511. *Heterocyclic Derivatives of Guanidine. Part V.*[1] *Reaction of Some Glycidic Esters with Guanidines.*

By J. E. Banfield and D. S. McGuinness.

Reaction of guanidine with ethyl phenylglycidate afforded α-guanidinocinnamic acid (V) which cyclised in acetic anhydride to 2-acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole (IX). Some alkylguanidines reacted with ethyl phenylglycidate to give, by hydrolysis, the guanidinium phenylglycidates. Reaction of some aliphatic glycidic esters with guanidines afforded salts; others gave β-hydroxy-α-guanidino-acids.

The utility of guanidines in place of thiourea in the synthesis of heterocyclic systems [2,3] has been shown [4] to be affected by the strong basicity of the guanidines. We now report reactions of some guanidines with some glycidic esters which, although lacking the synthetic versatility of similar reactions of thiourea,[2] nevertheless afford some parallel.

Guanidine and ethyl phenylglycidate (I) in ethanol at 0° afforded α-guanidinocinnamic acid (V), possibly by dehydration and hydrolysis of the presumed intermediate (II). Compound (V) was converted by hot alkali into the known [5] 2-amino-5-benzylidene-2-imidazolin-4-one (VII) and by acetic anhydride into the diacetyl derivative (IX). Compound (IX) was hydrolysed by hot acetic acid or by cold methanolic sodium hydroxide to the acetamido-derivative (VIII) and by aqueous alkali to the amino-compound (VII). Our monoacetyl compound (VII) had m. p. 252—255° close to that of 2-acetamido-6-phenylpyrimid-4-one (248°) [6] expected from cyclisation of the isomeric β-guanidinocinnamic acid, whereas 2-amino-3,4-dihydro-4-oxo-6-phenylpyrimidine has been reported

[1] Part IV, Banfield, *J.*, 1961, 4672.
[2] Culvenor, Davies, Maclaren, Nelson, and Savage, *J.*, 1949, 2573.
[3] Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491.
[4] Banfield, Part I, *J.*, 1960, 2108; see also *J.*, 1960, 456.
[5] (*a*) Johnson and Nicolet, *J. Amer. Chem. Soc.*, 1915, **37**, 2416; (*b*) Ruhemann and Stapleton, *J.*, 1900, **77**, 239.
[6] Johnson and Hill, *J. Amer. Chem. Soc.*, 1914, **36**, 1201.

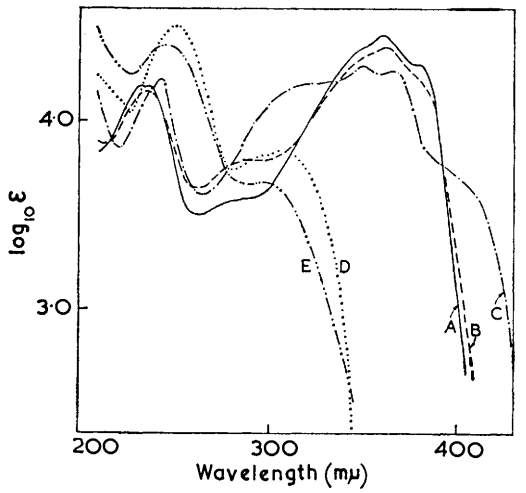


FIG. 1.

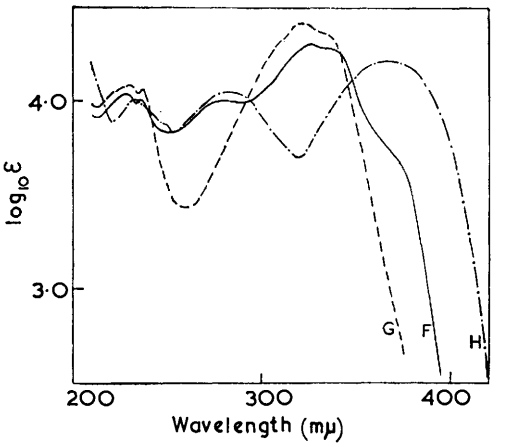


FIG. 2.

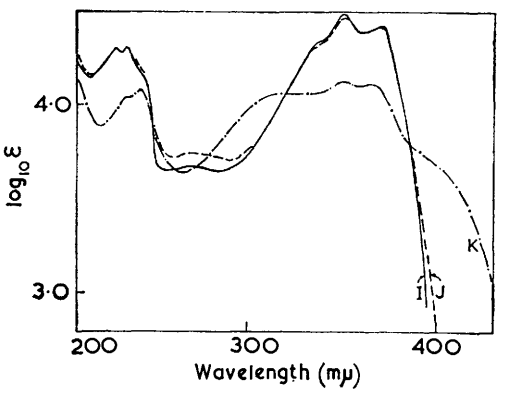


FIG. 3.

