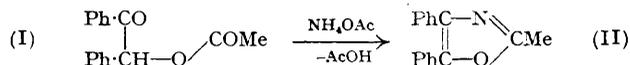


15. Synthesis of Oxazoles from Ethyl Acetoacetate. Ring-fission of Some Oxazole-5-carboxylic Acids.

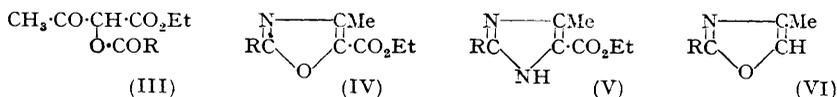
By J. W. CORNFORTH and MRS. R. H. CORNFORTH.

Ethyl 4-methyloxazole-5-carboxylates are obtained by heating ethyl α -chloroacetoacetate with the solution of an ammonium salt in its parent carboxylic acid. Oxazole-4 : 5-dicarboxylic acids, which can be prepared by modifying a known method, undergo ring-fission in boiling water with formation of acylaminopyruvic acids. The latter appear to exist largely in the enolic form, $R \cdot CO \cdot NH \cdot CH : C(OH) \cdot CO_2H$.

DAVIDSON, WEISS, and JELLING (*J. Org. Chem.*, 1937, 2, 319) showed that 2-methyl-4 : 5-diphenyloxazole (II) is formed when benzoïn acetate (I) is heated with ammonium acetate in acetic acid. Apart from the related observation that benzoïn benzoate affords triphenyloxazole with the same reagent, the synthesis was not further developed. If this method were generally applicable it would be important, for oxazole chemistry suffers in comparison with that of other heterocyclic systems from a scarcity of general methods. Some experiments to define the scope of the synthesis were therefore indicated.



Our first attempts were directed to the conversion of acetoxyacetone, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{OAc}$, into 2 : 4-dimethyloxazole. Neither ammonium acetate-acetic acid nor any of the alternative sources of ammonia which were tried proved effective. We turned then to α -acyloxy- β -keto-esters, on the supposition that a readily enolized carbonyl group (which is certainly present in the benzoïn esters) might be requisite for oxazole ring formation. Ethyl α -acetoxyacetoacetate (III; $R = \text{Me}$), easily accessible from acetoacetic ester and lead tetra-acetate (Dimroth and Schweizer, *Ber.*, 1923, 56, 1380), was heated with ammonium acetate in acetic acid. The principal product was the expected ethyl 2 : 4-dimethyloxazole-5-carboxylate (IV; $R = \text{Me}$); this was accompanied by a basic substance which



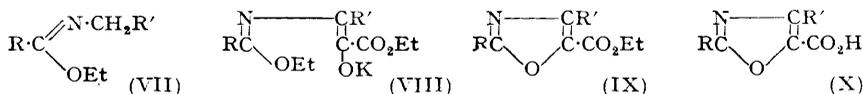
analysis showed to be the corresponding glyoxaline (V; $R = \text{Me}$). To explain the formation of (V) it seems necessary to assume an $O \rightarrow N$ acyl migration, thus: $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}(\text{OAc}) \cdot \text{CO}_2\text{Et} \xrightarrow{\text{NH}_3} \text{CH}_3 \cdot \text{C}(\text{NH}_2) \cdot \text{C}(\text{OAc}) \cdot \text{CO}_2\text{Et} \rightarrow \text{CH}_3 \cdot \text{CH}(\text{NHAc}) \cdot \text{CO} \cdot \text{CO}_2\text{Et} \xrightarrow{\text{NH}_3} (V)$. The possibility had also to be considered of an $O \rightarrow O$ acyl migration before closure of the oxazole ring. The orientation of substituents in (IV; $R = \text{Me}$) was therefore proved by hydrolysis to the corresponding acid and decarboxylation. The resulting 2 : 4-dimethyloxazole (VI; $R = \text{Me}$) was identified with a specimen prepared from acetamide and chloroacetone (Oesterreich, *Ber.*, 1897, 30, 2254). This degradation indicated also that oxazole-5-carboxylic acids, like the 4-isomers, are easily decarboxylated.

