Reaction of 2-Amino-2-deoxy-D-gluconic Acid with Hot Acetic Anhydride–Sodium Acetate

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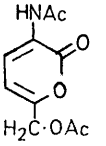
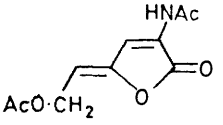
Reinvestigation of the title reaction has shown that 2-acetamido-6-acetoxyhexa-2,4-dien-5-olide (1) and (*Z*)- and (*E*)-2-acetamido-6-acetoxyhexa-2,4-dien-4-olide [(2) and (3)] are produced in the proportions *ca.* 4 : 9 : 7, respectively. The recrystallised materials described in previous literature were not compound (1) as was thought but were in fact compound (2) or mixtures of (2) and (3); several consequential corrections to structures derived from the supposed (1) are required.

In 1902 Neuberg [1] reported that the action of hot acetic anhydride–sodium acetate on 2-amino-2-deoxy-D-gluconic acid gave a material of composition $C_{10}H_{15}NO_5$, m.p. 125°. Bergmann *et al.* later investigated this reaction in detail, also obtaining material of m.p. 125°, although they were able to raise this to 154° by repeated recrystallisation: on the basis of numerous degradations and interconversions they deduced the structure (1).[2] More recently, Inoue [3] used material of m.p. 150—151° prepared in this way as the starting material in what was claimed to be a new route to 5-hydroxylysine involving hydrogenation, exchange of the acetoxy-function for an amino-group, and hydrolysis. However, we have now found that Inoue's synthesis is based on a false premise, as reinvestigation of the title reaction has shown that his starting material does not have structure (1), but was in



(1)



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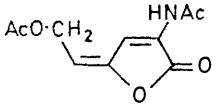

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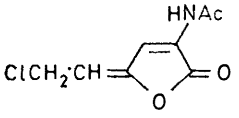

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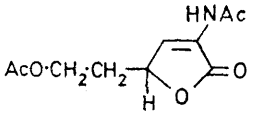

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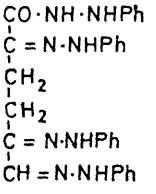


(6)

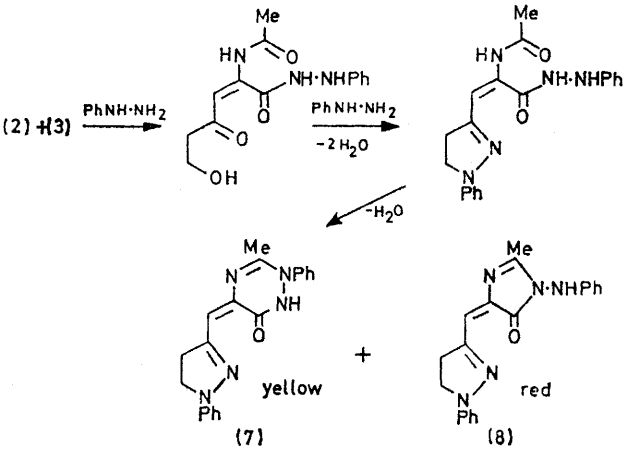
fact (2), so that his final product was presumably 4-hydroxylysine. The same substance has also been used, under the same misapprehension, by Kuhn's school [4] as an analogy to support the structure assigned to an unsaturated lactone obtained by them in their work on the base-catalysed rearrangement of 2-anilino-2-deoxy-D-hexononitriles: some reassessment may be called for here as well.

