# 107. *Synthesis of Alloxazine from 2-Aminoquinoxaline-3-carboxyamide.*

By A. H. Gowenlock, G. T. Newbold, and F. S. Spring.

The conversion of 2-aminoquinoxaline-3-carboxylic acid (and its derivatives) into alloxazine, although more difficult than the analogous conversion of anthranilic acid into dihydroxyquinazoline, has been achieved. Treatment of 2-aminoquinoxaline-3-carboxyamide with ethyl chloroformate gives 2-carbethoxyaminoquinoxaline-3-carboxyamide which on treatment with sodium ethoxide yields alloxazine in high yield.

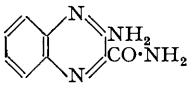
Alloxazine derivatives are usually prepared by the condensation of an *o*-diamine with alloxan (Kuhling, *Ber.*, 1891, **24**, 2363; Mohlau and Litter, *J. pr. Chem.*, 1906, **73**, 481); a second type of synthesis consists in the condensation of an *o*-quinone with 5 : 6-diamino-2 : 4-dihydroxypyrimidine (Kuhn and Cook, *Ber.*, 1937, **70**, 761), although the method fails in the case of *o*-benzoquinone. Both methods require a preformed pyrimidine ring, and in each a pyrazine ring is formed by the condensation reaction. A third method in which quinoxaline-2 : 3-dicarboxyamide is converted into alloxazine (Baxter and Spring, *J.*, 1945, 229) differs from the first two in that it requires a preformed pyrazine ring, the reaction resulting in the formation of the pyrimidine ring. The last method is comparable with the preparation of 2 : 4-dihydroxyquinazoline from phthalamide (Hoogewerff and van Dorp, *Rec. Trav. chim.*, 1891, **10**, 4; 1896, **15**, 107). This paper describes attempts to synthesise alloxazine and other pyrimidoquinoxaline derivatives by adaptations of methods for the synthesis of substituted quinazolines from benzene derivatives.

Anthranilic acid and anthranilamide have been converted into 2 : 4-dihydroxyquinazoline by heating with urea (Abt, *J. pr. Chem.*, 1889, **39**, 140). Similar treatment of 2-aminoquinoxaline-3-carboxylic acid and 2-aminoquinoxaline-3-carboxyamide gave complex mixtures, and, although there was some evidence of the formation of alloxazine, satisfactory conditions for using these routes to alloxazine were not developed. Equally unsuccessful was an attempt to condense 2-aminoquinoxaline-3-carboxylic acid with cyanogen in alcoholic solution using conditions which lead to the formation of 4-hydroxy-2-ethoxyquinazoline from anthranilic acid (Griess, *Ber.*, 1869, **2**, 416; 1878, **11**, 1987).

A method for the conversion of the readily available 2-aminoquinoxaline-3-carboxyamide (I) (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) into alloxazine was developed by condensation

of the amino-amide with ethyl chloroformate to give 2-*carbethoxyaminoquinoxaline*-3-*carboxyamide* (II) in 70% yield. When treated with ethanolic sodium ethoxide, (II) gave alloxazine (III) in 80% yield.

Treatment of 2-aminoquinoxaline-3-carboxyamide (I) with acetic anhydride gives 6-*hydroxy*-2-*methylbenzopteridine* (IV). A second product of this reaction is a *monoacetyl* derivative, $C_{13}H_{10}O_2N_4$, m. p. 104—105°, hydrolysis of which yields (IV). Acetylation of (IV) yields the same monoacetyl derivative. The relatively low melting point of the monoacetyl derivative suggests that it is 6-acetoxy-2-methylbenzopteridine rather than the isomeric *N*-acetyl compound.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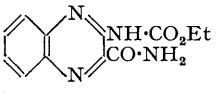
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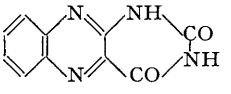
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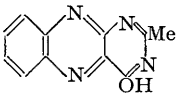
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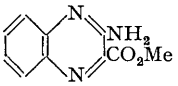
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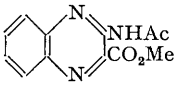
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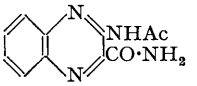
(VII.)

