950) and 248 mμ (ε 4740) in EtOH. Its picrate had m. p. 112° (from ethanol).

1-Ethyl-2-ethylthio-3-methylglyoxalinium Iodide (IV; R = Et, X = I).—Ethyl iodide (2·9 ml., 0·036 mol.) was added to 2-ethylthio-1-methylglyoxaline (4·7 g., 0·033 mol.) in acetone (20 ml.) and kept overnight. The crystals which separated were recrystallised from acetone–ethyl acetate to constant m. p., giving the *glyoxalinium iodide* (1·8 g.), m. p. 156° (Found: C, 31·6; H, 4·8; N, 9·4. $C_8H_{15}N_2SI$ requires C, 32·2; H, 5·1; N, 9·4%). Addition of ethyl acetate to the reaction mother-liquors gave a mixture of iodides (2·4 g.), m. p. 110°, which could not be separated by crystallisation.

1-Ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (III; R = Et).—1-Ethyl-2-ethylthio-3-methylglyoxalinium iodide (1·5 g.) was heated at 180° until low-boiling products had ceased to distil; then the residue was distilled under reduced pressure. The latter distillate was taken up in ether, washed with 2N-hydrochloric acid and saturated sodium hydrogen carbonate solution, and dried ($MgSO_4$). Distillation of the solution gave *1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline* (350 mg.), m. p. 51°, b. p. 166°/14 mm., $\lambda_{max.}$ 260 mμ (ε 14·800) in EtOH (Found: C, 50·9; H, 7·2; N, 19·4. $C_6H_{10}N_2S$ requires C, 50·7; H, 7·1; N, 19·7%). It gave a deep blue colour with Grote's reagent.[5] No picrate could be obtained. With ethyl iodide in acetone, 1-ethyl-2-ethylthio-3-methylglyoxalinium iodide was re-formed, m. p. and mixed m. p. 156°.

If the lower-melting mixture of iodides is used, an unidentified substance, m. p. 152°, sparingly soluble in ether, distils with the thioglyoxaline. It is removed by washing with hydrochloric acid, and pure thioglyoxaline is finally obtained.

Rearrangement of 2-Ethoxycarbonylthio-1-methylglyoxaline (II; R = CO_2Et).—The dried ($MgSO_4$) solution of 2-ethoxycarbonylthio-1-methylglyoxaline obtained by reaction of the hydrochloride (4 g.) with 2N-sodium hydroxide and extraction with ether (60 ml.) was divided into four equal parts and treated as follows: (*a*) Ethyl chloroformate (1 drop) was added. A little oil separated immediately and after 10 min. crystals began to separate. These were collected after 2 hr. and on recrystallisation from acetone gave 1-ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (470 mg., 56%), m. p. and mixed m. p. 123°. (*b*) Pyridine hydrochloride (*ca.* 1 mg.) was added. The effect was as recorded in (*a*) but 15 hr. were required before the separation of crystals appeared to be complete. (*c*) Pyridine (1 drop) was added. The thioglyoxaline (10 mg.) separated after 4 days. (*d*) Untreated. A trace of the thioglyoxaline separated after 3 weeks.

In a similar experiment, with the hydrochlorides of dimethylamine, aniline, and quinoline as catalysts, the separation of the thioglyoxaline was apparently complete after 4 days. With 2-ethoxycarbonylthio-1-methylglyoxaline hydrochloride as catalyst, separation was complete after 7 days. Ammonium chloride was ineffective.

[5] Grote, *J. Biol. Chem.*, 1931, **93**, 25.

Decarboxylation of Ethyl Chloroformate.—1-Ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (1 g.) in ethyl chloroformate (10 ml.) was heated at 65—70° until evolution of gases had ceased. The residue consisted of unchanged material, m. p. and mixed m. p. 123°.

Decarboxylation of 1-Ethoxycarbonyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline.—This thioglyoxaline (70 g.) was heated at 150—160° until evolution of carbon dioxide had ceased (2 hr.). Fractionation of the residue yielded an oil (32·5 g.), b. p. 116—118°/17 mm. (which gave 2-ethylthio-1-methylglyoxaline picrate, m. p. and mixed m. p. 112°), and 1-ethyl-2 : 3-dihydro-3-methyl-2-thioglyoxaline (9·6 g.), m. p. and mixed m. p. 51°, b. p. 172—174/17 mm., giving with ethyl iodide 1-ethyl-2-ethylthio-3-methylglyoxalinium iodide, m. p. and mixed m. p. 156°.

Decarboxylation of 2-Ethoxycarbonylthio-1-methylglyoxaline Hydrochloride.—2-Ethoxycarbonylthio-1-methylglyoxaline hydrochloride (2 g.) was heated at 80—90° until evolution of carbon dioxide ceased, then at 130° for a further 30 min. The residue was separated into neutral and basic fractions with 2N-hydrochloric acid. The neutral fraction was an oil (10 mg.) which gave no colour with Grote's reagent. The basic fraction was an oil (350 mg.) which gave 2-ethylthio-1-methylglyoxaline picrate, m. p. and mixed m. p. 112°.

The author thanks Professor R. D. Haworth, F.R.S., and Dr. P. G. Marshall for their interest and advice.

BRITISH SCHERING RESEARCH INSTITUTE,
ALDERLEY EDGE, CHESHIRE.

[*Received, February 11th,* 1958.]