110. *Purines, Pyrimidines, and Imidazoles. Part XVII.*[1] *A Synthesis of Willardiine.*

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Reaction of β-ethoxyacryloyl isocyanate with aminoacetaldehyde diethyl acetal gave a urea that was converted by alkali into 1-(2,2-diethoxyethyl)-uracil; with acid this gave uracil-1-ylacetaldehyde. A Strecker reaction then gave DL-α-amino-β-uracil-1-ylpropionic acid (DL-willardiine) which was resolved as a formyl derivative with (+)-α-methylphenethylamine to afford the (−)-enantiomorph identical with willardiine.

A NEW non-protein L-α-amino-acid, willardiine, was recently isolated from the seeds of *Acacia willardiana* and shown (by paper chromatography) to be present also in the seeds of *A. lemmoni* and *A. millefolia*.[2] The compound was formulated as α-amino-β-uracil-1-yl-propionic acid (I; R = H) by virtue of its stability to hot hydrobromic acid, its infrared absorption spectrum, the similarity of its ultraviolet absorption spectra at different pH values to those of uridine and 1-methyluracil, colour reaction with the ninhydrin reagent, and its formal resemblance to albizziin (L-α-amino-β-ureidopropionic acid) which accompanies willardiine in the seeds.[2] We now report [3] a synthesis of willardiine by an unambiguous method which confirms the structure (I; R = H).

Reaction of a solution of the acyl isocyanate [4] EtO·CH:CH·CO·NCO in benzene with aminoacetaldehyde diethyl acetal gave the linear urea (II) which cyclised to the uracil (III) when warmed with aqueous alkali. Hydrolysis of the acetal (III) with hydrochloric acid then gave uracil-1-ylacetaldehyde (IV) which was also obtained directly from the urea (II) by successive reaction with alkali and acid. The aldehyde (IV) with potassium cyanide, ammonia, and ammonium chloride under the conditions of the Strecker reaction then gave after hydrolysis, DL-willardiine (I; R = H). The ultraviolet absorption spectrum of the racemate was the same as that of the naturally occurring material at pH 1

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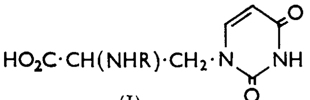
[1] Part XVI, *J.*, 1961, 4845.
[2] Gmelin, *Z. physiol. Chem.*, 1959, **316**, 164.
[3] Cf. Shaw and Dewar, *Proc. Chem. Soc.*, 1961, 216.
[4] Shaw and Warrener, *J.*, 1958, 157.

and pH 12, but there were marked differences in the infrared absorption curves of the two materials when measured in potassium bromide discs: in particular, a band at 10·8 μ in the naturally occurring material is absent in the racemate.

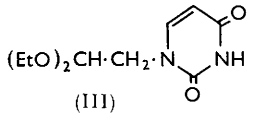
The racemate (I; R = H) with formic acid and acetic anhydride gave the formamide (I; R = CHO) which with (+)-α-methylphenethylamine or (—)-brucine gave crystalline salts. The first crop of the (+)-α-methylphenethylamine salt was hydrolysed with hydrochloric acid to give the (—)-enantiomorph of willardiine, the infrared spectrum of which was identical with that of the natural product. The rotation of the synthetic material, which undoubtedly is still not optically pure, was greater than that of the naturally occurring substance, which suggests that the latter may be partly racemised. Since completing our experiments we have been informed by Professor Anders Kjaer of The Royal Veterinary and Agricultural College, Copenhagen, Denmark, of an alternative synthesis of willardiine by hydrolysis of L-α-(toluene-*p*-sulphonamido)-β-uracil-1-ylpropionic acid which normally gave the racemic amino-acid but could be adapted to give small amounts of the (—)-enantiomorph. The toluene-*p*-sulphonamido-derivative was obtained by the reaction of alkali with the urea formed from β-ethoxyacryloyl isocyanate[4] and methyl L-β-amino-α-(toluene-*p*-sulphonamido)propionate. Our racemic willardiine and the Danish workers' material had identical infrared spectra.