Acetylation of methyl 2-aminoquinoxaline-3-carboxylate (V) (Gowenlock, Newbold, and Spring, *loc. cit.*) gives *methyl* 2-*acetamidoquinoxaline*-3-*carboxylate* (VI) in high yield. Treatment of (VI) with ammonia yields 2-*acetamidoquinoxaline*-3-*carboxyamide* (VII) which when heated with acetic anhydride gives the monoacetyl derivative of 6-hydroxy-2-methylbenzopteridine (IV). Attempts to cyclise 2-acetamidoquinoxaline-3-carboxyamide (VII) by simple solution in alkali, a procedure which leads to the formation of 4-hydroxy-2-methylquinoxaline from the analogously constituted 2-acetamidobenzamide, were unsuccessful.

## Experimental.

2-*Carbethoxyaminoquinoxaline*-3-*carboxyamide* (II).—2-Aminoquinoxaline-3-carboxyamide (Gowenlock, Newbold, and Spring, *loc. cit.*) (1 g.) and ethyl chloroformate (25 c.c.) were refluxed for 20 hours; hydrogen chloride was continuously evolved. The excess of ester was removed under reduced pressure and the residue crystallised from methanol to give 2-*carbethoxyaminoquinoxaline*-3-*carboxyamide* as pale yellow needles (yield, 70%). It is readily soluble in chloroform and glacial acetic acid at room temperature and in hot alcohol, benzene, acetone, and ethyl acetate; it decomposes above 300° (Found: C, 55·5; H, 4·4; N, 21·8. $C_{12}H_{12}O_3N_4$ requires C, 55·4; H, 4·6; N, 21·5%).

*Alloxazine.*—(*a*) 2-Carbethoxyaminoquinoxaline-3-carboxyamide (0·8 g.) was refluxed with a solution of potassium hydroxide (3·2 g.) in 60% alcohol (60 c.c.) for 3 hours. The hot solution was acidified (Congo-red) with hydrochloric acid and the yellow precipitate (0·43 g.) collected. The filtrate was evaporated to dryness under reduced pressure and the residue extracted with hot glacial acetic acid. When the extract was cooled, 2-aminoquinoxaline-3-carboxylic acid separated as yellow needles, m. p. 212° (decomp.) undepressed in m. p. when mixed with an authentic specimen prepared as described by Baxter and Spring (*loc. cit.*). The yellow precipitate was purified by dissolution in hot 2% sodium hydroxide; after filtration and cooling, the solution deposited the sodium salt of alloxazine as yellow needles. The sodium salt was dissolved in aqueous alcohol and the solution acidified with acetic acid, alloxazine separating as a pale yellow powder decomposing without melting above 300°. Light absorption in ethanol: Maxima at 3220 A. ($\varepsilon = 5900$) and 2460 A. ($\varepsilon = 19{,}000$). It was characterised by conversion into 1 : 3-dimethylalloxazine which separated from alcohol as bright yellow prisms, m. p. 234—236°, undepressed when mixed with an authentic specimen (Found: C, 59·2; H, 3·9; N, 23·2. Calc. for $C_{12}H_{10}O_2N_4$: C, 59·5; H, 4·1; N, 23·2%). Light absorption in ethanol: maxima at 2450 A. ($\varepsilon = 38{,}200$), 3245 A. ($\varepsilon = 6900$), and 3780 A. ($\varepsilon = 7200$).

(*b*) 2-Carbethoxyaminoquinoxaline-3-carboxyamide (450 mg.) was heated under reflux with a solution of sodium ethoxide in ethanol (from 70 c.c. of alcohol and 450 mg. of sodium). The amide quickly dissolved and the resulting yellow solution slowly deposited a bright yellow solid. The solvent was removed (reduced pressure) and the residual solid dissolved in hot 2% sodium hydroxide (25 c.c.). The hot solution was filtered, and on cooling deposited the sodium salt of alloxazine as yellow needles treatment of which as described above gave alloxazine (330 mg.) as a pale yellow powder decomposing without melting above 300°, characterised by conversion into 1 : 3-dimethylalloxazine which separated from methyl alcohol as yellow prisms, m. p. 238—240° undepressed when mixed with an authentic specimen.

