isoOxazolones. Part VI.* The Hydrogenation of 5-Aminoisooxazoles. A New Synthesis of Pyrimidines.

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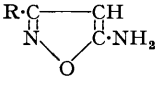
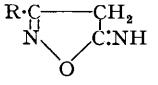
Hydrogenation of 5-amino-3-phenyl*iso*oxazole (I; R = Ph) gave β-aminocinnamamide (V), but the acyl derivatives (VII; R = Ph, Me, and H) gave mixtures of the amines (VIII; R = Ph, Me, and H), and the hydroxypyrimidines (X; R = Ph, Me, and H). The reactions of (VIII), in particular their ready conversion into (X), have been studied.

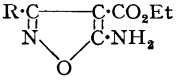
Earlier communications in this series have been concerned primarily with a study of the structures and properties of the hydrogenation products of certain *iso*oxazol-5-ones. We have extended this study to the behaviour of analogous *iso*oxazolone imines (I*a*) or tautomeric 5-amino*iso*oxazoles (I) towards hydrogenation; in the present paper we adhere to the latter formulation. A preliminary note on the findings has already appeared (Shaw and Sugowdz, *Nature*, 1953, **172**, 955).



(I)



(I*a*)



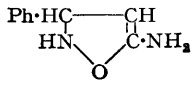
(II)

The only 5-amino*iso*oxazoles studied in any detail are (I; R = Me and Ph), prepared by the reaction of hydroxylamine with a cyanoacetylene (Moureu and Lazennec, *Compt. rend.*, 1907, **144**, 1281; *Bull. Soc. chim.*, 1907, **1**, 1084), a β-aminoacrylonitrile (Burns, *J. pr. Chem.*, 1893, **47**, 123), and a β-oxo-nitrile (Obregia, *Annalen*, 1891, **266**, 329), and more recently the reaction of benzhydroxamoyl chloride and ethyl cyanoacetate was shown to give the ester (II; R = Ph), which was hydrolysed to the acid and then decarboxylated to give (I; R = Ph) (Quilico and Fusco, *Rend. Ist. Lombardo Sci.*, 1936, **69**, 439); we have prepared the analogous ester (II; R = Me) by the reaction of hydroxylamine with ethyl 2-cyano-3-oxobutanoate and similarly converted it into (I; R = Me). In the present work, however, attention has been confined to 5-amino-3-phenyl*iso*oxazole (I; R = Ph), obtained in excellent yield from benzoylacetonitrile and hydroxylamine (Obregia, *loc. cit.*).

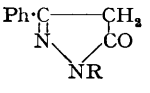
In the presence of Raney nickel or Adams platinum catalyst in ethanol at room temperature the amino*iso*oxazole (I; R = Ph) absorbed only 1 mol. of hydrogen, giving in good yield a crystalline dihydro-compound, provisionally regarded as the *iso*oxazoline (III) by analogy with the products of hydrogenation of *iso*oxazolones (Part II, *J.*, 1017). The compound was basic and formed monoacyl derivatives but with cold dilute acid it was

* Part V, *J.*, 1953, 3467.

rapidly hydrolysed to benzoylacetamide. Condensation of the compound, or its acyl derivatives, with hydrazine and phenylhydrazine in an attempt to prepare amino- or acylamino-pyrazoles, gave in each case only the pyrazolones (IV; R = H and Ph). These



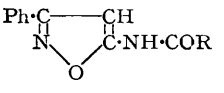
(III)



(IV)

$Ph\cdot C(NH_2){:}CH\cdot CO\cdot NH_2$
(V)

$Ph\cdot C(NH\cdot COR){:}CH\cdot CO\cdot NH_2$
(VI)



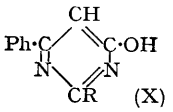
(VII)

results necessitated a revision of the structure of the dihydro-compound which was shown to be β-aminocinnamamide (V) by comparison with a sample prepared in very poor yield from ethyl benzoylacetate and ammonia (Guareschi, *Chem. Zentr.*, 1896, I, 603; 1905, II, 685). The *iso*oxazoline (III) is undoubtedly an intermediate in the formation of the linear compound, and a similar ring opening, following hydrogenation, has been observed with certain *iso*oxazolones (Part V, *loc. cit.*).