The cited preparation of ethyl α -acetoxyacetoacetate being rather a special case, we examined a potentially more general method, the conversion of α -halogenoacetoacetates into the α -acyloxy-analogues (III). Ethyl α -chloroacetoacetate (which was found superior to the α -bromo-ester for this purpose) with sodium phenylacetate suspended in hot toluene gave impure ethyl α -phenylacetoxyacetoacetate (III; $R = \text{Ph} \cdot \text{CH}_2$) in moderate yield, and this product with ammonium acetate in acetic acid afforded ethyl 2-benzyl-4-methyloxazole-5-carboxylate (IV; $R = \text{Ph} \cdot \text{CH}_2$) along with a minor amount of the glyoxaline (V; $R = \text{Ph} \cdot \text{CH}_2$). The overall yield of oxazole was poor; however, a combination of these two stages by heating the chloro-ester with ammonium phenylacetate in phenylacetic acid was more successful, the oxazole (IV; $R = \text{Ph} \cdot \text{CH}_2$) being formed directly in

30% yield. Hydrolysis to the 5-carboxylic acid and decarboxylation to 2-benzyl-4-methyloxazole (VI; R = Ph·CH₂) were effected without trouble.

The above composite process evidently proceeds by the stages: (a) replacement of halogen by the acyloxy-group; (b) reaction of the carbonyl group with ammonia; and (c) ring closure; (a) and (b) need not occur in that order. However, the condensation of amides with α -halogeno-ketones is a known oxazole synthesis, and amides might well be formed under these conditions. To test this alternative ethyl α -chloroacetoacetate was heated in acetic acid with (i) ammonium acetate and (ii) acetamide. The ammonium salt gave the oxazole (IV; R = Me); the amide gave none.

The synthesis was next applied to prepare the hitherto unknown 4-methyloxazole. Ethyl α -chloroacetoacetate was condensed with ammonium formate in formic acid, and the partly purified product [after separation from a little ethyl 4-methylglyoxaline-5-carboxylate (V; R = H)] was hydrolysed to 4-methyloxazole-5-carboxylic acid. This acid was smoothly decarboxylated to 4-methyloxazole (VI; R = H) which is thus available in four stages from ethyl acetoacetate, the overall yield being about 15%.



A previously reported synthesis of oxazole-4-carboxylic esters (*J.*, 1947, 96) and 4-cyano-oxazoles (*J.*, 1948, 1969) involves at one stage the reaction of a (1-alkoxyalkylidene)-aminoacetic acid derivative (VII; R' = CO₂Et or CN) with ethyl formate-potassium ethoxide. It is shown here that ethyl oxalate may be substituted for ethyl formate, and that the resulting potassium enolates (VIII) undergo the usual ring closure in boiling acetic acid to give oxazole-5-carboxylic esters (IX). This procedure, applied to ethyl 1-ethoxyethylideneaminoacetate (VII; R = Me, R' = CO₂Et), gave ethyl 2-methyloxazole-4 : 5-dicarboxylate (IX; R = Me, R' = CO₂Et). The ester was hydrolysed smoothly by alkali, but the resulting 2-methyloxazole-4 : 5-dicarboxylic acid (X; R = Me, R' = CO₂H) proved difficult to isolate from its salts. The difficulty was traced to a remarkable instability of the free acid; on boiling it with water, formation of a different acid was complete in a few minutes. Analysis of the new acid showed that addition of water and loss of carbon dioxide had taken place. Since the acid gave a deep blue colour with ferric chloride it was evidently acetamidopyruvic acid, or rather its enol Ac·NH·CH·C(OH)·CO₂H, for its intense absorption in the ultra-violet indicated that enolization was substantially complete. The alternative possibility, α -acetamidofornylacetic acid Ac·NH·CH(CHO)·CO₂H, is excluded by the relative stability of the acid and the fact that the colour with ferric chloride is blue and not red (cf. "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 805, where α -hexanamidofornylacetic acid is described). The related benzamidopyruvic acid, reported to give a blue-green colour with ferric chloride, was prepared by Wislicenus (*Ber.*, 1891, 24, 1262) by acid hydrolysis of ethyl 2-benzamido-3-keto-succinate.