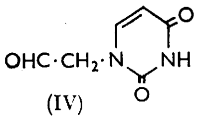
(I)

$EtO{\cdot}CH{:}CH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH(OEt)_2$

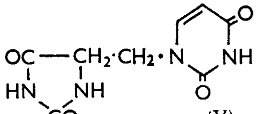
(II)



(III)



(IV)



(V)

As a possible alternative to the Strecker conversion of the aldehyde (IV) into willardiine we investigated the Bucherer hydantoin synthesis. Reaction of the aldehyde (IV) with potassium cyanide and ammonium carbonate in aqueous ethanol readily gave the hydantoin (V). This, however, resisted hydrolysis, being recovered after several hours in 10N-hydrochloric acid at 150° in a sealed tube.

EXPERIMENTAL

N-2,2-*Diethoxyethyl*-N′-β-*ethoxyacryloylurea*.—A solution of β-ethoxyacryloyl chloride[5] (5·55 g.) in anhydrous benzene (50 ml.) was boiled under reflux with silver cyanate (7·5 g.) for 30 min. To the cooled mixture, which contained β-ethoxyacryloyl isocyanate,[4] was added a solution of aminoacetaldehyde diethyl acetal (5·5 g.) in benzene (10 ml.). The filtered mixture was evaporated *in vacuo* to a small volume and then diluted with light petroleum to precipitate the *acylurea* which crystallised from ethanol as laths (3·9 g.), m. p. 95—96° (Found: C, 52·6; H, 8·15; N, 10·2. $C_{12}H_{22}N_2O_5$ requires C, 52·55; H, 8·1; N, 10·2%). A further quantity (2·2 g.) of the urea was recovered from the mother-liquors.

1-(2,2-*Diethoxyethyl*)*uracil*.—The foregoing acylurea (4·65 g.) was heated on a steam-bath with water (15 ml.) and 4N-sodium hydroxide (5 ml.) for 10 min. The solution was then acidified with 5N-hydrochloric acid (4·1 ml.) and cooled, to give a crystalline precipitate of 1-(2,2-*diethoxyethyl*)*uracil* (1·2 g.) which recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) as rods, m. p. 91° (Found: C, 52·35; H, 7·2; N, 12·2. $C_{10}H_{16}N_2O_4$ requires C, 52·6; H, 7·05; N, 12·25%). A further quantity (0·2 g.) of the uracil was obtained by extraction of the mother-liquors with ether. The compound gave a precipitate with 2,4-dinitrophenylhydrazine only after being warmed for some time in acid solution.

Uracil-1-*ylacetaldehyde*.—(*a*) The foregoing acetal (2·18 g.) was heated on a steam-bath for 15 min. with 4N-hydrochloric acid (2·5 ml.) and water (17 ml.). The solution was then cooled

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[5] Shaw and Warrener, *J.*, 1958, 153.

to precipitate *uracil-1-ylacetaldehyde monohydrate* (0·8 g.) which recrystallised from water as prisms, m. p. 207° (decomp. with darkening from 175°) (Found: C, 41·4; H, 4·65; N, 16·5. $C_6H_6N_2O_3,H_2O$ requires C, 41·8; H, 4·7; N, 16·3%). The 2,4-*dinitrophenylhydrazone* formed yellow needles, m. p. 250° (decomp.) (Found: C, 42·75; H, 3·3; N, 25·2. $C_{12}H_{10}N_6O_6$ requires C, 43·1; H, 3·0; N, 25·15%). (*b*) The foregoing acylurea (18 g.) was heated for 45 min. on a steam bath with 4N-sodium hydroxide (20 ml.) and water (50 ml.). The cooled solution was extracted with ether, and the aqueous phase acidified with 10N-hydrochloric acid (9 ml.), then set aside overnight. The dark brown solution was then evaporated *in vacuo* until a crystalline precipitate appeared. The aldehyde (2·03 g.) had m. p. 207° (decomp.).