5-Acetamido-3-phenyl*iso*oxazole (VII; R = Me) also readily absorbed 1 mol. of hydrogen in the presence of nickel or platinum catalysts, but the product was a mixture from which were isolated three compounds in variable yields; the compounds were (*a*) an amphoteric substance with predominantly basic properties, (*b*) an amphoteric substance which was essentially acidic, and (*c*) a compound which appeared to be a salt of (*a*) and (*b*). The basic substance was very readily hydrolysed by cold dilute acid with loss of ammonia, and further hydrolysis of the product gave benzoylacetamide; in addition the base reacted with hydrazine and phenylhydrazine to give the pyrazolones (IV; R = H and Ph) respectively. These results and the analytical data indicated that the base was *N*-(β-aminocinnamoyl) acetamide (VIII; R = Me) and the first hydrolysis product *N*-(benzoylacetyl)acetamide (IX; R = Me).

$Ph\cdot C(NH_2){:}CH\cdot CO\cdot NH\cdot COR$
(VIII)

$Ph\cdot CO\cdot CH_2\cdot CO\cdot NH\cdot COR$
(IX)



(X)

The base (VIII; R = Me) was remarkably labile, and lost a mol. of water when melted, when its aqueous or alcoholic solutions were boiled for a short time, when an aqueous-alcoholic solution was incubated at 35° for a few hours, or when its solution in dilute sodium hydroxide was kept at room temperature for a few minutes. The product in each case was the acidic compound (*b*); this was the hydroxypyrimidine (X; R = Me) (Pinner, *Ber.*, 1889, **22**, 1618). The lability of the base explains the variation in composition of the mixtures obtained by hydrogenation of (VII; R = Me), and when these mixtures were heated with water, or treated with dilute alkali, an almost quantitative yield of the pyrimidine (X; R = Me) resulted.

Similar compounds were obtained by hydrogenation of the *iso*oxazoles (VII; R = H and Ph) although acid hydrolysis of (VIII; R = H) was anomalous in giving a substance $C_9H_7O_2N$ as well as (IX; R = H). The reaction thus provides a method for introducing substituents into the 2-position in the pyrimidine ring in good yield without using amidines which are often not easily accessible and frequently give poor yields. The reaction, in addition, includes a new synthesis of certain diacylamides, notably (VIII) and (IX), and, moreover, suggests other routes to this type of compound from an appropriate heterocyclic amino-compound; these and related problems are being investigated.

Not unexpectedly, when the acyl derivatives (VI; R = Me and Ph) were melted the corresponding pyrimidines (X; R = Me and Ph) were obtained; the compounds (VI) however were much less labile than (VIII) and failed to cyclise in boiling ethanol or water. During a preparation of (VI; R = Ph) from the base (V) and benzoyl chloride in sodium hydroxide solution a small amount of the pyrimidine (X; R = Ph) was isolated, and this prompted an investigation of the action of sodium hydroxide on (VI; R = Ph); surprisingly, cyclisation occurred when a solution of the latter compound in N-sodium hydroxide was warmed for 10 min.