From 2-benzylloxazole-4 : 5-dicarboxylic acid (X; R = Ph·CH₂, R' = CO₂H), phenylacetamidopyruvic acid was obtained under similar conditions. On the other hand, 2 : 4-dimethyloxazole-5-carboxylic acid resisted the action of boiling water or dilute acid. The inference that an electron-attracting group in the 4-position is necessary for this ring-fission was supported by the behaviour of 2-benzyl-4-cyano-oxazole-5-carboxylic acid (X; R = Ph·CH₂, R' = CN); this acid was slowly decomposed by boiling water to a product which, though not obtained pure, gave a blue colour with ferric chloride. Some attempts were made to prepare the aldehydo-acid (X; R = Ph·CH₂, R' = CHO), or its ester, from the corresponding nitriles, but the Stephen reduction was ineffective and treatment of the thioamides (IX and X; R = Ph·CH₂, R' = CS·NH₂) with Raney nickel was equally unsuccessful.

EXPERIMENTAL

Experiments with Acetoxyacetone.—Acetoxyacetone was heated with (i) ammonium carbamate at 85–90°, (ii) ammonium oxalate and oxalic acid in boiling acetic acid, and (iii) ammonium acetate in boiling acetic acid. The mixtures were worked up for volatile alkali-stable products. No indication of 2 : 4-dimethyloxazole was found.

Reaction of Ethyl α -Acetoxyacetoacetate with Ammonium Acetate.—Ethyl α -acetoxyacetoacetate (7 g.) and ammonium acetate (13 g.) in acetic acid (33 c.c.) were boiled under reflux for 1½ hours. Most of the acetic acid was removed at low pressure; the residue was diluted with water, and solid potassium carbonate was gradually added. Precipitation occurred while the solution was still acid. The mixture was chilled in ice, and the solid product (A) collected and dissolved in a little light petroleum. After decantation from a small oily residue the solvent was removed, leaving a crystalline solid (4 g.), m. p. ca. 48°. Two recrystallizations from light petroleum (b. p. 40—60°) gave *ethyl 2:4-dimethyloxazole-5-carboxylate* in colourless needles, m. p. 55—56° (Found: C, 56.5; H, 6.3; N, 7.8. $C_8H_{11}O_3N$ requires C, 56.8; H, 6.5; N, 8.3%). The ester was moderately soluble in water and easily soluble in all other solvents tried. A sample volatilized when kept overnight in a vacuum-desiccator. The filtrate from (A) was made alkaline with potassium carbonate. The precipitated solid (0.75 g.) was recrystallized thrice from benzene (the first time with charcoal). The resulting *ethyl 2:4-dimethylglyoxaline-5-carboxylate* formed colourless leaflets, m. p. 165—167°, sparingly soluble in warm ether and insoluble in light petroleum (Found: C, 57.5; H, 7.1; N, 16.1. $C_8H_{12}O_2N_2$ requires C, 57.1; H, 7.1; N, 16.6%).

2:4-Dimethyloxazole-5-carboxylic Acid and 2:4-Dimethyloxazole.—The crude oxazole ester (4.6 g.) was obtained when a mixture prepared as above was neutralized (without prior removal of acetic acid) with potassium carbonate, and the extract obtained by light petroleum was separated from the insoluble glyoxaline and evaporated at low pressure. 2N-Sodium hydroxide (20 c.c.) was added; after a few minutes' boiling, charcoal was stirred in. The cooled filtered solution was acidified (Congo-red). The crystalline *2:4-dimethyloxazole-5-carboxylic acid* was dried (4 g.); recrystallization from ethanol-ethyl acetate or from much hot water gave needles, m. p. 247° (decomp.) (Found: C, 51.4; H, 4.8; N, 10.0. $C_6H_7O_3N$ requires C, 51.1; H, 5.0; N, 9.9%).

The acid (2 g.) was heated in quinoline (20 c.c.) with a trace of copper oxide, so that the oxazole distilled slowly along with some quinoline. Two redistillations, the second over potassium hydroxide, gave *2:4-dimethyloxazole* (0.6 g.). The base was characterized as the *picrate*, m. p. 110—111° (softening from 100°), from ethanolic picric acid (Found: C, 40.4; H, 3.0; N, 17.0. $C_6H_7ON, C_6H_3O_7N_3$ requires C, 40.5; H, 3.1; N, 17.2%), and the mercuric chloride *adduct*, prisms, m. p. 147—148°, from ether (Found: C, 15.7; H, 2.2; N, 3.9. $C_6H_7ON, HgCl_2$ requires C, 16.3; H, 2.0; N, 3.8%). This adduct crystallizes from benzene in fine needles melting at 130° to 138° (dependent on rate of heating) to a turbid liquid. The two forms are interconvertible.