FIGS. 1—3. Ultraviolet absorption spectra.

2-Acetamido-5-benzylidene-2-imidazolin-4-one (VIII), (A) in EtOH [max.: 233, 237, 362 mμ (log ε 4·19, 4·19, 4·46)], (B) in acid [max.: 237, 362 mμ (log ε 4·16, 4·39)], (C) in alkali [max.: 243, 349, 366 mμ (log ε 4·23, 4·29, 4·26)]. 2-Acetamido-3,4-dihydro-6-phenylpyrimidin-4-one, (D) in EtOH [max.: 251, 307 mμ (log ε 4·51, 3·84), (E) in alkali [max.: 246, 298 mμ (log ε 4·40, 3·67)].

2-Amino-5-benzylidene-2-imidazolin-4-one (VII), (F) in EtOH [max.: 229, 236, 280, 326 mμ (log ε 4·04, 4·01, 4·00, 4·31)], (G) in acid [max.: 230, 236, 321 mμ (log ε 4·08, 4·05, 4·42)], (H) in alkali [max.: 232, 283, 367 mμ (log ε 4·00, 4·05, 4·22)].

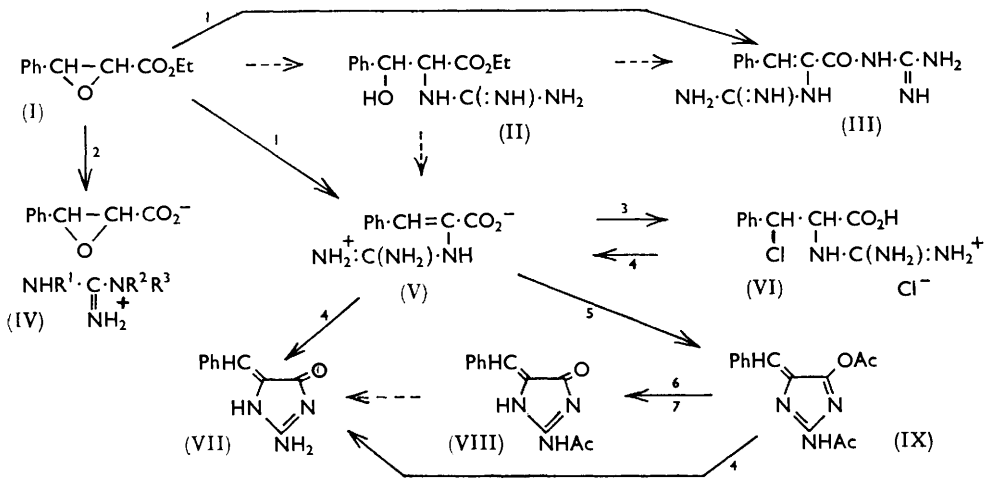
2-Acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole (IX), (I) in EtOH [max.: 236, 273, 350, 369 mμ (log ε 4·31, 3·68, 4·49, 4·43)], (J) in acid [max.: 236, 273, 350, 369 mμ (log ε 4·31, 3·74, 4·48, 4·42)], and (K) in alkali [max.: 243, 350, 364 mμ (log ε 4·08, 4·13, 4·12)].

in several forms * whose melting points (272°, 295°;[7] 280°, 303°[6]) bracket that of our compound (VII); and the proton magnetic resonance spectrum of our diacetyl compound was consistent with either a pyrimidine or an imidazole structure; the spectra of acetyl compounds of the two series are shown below to be qualitatively similar (Fig. 4). However, the synthetic 2-acetamidopyrimidone differed from our monoacetyl compound.

* This will be discussed in a later Part of this series.

[7] Warmington, *J. prakt. Chem.*, 1893, **47**, 201.

Moreover, compound (VIII) was prepared from reaction of glycocyamidine with benzaldehyde in acetic acid containing sodium acetate, conditions previously reported [5a] to give compound (VII). A convenient and direct synthesis of compound (IX) from



Reagents: 1, $NH_2 \cdot C(:NH) \cdot NH_2$. 2, $R^1 \cdot NH \cdot C(:NH) \cdot NR^2R^3$. 3, HCl. 4, NaOH. 5, Ac_2O. 6, NaOH–MeOH. 7, AcOH.

α-guanidinoacetic acid is described in the Experimental section and provides a ready route to this series.