Experimental

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

Hydrogenation of 5-Amino-3-phenylisooxazole (I; R = Ph).—The *iso*oxazole, prepared from benzoylacetonitrile and hydroxylamine (Obregia, *loc. cit.*), crystallised from ethanol–water as needles, m. p. 112°; the reaction, when carried out in more concentrated solution than that used by Obregia (*loc. cit.*) gave better yields (80—90%). The *iso*oxazole (2 g.) in ethanol (30 ml.) was reduced with hydrogen and Raney nickel (2 ml.), hydrogen (290 ml. Calc. for 1 mol. : 280 ml.) being absorbed during 3 hr. (less when Adams platinum catalyst was used). Evaporation of the filtered solution *in vacuo* gave a very pale yellow solid; β-aminocinnamamide (1·8 g.) separated from ethanol as needles, m. p. 164° (Found : C, 66·55; H, 6·35; N, 17·0. Calc. for $C_9H_{10}ON_2$: C, 66·65; H, 6·2; N, 17·25%), undepressed when mixed with an authentic specimen, m. p. 164° (Guareschi, *loc. cit.*). The amine (0·5 g.) was warmed with N-hydrochloric acid (6 ml.) and from the clear solution benzoylacetamide (0·4 g.) separated on cooling, and recrystallised from water as needles, m. p. 112—113° (Found : C, 66·25; H, 5·35; N, 8·4. Calc. for $C_9H_9O_2N$: C, 66·25; H, 5·55; N, 8·0%), undepressed when mixed with an authentic specimen, m. p. 112° (Guareschi, *Chem. Zentr.*, 1904, II, 905). A solution of the amine (0·5 g.) in ethanol (10 ml.) containing phenylhydrazine (0·34 g.) was boiled under reflux for 2 hr.; evaporation of the solvent *in vacuo* gave 1 : 3-diphenylpyrazol-5-one (0·5 g.) which crystallised from ethanol as needles, m. p. 136—137° (Found : C, 76·05; H, 5·15; N, 11·95. Calc. for $C_{15}H_{12}ON_2$: C, 76·25; H, 5·1; N, 11·85%). Similarly the amine and hydrazine gave 3-phenylpyrazol-5-one as colourless plates (from ethanol), m. p. 236° (Found : C, 67·5; H, 5·15; N, 14·45. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·05; N, 14·5%); the m. p.s of the pyrazolones were undepressed when mixed with authentic specimens, prepared from ethyl benzoylacetate and the appropriate hydrazine (Knorr and Klotz, *Ber.*, 1887, **20**, 2546; Curtius, *J. pr. Chem.*, 1894, **50**, 515).

β-Acylaminocinnamamides (VI).—β-Aminocinnamamide (1 g.) and acetic anhydride (4 ml.) were warmed together on a water-bath for 15 min.; addition of water to the cooled solution precipitated an oil which soon crystallised; *β-acetamidocinnamamide* (0·8 g.) separated from ethanol–water as colourless needles, m. p. 238—240° (Found : C, 64·7; H, 5·9; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·6; N, 13·7%). The amide (0·1 g.) was melted and the product crystallised from ethanol as colourless needles, m. p. 242—243° (Found : C, 70·7; H, 5·25; N, 15·05. Calc. for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%) undepressed when mixed with 6-hydroxy-2-methyl-4-phenylpyrimidine, m. p. 242° (Pinner, *loc. cit.*). A solution of the amide (0·1 g.) in N-sodium hydroxide (10 ml.) was warmed on a water-bath for 10—15 min., cooled, and neutralised with hydrochloric acid, to give 6-hydroxy-2-methyl-4-phenylpyrimidine (0·06 g.). β-Aminocinnamamide (1 g.) and benzoyl chloride (1·5 g.) were shaken together in 2N-sodium hydroxide (10 ml.), and the precipitate of *β-benzamidocinnamamide* (1·1 g.) crystallised from ethanol as colourless needles, m. p. 216—218° (Found : C, 72·0; H, 5·05; N, 10·25. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). Acidification of the alkaline filtrate and crystallisation of the precipitate from ethanol gave 6-hydroxy-2 : 4-diphenylpyrimidine (0·1 g.), m. p. and mixed m. p. 289—290° (Found : C, 77·7; H, 4·7; N, 11·0. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·85; N, 11·3%) (Pinner, *loc. cit.*; Ruhemann and Stapleton, *J.*, 1900, **77**, 244). The hydroxydiphenylpyrimidine was also obtained from β-benzamidocinnamamide by the action of heat or of sodium hydroxide solution.