Treatment of 2-amino-2-deoxy-D-gluconic acid with acetic anydride–sodium acetate followed by extraction with chloroform as performed by previous workers [1-3] gave an oil which was shown by n.m.r. to be a mixture of the three isomeric lactones (1)—(3) in the proportions *ca.* 4 : 9 : 7 respectively. Crystallisation from benzene gave a good recovery of crystalline material of m.p. 121—123° which was free of (1) but which was still a mixture of (2) and (3) in the proportions *ca.* 3 : 2. Repeated recrystallisation from benzene raised the m.p. to 126—127° and sharpened it but the proportions of (2) and (3) remained almost constant. This mixture of (2) and (3) appears to be identical with the material of m.p. 125° obtained by Neuberg [1] and by Bergmann and his colleagues.[2] We were able to isolate a small crop of the single isomer (2) [distinguished from (3) by nuclear Overhauser effect (n.O.e.) investigations] by crystallisation of the crude product from chloroform–ether: this compound had m.p. 150—151° and is presumably identical with the compound melting in this range which was isolated by Bergmann *et al.*[2] (their compound V) and used by Inoue.[3] A sample of the minor product (1) was isolated by p.l.c. from the liquors remaining after crystallisation of the mixture of (2) and (3): this appears to be identical with the compound XX described [2] by Bergmann's group which they obtained by an entirely different route and which was erroneously formulated by them as (2) or (3). They obtained their compound XX by successive treatment of a derivative supposed by them to be ethyl 2-amino-5,6-*O*-benzylidene-2-deoxy-D-gluconate hydrochloride with hot acetic anhydride–sodium acetate, cold concentrated hydrochloric acid, and hot acetic anhydride–sodium acetate. However the starting material they used has since been shown to be 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconic acid ethanol solvate hydrochloride,[5,6] and in the light of this, Ferrier [7] has pointed out that the compound XX of Bergmann *et al.*[2] is probably pyranoid, not furanoid.

[1] C. Neuberg, *Ber.*, 1902, **35**, 4009.
[2] M. Bergmann, L. Zervas, and E. Silberkweit, *Ber.*, 1931, **64**, 2428.
[3] Y. Inoue, Jap. P. 6511/1962 (*Chem. Abs.*, 1963, **59**, 760e).
[4] R. Kuhn, D. Weiser, and H. Fischer, *Annalen*, 1959, **628**, 207.
[5] P. Karrer and J. Meyer, *Helv. Chim. Acta*, 1937, **20**, 407.
[6] D. B. Hope and P. W. Kent, *J. Chem. Soc.*, 1955, 1831.
[7] R. J. Ferrier, *Adv. Carbohydrate Chem.*, 1965, **20**, 67 (see p. 107).

As Bergmann *et al.*[2] wrongly supposed that their lactone V had structure (1), the six-membered ring structures assigned by them to the derivatives obtained from it all require correction: we have repeated two of their preparations. Thus brief treatment of the *ZE*-mixture of (2) and (3) with warm concentrated hydrochloric acid gave their compound XII, which is a single stereoisomer for which structure (4) is correct. Brief hydrogenation of the mixture of (2) and (3) gave their derivative IX, which in fact has structure (5).

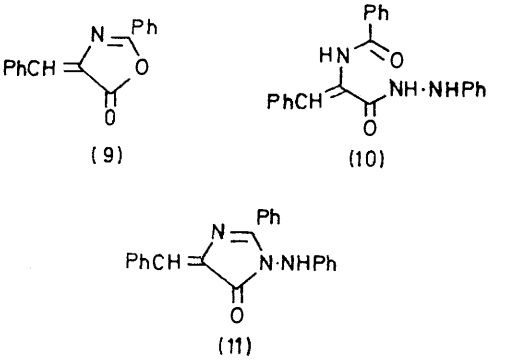
The erroneous proposal [2] of structure (1) rested heavily upon the outcome of the reaction with phenylhydrazine in 50% aqueous acetic acid. Bergmann *et al.* obtained in low yield a yellow compound which they numbered XV to which they assigned the osazone structure (6). They argued that this was consistent with their lactone V having structure (1), since an α-hydroxy-ketone function capable of osazone formation might be generated from (1) on ring opening, but that it was incompatible with formulation of V as (2) or (3) because these structures would lead on ring opening to a β-hydroxy-ketone incapable of osazone formation. We have therefore re-examined the reaction of the mixture of (2) and (3) with phenylhydrazine in 50% aqueous acetic acid under the conditions used by Bergmann *et al.*:[2] the resulting mixture was complex, showing at least fifteen components on t.l.c. although only two were coloured (one red, one yellow). The directions given [2] enabled us to isolate the yellow compound, the properties of which corresponded exactly with the description given [2] for compound XV: the red component crystallised from the liquors remaining after removal of the yellow compound. These compounds proved to be closely related isomers of molecular formula $C_{20}H_{19}N_5O$, corresponding to the addition of two molecules of phenylhydrazine with the loss of three molecules of water. Their n.m.r. spectra were similar, each showing ten aromatic protons, an isolated vinylic proton, an isolated $CH_2{\cdot}CH_2$ system, an isolated methyl group, and a single proton which underwent exchange on addition of deuterium oxide. The chemical shifts were similar except for that of the exchangeable proton, which resonated at much higher field in the red compound (τ *ca.* 3) than in the yellow one (−0.8). The observation of a substantial n.O.e. on the intensity of the vinylic singlet on irradiation at the frequency of one of the methylene signals in the spectrum of the yellow compound implied the presence of the isolated structural element ·CH_2·CH_2·C(·CH:):. The i.r. spectra of the two isomers were also similar, the most obvious difference being the fact that the carbonyl band was at 1 700 cm^{-1} in the spectrum of the red compound but at 1 660 cm^{-1} in that of the yellow one. Attempts to prepare acetyl derivatives failed in both cases. Neither compound was an intermediate in the formation of the other, as both were unchanged by extended heating under the conditions of the reaction. The compounds both gave mass spectra which revealed that acetyl groups were absent (no CH_3CO^+ peaks). The reactions and structures shown in the Scheme are consistent with all these observations: the assignment of structures (7) and (8) to the yellow and red compounds, respectively, follows from the fact that the carbonyl i.r. band of the red compound is at a higher frequency than that of the yellow one, and from the observation that the mass