2:4-Dimethyloxazole was prepared from acetamide and chloroacetone. The picrate and mercuric chloride adduct were identical with the above derivatives.

Reaction of Ethyl α -Chloroacetoacetate with Sodium Phenylacetate.—A mixture of the ester (2.5 g.) and the sodium salt (5 g.) with dry toluene (15 c.c.) was boiled under reflux for 1 hour, cooled, washed with water and aqueous sodium hydrogen carbonate, dried, and distilled. The fraction, b. p. 115—120°/0.05 mm. (1.6 g.), on redistillation had b. p. 104°/0.02 mm. This fraction, an oil, gave a slowly developing deep red colour with ferric chloride in ethanol and contained the desired ethyl α -phenylacetoxyacetoacetate; analyses, however, were erratic. The product was characterized by heating it with phenylhydrazine acetate, whereupon *5-methyl-2-phenyl-4-phenylacetoxy-pyrazol-3-one* was obtained in almost colourless prisms after crystallization from ethanol and then from benzene (Found: C, 70.0; H, 5.4. $C_{18}H_{16}O_3N_2$ requires C, 70.1; H, 5.2%).

The use of benzene or ethanol as reaction media, or the substitution of ethyl α -bromoacetoacetate for the α -chloro-ester, gave inferior yields.

Ethyl 2-Benzyl-4-methyloxazole-5-carboxylate.—(i) Crude ethyl α -phenylacetoxyacetoacetate (4.25 g.) was refluxed in acetic acid (20 c.c.) with ammonium acetate (7.4 g.) for 1½ hours. Water and ether were added to the cooled solution; the ether was washed with water and aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residue was extracted with hot light petroleum (b. p. 60—80°). Removal of the solvent and distillation gave the *oxazole* ester, a colourless oil (2.1 g.), b. p. 112°/0.05 mm. (Found: N, 5.4. $C_{14}H_{15}O_3N$ requires N, 5.7%). From the petroleum-insoluble residue and by neutralization of the aqueous layer from the ether-extraction, a total of 0.5 g. of crystalline solid was recovered. Recrystallization from benzene gave *ethyl 2-benzyl-4-methylglyoxaline-5-carboxylate*, colourless plates, m. p. 167—168° (Found: C, 68.6; H, 6.7; N, 11.7. $C_{14}H_{16}O_2N_2$ requires C, 68.8; H, 6.6; N, 11.5%). The oxazole ester (1.05 g.) was heated with 2N-sodium hydroxide (3 c.c.) and ethanol (1 c.c.) for ½ hour. The cooled diluted solution was acidified. The precipitated *2-benzyl-4-methyloxazole-*

5-carboxylic acid crystallized from alcohol in prisms (0.8 g.), m. p. 238° (decomp.) with previous softening (Found : C, 66.5; H, 5.2; N, 6.0. $C_{12}H_{11}O_3N$ requires C, 66.4; H, 5.1; N, 6.5%).

(ii) Aqueous ammonia (4.2 c.c.; d 0.88) was added to phenylacetic acid (20 g.), and the water removed by heating at low pressure. Ethyl α -chloroacetoacetate (2.5 g.) was added and the mixture heated for 4—5 hours (bath at 130°), initially under reflux at low pressure. The cooled mixture was diluted with water, made alkaline with potassium carbonate, and extracted with light petroleum (60—80°). Distillation gave the oxazole ester (1.15 g.) which was hydrolysed to the acid (0.9 g.).

2-Benzyl-4-methyloxazole.—2-Benzyl-4-methyloxazole-5-carboxylic acid (0.9 g.) was heated to 280—290° (metal-bath) and gave *2-benzyl-4-methyloxazole* (0.6 g.), a colourless oil, b. p. 250° (Found : C, 76.0; H, 7.2; N, 8.6. $C_{11}H_{11}ON$ requires C, 76.0; H, 6.4; N, 8.1%). The mercuric chloride adduct crystallized in prisms, m. p. 88°, from ether—light petroleum (Found : N, 3.4. $C_{11}H_{11}ON, HgCl_2$ requires N, 3.2%).