5-Formamido-3-phenylisooxazole (VII; R = H).—A solution of 5-amino-3-phenyl*iso*oxazole (2 g.) in formic acid (5 ml. 98%) was warmed to 60° and acetic anhydride (4 ml.) added slowly so that the temperature did not exceed 60°; the solution was kept at 60° for 2 hr., then cooled, and water (20 ml.) was added to precipitate *5-formamido-3-phenylisooxazole hemihydrate* (1·9 g.) which crystallised from water as colourless needles, m. p. 115—117° (decomp.) (Found : C, 60·8; H, 4·35; N, 14·3. $C_{10}H_8O_2N_2,\frac{1}{2}H_2O$ requires C, 60·9; H, 4·6; N, 14·2%). The acetyl (Burns, *loc. cit.*) and benzoyl (Moureu and Lazennec, *loc. cit.*) derivatives were similarly prepared.

Hydrogenation of Acylaminoisooxazoles.—5-Acetamido-3-phenyl*iso*oxazole (1 g.) in ethanol (30 ml.) was hydrogenated over Raney nickel (2 ml.), hydrogen (116 ml. Calc. for 1 mol. : 111 ml.) being absorbed during 6 hr. (1—2 hr. when Adams platinum catalyst was used). Evaporation of the filtered solution *in vacuo* gave a solid mixture which had a wide melting range. The properties of this varied somewhat in different experiments, but rapid crystallisation from ethanol gave *N-β-aminocinnammoylacetamide* (0·3 g.) as prisms, m. p. 136° (decomp.)

(Found: C, 64·65; H, 5·7; N, 13·85. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). From the ethanolic solution 6-hydroxy-2-methyl-4-phenylpyrimidine (0·2 g.) gradually separated; this crystallised from ethanol as needles, m. p. and mixed m. p. 243°. On one occasion, careful evaporation of the last-mentioned ethanolic solution *in vacuo*, and crystallisation of the residue from ethanol, gave a *substance*, possibly a salt of *N*-β-aminocinnamoylacetamide and the hydroxypyrimidine as colourless needles, m. p. 238° (Found: C, 67·2; H, 5·8; N, 14·35. $C_{11}H_{12}O_2N_2,C_{11}H_{10}ON_2$ requires C, 67·7; H, 5·7; N, 14·35%); this was converted into the hydroxypyrimidine when boiled with water. The last hydrogenation was repeated and the solid residue boiled with water (5 ml.) for 2 hr.; the solution was cooled, to give 6-hydroxy-2-methyl-4-phenylpyrimidine (0·8 g.), m. p. and mixed m. p. 238—240°. A solution of *N*-β-aminocinnamoylacetamide (0·5 g.) in N-hydrochloric acid (6 ml.) was warmed for a few min., then cooled, and the precipitate collected; N-(*benzoylacetyl*)*acetamide* (0·3 g.) crystallised from ethanol–water as colourless needles, m. p. 104—105° (Found: C, 64·45; H, 5·45; N, 6·85. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·85%). The amide (0·2 g.) in 2N-sodium hydroxide (2 ml.) was kept at room temperature for 1 hr.; acidification of the solution precipitated benzoylacetamide (0·1 g.) which separated from water as needles, m. p. and mixed m. p. 112—113°. Similarly, hydrogenation of 5-benzamido-3-phenyl*iso*oxazole gave N-β-*aminocinnamoylbenzamide* which crystallised from ethanol as needles, m. p. 179° (decomp.) (Found: C, 72·25; H, 5·3; N, 10·6. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%), hydrolysed to N-(*benzoylacetyl*)*benzamide*, needles (from ethanol), m. p. 168—169° (Found: C, 71·6; H, 4·95; N, 5·35. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·25%), and in addition 6-hydroxy-2 : 4-diphenylpyrimidine, m. p. and mixed m. p. 290°.