(7) (8)

spectrum of the red compound shows abundant $(M - PhNH)^+$ and $PhNH^+$ ions which are absent from that of the yellow compound.

The ring formation shown in the Scheme as occurring first is an example of a well known process [8] for the conversion of β-hydroxy-ketones into 1-phenyl-Δ^2-pyrazolines under these conditions. In contrast, we have traced only one substantiated partial analogy for the ambiguous α-acetamido-phenylhydrazide cyclisation, in which the



oxazolone (9) gives the imidazolinone (11) *via* the phenylhydrazide (10) on heating with phenylhydrazine in acetic acid,[9] although there are several examples [10] of *as*-triazine formation from αβ-unsaturated α-acylamino simple hydrazides.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. and u.v. spectra were recorded with Perkin-Elmer 257 and Carey 14M spectrometers, respectively. N.m.r. spectra

[8] C. H. Jarboe, in 'The Chemistry of Heterocyclic Compounds,' vol. 22, part 2, Interscience, New York, 1967, p. 185.

[9] A. Mustafa, W. Asker, A. H. Harhash, M.-A. E. Khalifa, and E. M. Zayed, *Annalen*, 1968, **713**, 151.

[10] K. Napela and J. Slonka, *Monatsh.*, 1967, **98**, 412.

were recorded with a Perkin-Elmer R32 spectrometer operating at 90 MHz, with deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS9 instrument operating at 70 eV: only ions of $m/e > 90$ and relative intensity $> 10\%$ are listed. Analytical t.l.c. was performed with Kieselgel $HF_{254+366}$ plates, eluted with chloroform–methanol (9 : 1).

2-Amino-2-deoxy-D-gluconic Acid.—This was prepared by oxidation with mercury(II) oxide of D-glucosamine hydrochloride.[11] Some 2,5-bis-(D-*arabino*-tetrahydroxybutyl)pyrazine [fructosazine] is formed as a by-product. When the crude product (13.5 g) was used directly in the reaction with acetic anhydride described below, recrystallisation of the product gave analytically pure fructosazine octa-acetate (4.1 g), identical (m.p., specific rotation, and i.r. and n.m.r. spectra) with that described [12] previously.

Reaction of 2-Amino-2-deoxy-D-gluconic Acid with Hot Acetic Anhydride–Sodium Acetate.—Pure 2-amino-2-deoxy-D-gluconic acid (1—5 g) was treated with acetic anhydride–sodium acetate as described by Bergmann *et al.*,[2] and the mixture was worked up according to their procedure. Evaporation of the chloroform extract gave *crude product* as a yellow-brown semi-solid (*ca.* 0.6 g per g of starting material). N.m.r. examination of this material showed it to be a mixture of the isomers (1)—(3) in the proportions 4 : 9 : 7 respectively—the relative amounts of the isomers did not vary significantly between runs.

