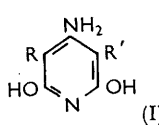
901. *The Preparation of Glutazine and Some of its Derivatives.*

By H. N. Rydon and K. Undheim.

Some improved syntheses, covered by the title, are described as work preparatory for the synthesis of some folic acid antagonists.

Glutazine (4-amino-2,6-dihydroxypyridine) (I; R = R′ = H), required as starting material for a projected synthesis of some folic acid antagonists based on the 1,4,6-triazanaphthalene ring system, was first prepared by Stokes and von Pechmann [1] from ethyl acetone-1,3-dicarboxylate. It was later obtained, in unspecified yield, by Baron, Remfry, and Thorpe [2] by the action, under drastic conditions, of sodium hydroxide on its 3-ethoxycarbonyl derivative (I; R = CO_2Et, R′ = H), which is readily prepared from ethyl cyanoacetate.



(I)

In our hands, neither of these methods was satisfactory, and we describe below a modification of the method of Baron, Remfry, and Thorpe,[2] in which the ethoxycarbonyl derivative (I; R = CO_2Et, R′ = H) is treated with aqueous ammonia under pressure at 90—95°, which enables glutazine to be prepared conveniently, in three stages, from ethyl cyanoacetate in 35% overall yield.

Treatment of glutazine with phosphorus oxychloride yields 4-amino-2,6-dichloropyridine, previously obtained, by a different procedure, by Meyer and Beck.[3] Both glutazine and its 3-ethoxycarbonyl derivative couple readily with diazotised *p*-chloroaniline to yield the chlorophenylazo-derivatives (I; R = H or CO_2Et, R′ = $N_2 \cdot C_6H_4Cl$), but the reduction products of neither of these yielded isolable 1,4,6-triazanaphthalene derivatives on reaction with biacetyl or benzil.

[1] Stokes and von Pechmann, *Ber.*, 1886, **19**, 2694.
[2] Baron, Remfry, and Thorpe, *J.*, 1904, **85**, 1726.
[3] Meyer and Beck, *Monatsh.*, 1915, **36**, 731.

In an attempt to improve the preparation of ethyl β-amino-β-hydroxyglutaric monoamide from ethyl acetonedicarboxylate, the saturated aqueous ammonia employed by Stokes and von Pechmann was replaced by a mixture of aqueous ammonia and liquid ammonia; the product was 2,4-diamino-6-hydroxypyridine, no doubt arising by dehydration and cyclisation of β-amino-β-hydroxyglutaric diamide.

Experimental

Glutazine (I; R = R′ = H).—Ethyl α-cyano-β-iminoglutarate, m. p. 52°, was obtained in 70% yield by the method of Baron, Remfry, and Thorpe [2] and converted into ethyl glutazine-3-carboxylate (I; R = CO_2Et, R′ = H), m. p. >360°, in 100% yield by the procedure of these authors.

The ethoxycarbonyl compound (30 g.), suspended in aqueous ammonia (*d* 0·880) (300 ml.), was heated in an autoclave at 90—95° for 30 hr. The resulting solution was evaporated to dryness under reduced pressure; recrystallisation of the residue from hot water (charcoal) afforded glutazine (9·7 g., 51%), m. p. 300° (decomp.) (Found: C, 47·7; H, 4·9; N, 21·8. Calc. for $C_5H_6N_2O_2$: C, 47·6; H, 4·8; N, 22·2%); the m. p. was not depressed on admixture with a less pure specimen (m. p. 285—290°) obtained from 2,4,6-trihydroxypyridine [2] by fusion with ammonium acetate.[1] The identity was further confirmed by paper chromatography and conversion into the 4-acetyl derivative, m. p. 294° (lit.,[1] m. p. 285—290°).

4-*Amino*-2,6-*dichloropyridine*.—Glutazine (2·4 g.) was heated with phosphorus oxychloride (10 ml.) in a sealed tube at 150° for 5 hr. The product was evaporated to dryness under reduced pressure and the residue treated with ethanol (40 ml.), saturated with ammonia at 0°. Insoluble material was filtered off and extracted with hot benzene (100 ml.). The benzene extract and the ethanolic filtrate were combined and evaporated to dryness under reduced pressure. Sublimation at 225°/0·05 mm. gave the dichloro-compound (1·87 g., 60%), which crystallised from benzene in needles, m. p. 170° (lit.,[3] m. p. 176°) (Found: N, 17·05. Calc. for $C_5H_4Cl_2N_2$: N, 17·2%).

p-*Chlorophenylazo-derivatives*.—Glutazine (2·52 g.) was dissolved in water (40 ml.) containing sodium hydrogen carbonate (3·4 g.) and the solution, cooled in ice, treated during 20 min., with stirring, with an ice-cold solution of diazotised *p*-chloroaniline, prepared by adding sodium nitrite (1·38 g.) in water (10 ml.) to an ice-cooled solution of *p*-chloroaniline (2·55 g.) in 2N-hydrochloric acid (25 ml.) and water (10 ml.); 2N-sodium carbonate (5 ml.) was added when half the diazo-solution had been added. After being kept for 30 min. at 0°, the mixture was allowed to warm to room temperature and neutralised with 2N-hydrochloric acid. Filtration, followed by washing with water, afforded 4-*amino*-3-p-*chlorophenylazo*-2,6-*dihydroxypyridine* (5·29 g., 96%) which, after recrystallisation from acetic acid, had m. p. 315° (decomp.) (Found: C, 49·2; H, 3·6; Cl, 13·7; N, 21·3. $C_{11}H_{19}ClN_4O_2$ requires C, 49·9; H, 3·4; Cl, 13·4; N, 21·2%).

Ethyl 4-*amino*-5-p-*chlorophenylazo*-2,6-*dihydroxypyridine*-3-*carboxylate*, prepared similarly from ethyl glutazine-3-carboxylate in theoretical yield, crystallised from acetic acid in needles, m. p. 259° (decomp.) (Found: C, 49·8; H, 4·4; Cl, 10·1; N, 16·6. $C_{14}H_{13}ClN_4O_4$ requires C, 49·9; H, 3·9; Cl, 10·5; N, 16·6%).

2,4-*Diamino*-6-*hydroxypyridine*.—Ethyl acetone-1,3-dicarboxylate (10 g.) was cooled in ice–salt and treated slowly with a mixture (12 ml.; 1 : 1 v/v) of aqueous ammonia (*d* 0·880) and liquid ammonia. After the mixture had warmed to room temperature a further 6 ml. of the ammonia were added; the flask was then tightly stoppered and the mixture kept at room temperature for 5 days. The crystalline product (4·4 g.; 55%) was collected by filtration and recrystallised from ethanol, yielding the *diamino-compound* in prisms, m. p. 178° (Found: C, 42·0; H, 6·9; N, 28·7. $C_5H_7N_3O,H_2O$ requires C, 42·0; H, 7·0; N, 29·4%). The proposed structure, in its α-pyridone form,[4] is supported by the presence in the infrared spectrum [5] (KBr disc) of the following strong bands: 3439 and 3316 (NH stretching in amino-group), 3197 (ring NH stretching), and 1656 (ring CO stretching) $cm.^{-1}$.

We thank Messrs. Parke, Davis and Co. Ltd. for a research studentship awarded to K. U.

Washington Singer Laboratories,
University of Exeter.

[*Received, May 1st,* 1962.]

[4] Mason, *J.*, 1957, 4874; 1958, 3619.
[5] Undheim, Ph.D. Thesis, Exeter, 1959.