5-Formamido-3-phenyl*iso*oxazole hemihydrate gave N-β-*aminocinnamoylformamide* which separated from ethanol as laths, m. p. 155—156° (Found: C, 63·1; H, 5·15; N, 14·75. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·75%), hydrolysed to *N*-(benzoylacetyl)formamide, needles (from water), m. p. 114° (Found: C, 62·3; H, 4·4; N, 7·4. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·75; N, 7·35%); at the same time a second *substance* was isolated, and crystallised as needles (from ethanol), m. p. 144—145° (decomp.) (Found: C, 67·2; H, 4·55; N, 8·7. $C_9H_7O_2N$ requires C, 67·1; H, 4·35; N, 8·7%), and in addition 2-hydroxy-4-phenylpyrimidine, m. p. 268° (Found: C, 69·5; H, 4·5; N, 16·05. Calc. for $C_{10}H_8ON_2$: C, 69·75; H, 4·7; N, 16·25%). Seide (*Ber.*, 1925, **58**, 352) gives m. p. 267°.

Cylisation of β-*Aminocinnamoylacylamines* (VIII).—(i) *N*-β-Aminocinnamoylacetamide (40·8 mg.) was heated for a short time at the m. p.; a loss in weight (4·1 mg. Calc. for $1H_2O$: 3·7 mg.) occurred. Crystallisation of the product gave 6-hydroxy-2-methyl-4-phenylpyrimidine. (ii) The amine (0·6 g.) was boiled with water (60 ml.) for 2 hr.; a crystalline precipitate appeared after 1½ hr. The solution was evaporated to a small volume and the solid hydroxypyrimidine (0·5 g.) collected. (iii) A solution of the amine (0·05 g.) in ethanol (5 ml.) and water (10 ml.) was kept at 35°; the hydroxypyrimidine crystallised from the solution overnight. (iv) A solution of the amine (0·1 g.) in N-sodium hydroxide (4 ml.) was kept at room temperature for 10 min.; acidification of the solution precipitated the hydroxypyrimidine (0·07 g.). Similar series of reactions were performed with the benzamide and formamide derivatives, the latter compound proving the most labile.

Ethyl 5-*Amino*-3-*methyl*iso*oxazole*-4-*carboxylate* (II; R = Me).—A solution of ethyl 2-cyano-3-oxobutanoate (3·1 g.) in ethanol (50 ml.) containing hydroxylamine hydrochloride (1·4 g.) and pyridine (2 ml.) was warmed on a water-bath for 1 hr. The solution was evaporated to a small volume, and water (50 ml.) added, to precipitate the iso*oxazole* ester (2·1 g.) which recrystallised from water as colourless needles, m. p. 133—134° (Found: C, 49·65; H, 5·7; N, 17·0. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%). The ester (1 g.) was kept at room temperature with N-sodium hydroxide (5 ml.) for 30 min. and the solution then acidified, to give 5-*amino*-3-*methyl*iso*oxazole*-4-*carboxylic acid* (0·6 g.) which recrystallised from ethanol–water as colourless needles, m. p. 161—162° (decomp.) (Found: C, 42·2; H, 4·15; N, 19·1. $C_5H_6O_3N_2$ requires C, 42·25; H, 4·25; N, 19·7%); the acid gave a red colour with ferric chloride in ethanol. A solution of the acid (0·5 g.) in N-sodium hydroxide solution (5 ml.) was warmed on a water-bath for 10 min., then cooled, and the solid collected; 5-amino-3-methyl*iso*oxazole (0·25 g.) crystallised from water as needles, m. p. 85° undepressed on admixture with an authentic specimen of m. p. 84—85° (Burns, *loc. cit.*).

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