Recrystallisation of the crude product (0.6 g) from chloroform–ether, chloroform–light petroleum, and benzene gave (Z)-*2-acetamido-6-acetoxyhexa-2,4-dien-4-olide* (2) as a powder (55 mg), m.p. 151—152° (lit.,[2] m.p. 154° for the lactone V), τ 1.9br (1 H, s, NH), 2.51 (1 H, s, irradiation at τ 5.1 caused no increase in the integrated intensity, :CH·C:), 4.63 (1 H, t, *J* 7.2 Hz, :C*H*·CH_2·), 5.12 (2 H, d, *J* 7.2 Hz, :CH·C*H*$_2$·), and 7.79 and 7.94 (each 3 H, s, Ac) (Found: C, 53.7; H, 5.0; N, 6.15. $C_{10}H_{11}NO_5$ requires C, 53.4; H, 4.9; N, 6.22%).

Trituration of the crude product (0.6 g) with ether followed by recrystallisation from benzene gave a pale buff crystalline solid (0.5 g), m.p. 121—123°. Further recrystallisation from benzene raised the m.p. to 126—127° but did not cause a significant change in the n.m.r. spectrum, which consisted of the spectrum of the *Z*-isomer (2) described above together with the spectrum of the *E*-isomer (3) [τ 1.8br(1 H, s, NH), 2.20 (1 H, s, integrated intensity increased *ca.* 15% on irradiation at τ 5.2, :CH·C:), 4.24 (1 H, t, *J* 7.2 Hz, :C*H*·CH_2·), 5.21 (2 H, d, *J* 7.2 Hz, :CH·C*H*$_2$·), and 7.79 and 7.94 (each 3 H, s, Ac)] in relative intensities corresponding to *ca.* 3 : 2 proportions of (2) and (3), respectively.

P.l.c. (Kieselgel $HF_{254+366}$ plates eluted four times with ether) of the material (70 mg) obtained from the liquors remaining after the separation of (2) and (3) described above gave two fractions: the more mobile (30 mg) was more of the mixture of (2) and (3): recrystallisation of the less mobile from light petroleum (b.p. 60—80°) gave *2-acetamido-6-acetoxyhexa-2,4-dien-5-olide* (1) as a white powder (29 mg), m.p. 115—116° (lit.,[2] m.p. 115° for compound XX), τ 1.82 (1 H, d, *J* 4.45 Hz, :CH·), 2.0br (1 H, s, NH), 3.70 (1 H, d, *J* 4.45 Hz, :CH·), 5.16 (2 H, s, CH_2O), and 7.79 and 7.88 (each 3 H, s, Ac) (Found: C, 53.15; H, 5.2; N, 6.2%).

2-Acetamido-6-chlorohexa-2,4-dien-4-olide (4).—The *ZE*-mixture of (2) and (3) described above (m.p. 126—127°; 0.5 g) was treated with concentrated hydrochloric acid as described by Bergmann *et al.*[2] for their lactone V. The solid precipitated (0.4 g) was washed with water and recrystallised from benzene to give the *chloro-lactone* (4) as a pale yellow powder (80 mg) m.p. *ca.* 200° (decomp.) with softening from 170° (lit.,[2] m.p. 197° for compound XII), τ 2.3br (1 H, s, NH), 2.56 (1 H, s, :CH·C:), 4.61 (1 H, t, *J* 5.0 Hz, :C*H*·CH_2·), 5.64 (2 H, d, *J* 5.0 Hz, CH_2Cl), and 7.77 (3 H, s, Ac) (Found: C, 48.3; H, 4.2; N, 6.9. $C_8H_8ClNO_3$ requires C, 47.6, H, 4.0, N, 6.95%).