The *ON*-diacetyl structure for compound (IX) is preferred to an *NN*- or an *NN'*-type on several grounds. The band at 1748 cm.$^{-1}$ is within the usual range for enol acetates

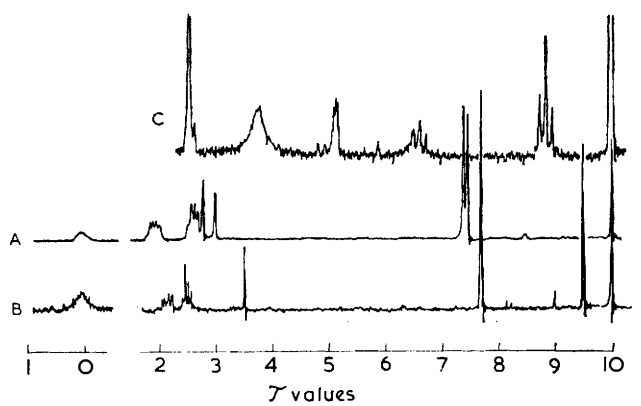
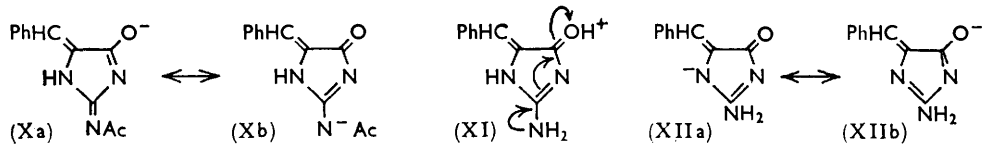


FIG. 4. Proton magnetic resonance spectra, at 60 mc.

(A) 2-Acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole (IX) in CCl_3D; (B) 2-acetamido-3,4-dihydro-6-phenylpyrimidin-4-one in SO_2; (C) 5-α-ethoxybenzylhydantoin (XIV) in SO_2.

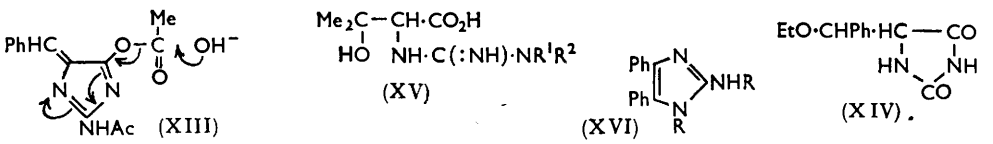
and just outside that for *NN*-diacetyl derivatives. The *ON*-structure is also indicated by comparison of the ultraviolet absorption spectra of the acetyl derivatives and of the base (VII) in acidic, neutral, and alkaline solution (Figs. 1—3), and by the proton magnetic resonance spectrum. The spectra of the protonated amine (Fig. 2G), the amine (VII) (Fig. 2F), and the anion (XII) (Fig. 2H) were each of a distinct type. That of the monoacetyl derivative (VIII), in neutral solution (Fig. 1A) was comparable, notwithstanding a shift of *ca.* 40 mμ of the long-wavelength bands, with that (Fig. 2G) of the protonated

form of compound (VII), presumably the cation (XI). The spectrum (Fig. 1A—B) was but slightly changed in acid, whilst in alkali (Fig. 1C) a profound change indicated that the enolate (Xa, b) was formed; this spectrum (Fig. 1C) is of a different type from that (Fig. 2H) of the enolate (XIIa, b) in accord with the proposed structures. The anion (Xa, b) was formed by hydrolysis of compound (IX) in ethanol within a few seconds of the addition of alkali; the ready hydrolysis can be rationalised in terms of charge delocalisation and the stability of the leaving anion, a tautomer of (Xa, b), as indicated in (XIII). Structure (IX) was also supported by the infrared spectrum (p. 2752).



A by-product of the reaction of guanidine with ethyl phenylglycidate was α-guanidinocinnamoylguanidine (III). Like compound (V), the sulphate of this substance had a strong peak at *ca.* 240 mμ, unexpected for derivatives of cinnamic acid (272 mμ). No such absorption was observed for β-chloro-α-guanidino-β-phenylpropionic acid hydrochloride (VI), readily formed from compound (V). However, strong absorption in the 240 mμ region appeared when compound (VI) was basified, indicating the regeneration of an olefinic bond. Conductivity data support these structures.