*Methyl* 2-*Acetamidoquinoxaline*-3-*carboxylate.*—A solution of methyl 2-aminoquinoxaline-3-carboxylate (0·5 g.) in acetic anhydride (3 c.c.) was heated under reflux for 1 hour. The solution was evaporated under reduced pressure and the residue crystallised from benzene–light petroleum (b. p. 40—60°) to give *methyl* 2-*acetamidoquinoxaline*-3-*carboxylate* (0·41 g.) as needles, m. p. 143—144° (Found: C, 59·1; H, 4·3; N, 16·9. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%).

2-*Acetamidoquinoxaline*-3-*carboxyamide.*—A solution of methyl 2-acetamidoquinoxaline-3-carboxylate (0·48 g.) in methanol (25 c.c.) was saturated with dry ammonia at 0° and kept at this temperature for

1 hour. The crystalline deposit was collected and recrystallised from aqueous methanol; *2-acetamidoquinoxaline-3-carboxyamide* (0·39 g.) was thus obtained as fine needles, m. p. 207° (decomp.) (Found : C, 57·4; H, 4·2; N, 24·2 : $C_{11}H_{10}O_2N_4$ requires : C, 57·4; H, 4·3; N, 24·3%).

*6-Hydroxy-2-methylbenzopteridine*—(*a*) 2-Aminoquinoxaline-3-carboxyamide (2 g.) was refluxed with acetic anhydride (15 c.c.) for ¾ hour. The solution was evaporated under reduced pressure and the residue extracted with hot methanol. Fractional crystallisation of the extracted material from aqueous methanol gave a less soluble fraction which separated as fine needles; these after recrystallisation from the same solvent or from *n*-hexane gave the *monoacetyl* derivative of 6-hydroxy-2-methylbenzopteridine (0·57 g.) as needles, m. p. 104—105° (Found : C, 61·2; H, 4·2; N, 22·5. $C_{13}H_{10}O_2N_4$ requires C, 61·4; H, 3·9; N, 22·0%). Light absorption in ethanol : maxima at 2480 A. ($\varepsilon = 2930$) and 3295 A. ($\varepsilon = 6000$).

The mother liquors obtained after the isolation of the monoacetyl derivative gave a second crop of crystalline solid on standing. Recrystallisation of this yielded *6-hydroxy-2-methylbenzopteridine* (0·32 g.) which after several recrystallisations from aqueous methanol separated as felted needles, m. p. 185—187°. It is moderately soluble in hot water, from which it can be crystallised, and readily soluble in methanol, ethanol, and acetic acid. It is soluble in cold N-sodium hydroxide and precipitated from the alkaline solution by acidification with N-hydrochloric acid (Found : C, 62·0; H, 4·1. $C_{11}H_8ON_4$ requires C, 62·3; H, 3·8%). Light absorption in ethanol : maxima at 2440 A. ($\varepsilon = 28{,}300$) and 3420 A. ($\varepsilon = 5{,}800$).

The monoacetyl derivative (50 mg.) was warmed with 0·5N-sodium hydroxide (1·8 c.c.) until solution was complete. The bright yellow solution was treated with N-hydrochloric acid (0·9 c.c.) and the precipitated solid collected and crystallised from aqueous methanol; 6-hydroxy-2-methylbenzopteridine was thus obtained as needles, m. p. 185—187° undepressed when mixed with the specimen described above.

6-Hydroxy-2-methylbenzopteridine (70 mg.) was refluxed with acetic anhydride (2 c.c.) for ¾ hour. The solution was evaporated under reduced pressure and the residue crystallised from aqueous methanol to give the monoacetyl derivative as fine needles, m. p. 103—104° not depressed when mixed with the specimen described above.

(*b*) A solution of 2-acetamidoquinoxaline-3-carboxyamide (0·5 g.) in acetic anhydride (7·5 c.c.) was heated under reflux for 3 hours. The solvent was removed under reduced pressure and the residual solid extracted with boiling *n*-hexane (2 × 10 c.c.). Removal of the solvent from the extract followed by crystallisation from aqueous methanol gave the acetyl derivative of 6-hydroxy-2-methylbenzopteridine as fine needles, m. p. 104—105° not depressed on admixture with the specimen described above.

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