2-Acetamido-6-acetoxyhex-2-en-4-olide (5).—The *ZE*-mixture of (2) and (3) described above (m.p. 126—127°; 1 g) was hydrogenated as described by Bergmann *et al.*[2] Recrystallisation of the product from benzene gave the *lactone* (5) as a white crystalline solid (0.4 g), m.p. 111—112° (lit.,[2] m.p. 113° for compound IX), τ 1.95br (1 H, s, NH), 2.53 (1 H, d, *J* 2.0 Hz, :C*H*·CH<), 4.82 (1 H, dt, *J* 2.0 and 5.9 Hz, :CH·C*H*·CH_2·), 5.78 (2 H, m, CH_2O), and 8.0—7.7 (6 H, m, 2 Ac and C*H*$_2$·CH_2·O) (Found: C, 52.9; H, 5.8; N, 6.2. $C_{10}H_{13}NO_5$ requires C, 52.9; H, 5.8; N, 6.2%).

Reaction of the ZE-Mixture of Lactones with Phenylhydrazine.—The *ZE*-mixture of lactones described above (m.p. 126—127°; 5.0 g) was treated with phenylhydrazine in 50% acetic acid as described by Bergmann *et al.*,[2] and the material precipitated on dilution with water was taken up in the minimum volume of boiling ethanol. A yellow powder separated immediately on cooling to 0 °C: this was collected and recrystallised from ethanol to give *2,6-dihydro-3-methyl-2-phenyl-5-(1-phenyl-Δ²-pyrazolin-3-ylmethylene)-1,2,4-triazin-6*(1H)-one (7) as fine yellow needles (67 mg, 1%), m.p. 220—222° (lit.,[2] for compound XV obtained in this way in low yield as yellow needles, m.p. 219°), $\nu_{max.}$ (Nujol) 1 660, 1 625, and 1 595 cm^{-1}, $\lambda_{max.}$ (MeOH) 248.5, 308, and 424.5 nm (log ε 4.22, 3.99, and 4.38), τ — 0.8br (1 H, s, disappears on adding D_2O, NH), 2.30—3.20 (10 H, m, aromatic), 3.90 (1 H, s, integrated intensity increases *ca.* 15% on irradiation at τ 6.95, vinylic), 6.25 and 6.95 (each 2 H, t, *J* 9.0 Hz, CH_2·CH_2), and 7.75 (3 H, s, CH_3), *m/e* 346 (*M* + 1, 25%), 345 (*M*·⁺, 100), 344 (63), 184 (36), 158 (55), 157 (17), 107 (11), 104 (18), 92 (25), and 91 (68) (Found: C, 69.3; H, 5.5; N, 20.4%; *M*⁺, 345.157. $C_{20}H_{19}N_5O$ requires C, 69.55; H, 5.55; N, 20.3%; *M*, 345.159).

The liquors remaining after removal of (7) slowly (1 week) deposited dark red chunky crystals, which were separated and recrystallised from benzene to give *3-anilino-2-methyl-5-(1-phenyl-Δ²-pyrazolin-3-ylmethylene)-Δ¹-imidazoline-4-one* (8) as a scarlet powder (70 mg, 1%), m.p. 240—245° (decomp.), $\nu_{max.}$ (Nujol) 1 700, 1 625, and 1 595 cm^{-1}, $\lambda_{max.}$ (MeOH) 230, 269, and 473 nm (log ε 4.23, 3.91, and 4.61), τ 2.50—3.40 [11 H (10 H after addition of D_2O), m, aromatic and NH], 3.60 (1 H, s, vinylic), 5.8—6.7 (4 H, m, CH_2·CH_2), and 7.7 (3 H, s, CH_3), *m/e* 346 (*M* + 1, 24%), 345 (*M*·⁺, 100), 344 (76), 253 (*M*·⁺ — PhNH·, corroborated by the spectrum after exchange with D_2O, 27), 185 (14), 184 (92), 183 (13), 104 (16), 93 (19), 92 (PhNH⁺, corroborated by the spectrum after D_2O exchange, 56), and 91 (18) (Found: C, 69.7; H, 5.6; N, 20.3%).

T.l.c. of the liquors remaining after the crystallisation of (7) and (8) showed that only traces of these compounds remained. There were no other strongly coloured components in the mixture, which contained at least thirteen other compounds.

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[11] M. L. Wolfrom and M. J. Cron, *J. Amer. Chem. Soc.*, 1952, **74**, 1715.

[12] S. Fujü, R. Kikuchi, and H. Kishida, *J. Org. Chem.*, 1966, **31**, 2239.