DL-*Willardiine.*—A solution of the foregoing aldehyde (2·03 g.) in water (7 ml.), aqueous ammonia (1·8 ml.; *d* 0·88), potassium cyanide (0·935 g.), and ammonium chloride (0·79 g.) was heated at 55—60° for 5 hr. The solution was mixed with 10N-hydrochloric acid (25 ml.) and boiled under reflux for 1 hr., then set aside overnight. The solution was evaporated to a small volume, mixed with 10N-hydrochloric acid (15 ml.), and boiled under reflux for 3 hr. The solution was evaporated to dryness *in vacuo* and the residue evaporated *in vacuo* with water. The residue was dissolved in a small volume of water to give an acid solution which was adjusted to pH 4 with aqueous ammonia and set aside. A crystalline precipitate of DL-willardiine (1·58 g.) was soon obtained. The amino-acid was obtained as colourless needles when a solution in aqueous ammonia was treated with charcoal, filtered, and adjusted to pH 4 with hydrochloric acid. It had m. p. 205—209° (decomp.) which varied considerably with the rate of heating, and it formed a *monohydrate* (Found: C, 38·3; H, 5·45; N, 19·4. $C_7H_9N_3O_4,H_2O$ requires C, 38·7; H, 5·1; N, 19·35%). It had $\lambda_{max.}$ 262—263 (ε 8750) $\lambda_{min.}$ 229—230 (ε 1500) at pH 1, and $\lambda_{max.}$ 265—266 mμ (ε 6250), $\lambda_{min.}$ 242 mμ (ε 3150) at pH 12. The compound gave an intense blue colour with the ninhydrin reagent.

α-Formamido-β-uracil-1-ylpropionic Acid.—A mixture of DL-willardiine (1 g.), formic acid (10 ml.), and acetic anhydride (3·5 ml.) was heated on a steam-bath for 15 min., then evaporated to dryness *in vacuo*, and the residue was rubbed with ethanol, to give a crystalline *formyl derivative* (0·83 g.). This recrystallised from 50% aqueous ethanol as needles, m. p. 223° (decomp.) (Found: C, 42·15; H, 4·15; N, 18·7. $C_8H_9N_3O_5$ requires C, 42·3; H, 4·0; N, 18·5%).

(−)-*Willardiine.*—A solution of the foregoing formamide (0·6 g.) in warm ethanol (50 ml.) containing (+)-α-methylphenethylamine (0·4 ml.) was evaporated to *ca.* 20 ml., then treated with ether until faintly turbid and set aside to give a crystalline precipitate of the *amine salt* (0·14 g.), m. p. 179—184° (decomp.), which retained a little ethanol (Found: C, 55·6; H, 6·3; N, 14·2. $C_{17}H_{22}N_4O_5,\frac{1}{2}C_2H_6O$ requires C, 56·1; H, 6·55; N, 14·55%). This first crop of salt was boiled under reflux with 6N-hydrochloric acid for 50 min. The solution was evaporated to dryness *in vacuo*, the residue dissolved in a small volume of water, and the pH of the solution adjusted to 4 with aqueous ammonia. This gave a crystalline precipitate of (−)-willardiine (0·05 g.), m. p. 206—211° (decomp.), $[\alpha]_D^{20}$ −20° (*c* 2·0 in N-HCl). Gmelin[2] gives m. p. 204—205° (decomp.), $[\alpha]_D^{22}$ −12·1° (*c* 1·16 in N-HCl). The infrared absorption curve of the synthetic material was identical with that of the natural compound.

Equimolar amounts of the foregoing formamide and brucine in ethanol also gave, after evaporation, a *brucine salt hydrate* which crystallised from ethanol rather slowly as needles, m. p. 195—197° (decomp.) (Found: C, 57·4; H, 5·95; N, 11·2. $C_{31}H_{35}N_5O_9,1\frac{1}{2}H_2O$ requires C, 57·4; H, 5·9; N, 10·8%).

5-(*Uracil-1-ylmethyl*)*hydantoin.*—A solution of uracil-1-ylacetaldehyde (0·65 g.), potassium cyanide (0·61 g.), and ammonium carbonate (1·6 g.) in 50% aqueous ethanol (7 ml.) was heated at 66—70° for 5 hr. The solution was then evaporated to dryness *in vacuo*, the residue dissolved in a small volume of water, and the solution adjusted to pH 3 with hydrochloric acid; a crystalline precipitate was soon obtained. The *hydantoin* (0·2 g.) recrystallised from water (charcoal) as needles, m. p. 346° (decomp. with sublimation) (Found: C, 42·6; H, 3·85; N, 25·1. $C_8H_8N_4O_4$ requires C, 42·8; H, 3·6; N, 25·0%).

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