4-Methyloxazole-5-carboxylic Acid.—Ethyl α -chloroacetoacetate (5 g.) was refluxed for 5 hours with ammonium formate (10 g.) in formic acid (30 c.c.). After addition of water the reaction mixture was neutralized with potassium carbonate and extracted with ether. The extract on distillation gave a fraction (2.4 g.), b. p. 90—110°/20 mm., containing unchanged chloro-ester. It was hydrolysed by boiling 2N-sodium hydroxide (10 c.c.) in a few minutes. Acidification gave a crystalline precipitate and a small second crop was obtained by concentrating the filtrate (total yield, 1 g.). On recrystallization from ethyl acetate *4-methyloxazole-5-carboxylic acid* separated in needles, m. p. 237—238° (decomp.) (Found : C, 47.0; H, 4.1. $C_5H_5O_3N$ requires C, 47.2; H, 3.9%). A somewhat lower yield was obtained in several experiments where the reaction time and the quantities taken were varied. In some experiments *ethyl 4-methylglyoxaline-5-carboxylate* was isolated; it remained undissolved on addition of ether to the diluted reaction mixture and was purified by crystallization from ethanol. It formed colourless plates, m. p. 204—205° (Found : C, 54.3; H, 6.2; N, 18.0. $C_7H_{10}O_2N_2$ requires C, 54.5; H, 6.5; N, 18.2%).

4-Methyloxazole.—4-Methyloxazole-5-carboxylic acid (5 g.; not recrystallized) was heated in 1-g. portions with a little copper oxide, so that the product (2.65 g.) distilled slowly. Redistillation over solid sodium hydroxide gave *4-methyloxazole* as a mobile liquid, b. p. 88—89°, of strong pyridine-like odour (Found : C, 58.1; H, 6.0; N, 17.4. C_4H_5ON requires C, 57.8; H, 6.0; N, 16.9%). An unstable picrate separated slowly in small amount from aqueous picric acid. A mercuric chloride adduct, prepared in aqueous solution, crystallized from ether—light petroleum in needles changing to prisms, m. p. 122°, which reverted to mercuric chloride on drying *in vacuo*.

Ethyl 2-Methyloxazole-4 : 5-dicarboxylate.—A solution prepared from potassium (2 g.), ethanol (7.5 c.c.), and ether (25 c.c.) was diluted with ether (175 c.c.) and cooled to —5°. A mixture of ethyl 1-ethoxyethylideneaminoacetate (9.05 g.; freshly distilled) and ethyl oxalate (7.8 g.) was added. A crystalline precipitate appeared after about 20 minutes. Next day the fluffy, light yellow, hygroscopic potassium salt (VIII; R = Me, R' = CO₂Et) was collected (6.6 g.). It had m. p. 86—88° and deteriorated rapidly. Gradual addition of dilute alcoholic ferric chloride to a solution of the salt in alcohol gave a red colour deepening through purple to pure blue and then fading through green to yellow-brown. The salt and the concentrated mother-liquor were added separately to boiling acetic acid; after dilution with water and neutralization with potassium carbonate the products were isolated by means of ether, united, and distilled. *Ethyl 2-methyloxazole-4 : 5-dicarboxylate*, a colourless oil (7.2 g.), was collected at 82—84°/0.04 mm. (Found : C, 52.5; H, 5.8. $C_{10}H_{13}O_5N$ requires C, 52.9; H, 5.7%).

2-Methyloxazole-4 : 5-dicarboxylic Acid and Acetamidopyruvic Acid.—The above ester (1.5 g.) was heated for a few minutes with 2N-sodium hydroxide (7 c.c.). After concentration at low pressure the liquid was cooled in ice during the addition of concentrated hydrochloric acid (2 c.c.). After a few minutes' stirring the crystalline product was collected and washed rapidly with a little ice-water. The dried residue was extracted with hot ethyl acetate; concentration of the extract gave *2-methyloxazole-4 : 5-dicarboxylic acid*, fine colourless needles (0.1 g.), m. p. 178—179.5° (decomp.) (Found, after drying at 80° : C, 41.9; H, 2.6; N, 8.6. $C_6H_5O_5N$ requires C, 42.1; H, 2.9; N, 8.2%). From the aqueous mother-liquors a further quantity (0.6 g.) of slightly less pure material was obtained by evaporation at low pressure, extraction with ethyl acetate, and recrystallization of the evaporated extract from methanol. When less hydrochloric acid was used for acidification the *sodium hydrogen* salt separated in hydrated needles, m. p. (after drying) 268° (decomp.) (Found : N, 7.8. $C_6H_4O_5NNa$ requires N, 7.3%).

When the free acid was boiled with water, or when a solution of the sodium hydrogen salt

was acidified to Congo-red and boiled, carbon dioxide was evolved. Extraction of the solution with much ether and recrystallization of the product from isopropanol-ether gave *acetamidopyruvic acid* in prisms, m. p. 184—188° (decomp.; dependent on rate of heating) (Found : C, 41.2; H, 5.1. $C_5H_7O_4N$ requires C, 41.4; H, 4.8%). The acid dissolved easily in water to a solution giving a deep blue colour with ferric chloride and showing an ultra-violet absorption maximum at 2700 Å (ϵ , 17,600) and a minimum at 2250 Å (ϵ , 2750). The 2 : 4-dinitrophenylhydrazone (prepared in cold 2N-hydrochloric acid) separated slowly as orange platelets, m. p. 206° (decomp.), before and after recrystallization from dioxan (Found : C, 40.7; H, 3.3; N, 21.3. $C_{11}H_{11}O_7N_5$ requires C, 40.6; H, 3.4; N, 21.6%).

2-Benzylloxazole-4 : 5-dicarboxylic Acid.—Potassium (1.7 g.) was dissolved in a mixture of ethanol (6.4 c.c.) and ether (30 c.c.). More ether (130 c.c.) was added and the solution cooled to -5°. A mixture of ethyl 1-ethoxy-2-phenylethylideneaminoacetate (10.5 g.) and ethyl oxalate (6.6 g.) was added. After being kept overnight at 0° the ether was removed at low pressure and the residue added to boiling acetic acid (30 c.c.). The product was worked up as usual. Distillation gave a fraction (4.3 g.), b. p. 136—140°/0.01 mm., which gradually deposited some crystals (0.4 g.; m. p. 81—82° after crystallization from benzene-light petroleum; hydrolysed by alkali to an acid, m. p. 142—143°) of unknown nature, which were removed. The filtrate was redistilled and the distillate (3 g.) hydrolysed with alcoholic potassium hydroxide (22 c.c. of N). The crystalline potassium salt was collected and recrystallized twice from methanol-ethanol. The salt (1.35 g.), m. p. 252° (decomp.), was dissolved in water, acidified with hydrochloric acid, and shaken with ethyl acetate until dissolution was complete. The ethyl acetate was dried and concentrated, whereupon crystallization set in. Recrystallization of the product (0.5 g.) from ethyl acetate gave *2-benzylloxazole-4 : 5-dicarboxylic acid* in prisms, m. p. 178° (decomp.) (Found : C, 58.3; H, 3.8; N, 5.4. $C_{15}H_9O_5N$ requires C, 58.3; H, 3.6; N, 5.7%).

Phenylacetamidopyruvic Acid.—The above acid (100 mg.) in water (4 c.c.) and hydrochloric acid (1 drop of 10N) were refluxed for 3 hours. The solid product was collected after cooling and crystallized from butanol : *phenylacetamidopyruvic acid* separated in prisms, sparingly soluble in water and most organic solvents (Found : C, 59.6; H, 5.3; N, 6.2. $C_{11}H_{11}O_4N$ requires C, 59.7; H, 5.0; N, 6.3%). It decomposed from 195° and was completely fused at 212°. When covered with aqueous alcoholic ferric chloride the crystals became blue; the reagent became green.

Ethyl 2-Benzyl-4-cyano-oxazole-5-carboxylate and Derivatives.—1-Ethoxy-2-phenylethylideneaminoacetonitrile was prepared from ethyl phenylacetimidate and aminoacetonitrile sulphate essentially as described for the 1-methoxy-analogue (*J.*, 1949, 1549). This technique was found more reliable than the previously described method (*loc. cit.*). The reaction with ethyl oxalate was carried out as described in the previous example; a crystalline potassium salt (VIII; R = Ph·CH₂; R' = CN) separated in small amount [m. p. 145—147° (decomp.); deep red → dark green → light green with ferric chloride in ethanol] but it was better to evaporate the reaction mixture and to add the total residue to boiling acetic acid. The product was isolated by distillation after the usual extraction procedures; from the nitrile (15.5 g.) was obtained a distillate (12.6 g.; b. p. ~130°/0.05 mm.) which crystallized. Recrystallization from light petroleum (b. p. 60—80°) gave *ethyl 2-benzyl-4-cyano-oxazole-5-carboxylate* in prismatic needles, m. p. 45—46° (Found : C, 65.7; H, 4.9; N, 11.0. $C_{14}H_{12}O_3N_2$ requires C, 65.6; H, 4.7; N, 10.9%).

Hydrogen sulphide was passed for 4 hours through a solution of this product (1 g.) and triethanolamine (0.6 g.) in ethanol (5 c.c.). Next day the orange crystals (0.9 g.; m. p. 132°) were recrystallized from ethanol. *Ethyl 2-benzyl-4-thiocarbamyloxazole-5-carboxylate* (IX; R = Ph·CH₂; R' = CS·NH₂) separated as orange plates (0.7 g.), m. p. 136—137° (Found : C, 57.9; H, 4.7; N, 9.5. $C_{14}H_{14}O_3N_2S$ requires C, 57.6; H, 4.8; N, 9.7%). In an earlier experiment diethanolamine had been used, but the *bis-2-hydroxyethylamide* was then the product (pale yellow prisms, m. p. 104—105°) (Found : C, 55.0; H, 5.3; N, 12.4. $C_{16}H_{19}O_4N_3S$ requires C, 55.0; H, 5.4; N, 12.0%).

2-Benzyl-4-cyano-oxazole-5-carboxylic Acid and Derivatives.—The 4-cyano-ester (1.28 g.) was treated with a slight excess of N-potassium hydroxide in methanol. After 1½ hours the crystalline potassium salt of the 5-carboxylic acid was collected (1.1 g.). A sample after recrystallisation from ethanol formed platelets, decomp. 229—230° (Found : N, 9.6. $C_{12}H_7O_3N_2K \cdot H_2O$ requires N, 9.8%). When this salt (0.5 g.) was dissolved in a little water and acidified (Congo-red), an acid potassium salt separated and crystallized from ethanol in plates (0.3 g.), m. p. 204—205° (Found : N, 11.4. $C_{12}H_7O_3N_2K \cdot C_{12}H_8O_3N_2$ requires N, 11.3%). The free *2-benzyl-4-cyano-oxazole-5-carboxylic acid* was obtained by shaking either potassium

salt with ether and an excess of dilute sulphuric acid; the acid recovered from the ethereal layer crystallized from benzene in colourless plates, m. p. 156—157° (softening) (Found: C, 63.1; H, 3.6; N, 12.1. $C_{12}H_8O_3N_2$ requires C, 63.2; H, 3.6; N, 12.3%).

When the cyano-ester was hydrolysed under more vigorous conditions (2N-aqueous alkali at 100° for 1 hour), 2-benzyl-4-carbamyl-oxazole-5-carboxylic acid (X; R = Ph·CH₂, R' = CO·NH₂) was isolated, having m. p. 200—202° after crystallization from ethanol (Found: N, 11.1. $C_{12}H_{10}O_4N_2$ requires N, 11.4%).

The thioamide ester (IX; R = Ph·CH₂, R' = CS·NH₂) was hydrolysed by dropwise addition of aqueous N-sodium hydroxide to a suspension of the ester (1.45 g.) in ethanol (15 c.c.) containing a little phenolphthalein. When the colour of the indicator was stable for 1 hour the alcohol was removed, and water and dilute hydrochloric acid were added. The precipitated solid was recrystallised from *n*-butanol, giving orange hexagonal prisms (1.06 g.), m. p. 196° (decomp.), of 2-benzyl-4-thiocarbamyl-oxazole-5-carboxylic acid (Found: C, 55.2; H, 3.7; N, 10.5. $C_{12}H_{10}O_3N_2S$ requires C, 55.0; H, 3.8; N, 10.7%).

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