Reaction of α-guanidinocinnamic acid with ethanolic sulphuric acid afforded a compound which might be, *inter alia*, ethyl α-ureidocinnamate or its tautomer ethyl α-carbamoylimino-β-phenylpropionate. The compound was not very soluble in chloroform and the proton magnetic resonance spectrum for its sulphur dioxide solution had a poor signal-to-noise ratio (Fig. 4C). Nonetheless, the aromatic peak at τ 2·58 (5 protons) is sharp, contraindicating a styrene-type structure. The methyl triplet of the ethoxy-group is at τ 8·75, 8·87, and 9·00 (3 protons), but the methylene quartet is obscured by noise and is seen as a (distorted) group of three peaks at τ 6·48, 6·60, and 6·72 (2 protons). A broad peak at τ 3·80 is attributed to the exchanging hydrogen atoms of an ureido-group, augmented by traces of water. The peak at τ 5·13 (2 protons) appears as a closely spaced triplet—this apparent structure might be merely the result of the high noise level. The shielding is rather too high for a vinyl-hydrogen atom, particularly as that of the vinyl-hydrogen of compound (IX) is at τ 2·98. The above-mentioned intensity (by electronic integration) is of importance in eliminating the ethyl α-ureidocinnamate structure. For ethyl α-carbamoylimino-β-phenylcinnamate with two equivalent (or nearly equivalent) protons the τ value is considered reasonable (cf. diphenylmethane, τ 6·09,[8] in the absence



of a close analogy). However, compound (XIV) was soluble in cold sodium hydroxide solution from which it was recovered by addition of ammonium chloride. This seems to exclude ester and acid structures and ethanol solvates, and supports a 5-α-ethoxybenzylhydantoin structure (XIV) for which near-degeneracy of hydrogen atoms at τ 5·13 must then be assumed.

Reaction of ethyl phenylglycidate with some alkylguanidines afforded salts of type (IV). Their infrared absorption in the 4000—1550 cm.$^{-1}$ region was similar to that

[8] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959, p. 60.

expected for zwitterionic homologues of type (V), although differences in the 1500—1550 cm.$^{-1}$ region were of some diagnostic value. However, conductivity measurements clearly proved the salt structures. Probably compounds of type (V) are also formed to some extent in these reactions; difficulties in isolation and crystallisation may account for our failure as yet to isolate them.

Aliphatic glycidic esters afforded salts of the guanidine, sodium salts of the β-hydroxy-α-guanidine-acids (XV), and an unsaturated α-guanidino-acid, severally.

An attempt to extend the Strecker α-amino-acid synthesis to α-guanidino-nitriles or their heterocyclic derivatives was unsuccessful. A compound, possibly the imidazole (XVI; R = H), was obtained; however the proton magnetic resonance spectrum of its acetyl derivative appears inconsistent with structure (XVI; R = Ac).

Experimental

Ultraviolet absorption spectra were determined for 95% EtOH solutions on a Carey Model 14M-50 recording spectrophotometer by Miss S. Gill, whom we thank, and on an Unicam S.P. 500 spectrometer. Microanalyses were carried out by Dr. K. W. Zimmermann and his staff. Proton magnetic resonance spectra were run at 60 Mc. by Varian Associates Applications Laboratory. Ethanolic solutions of the guanidines were prepared from the salts.[4]

Reaction of Guanidine with Ethyl Phenylglycidate.—(*a*) Guanidine (2·0 g.) in benzene (1 ml.) reacted violently with ethyl phenylglycidate (4 ml.), giving a red oil which with acetic anhydride gave *2-acetamido-5-acetoxy-4-benzylidene-4H-imidazole* (IX) (0·1 g.), m. p. 205—207° (from acetone) (Found: C, 62·2, 62·25; H, 4·9, 5·0; N, 15·0; OEt, 0. $C_{14}H_{13}N_3O_3$ requires C, 62·0; H, 4·8; N, 15·5%) (cf. below). On a larger scale this method gave poor yields.

(*b*) *α-Guanidinocinnamic acid* (V). Ethyl phenylglycidate (9·8 g.), and guanidine (10 g.) in ethanol (50 ml.), when kept at 0° for 2 days, gave an *acid* (5·1 g.); more acid was obtained on evaporation of the mother-liquors. From ethanol it formed plates, m. p. 156—158° (decomp.) (Found: C, 58·7; H, 5·3; N, 20·5. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%), $\lambda_{max.}$ 238 mμ (log ε 4·0), $\varepsilon_{max.}$ 3434ms, 3348sh, 3309ms,br (νNH$_2$), 3060ms,br, 1674s (C=C, δNH$_2$), 1608vs,br (CO_2^-), 1597vs,sh, 1529s,br, 1429sh,s, 1312, 1299, 1284, 1272, 946w, 885s, 812br, 789br, 743ms, 722br, 969sh, 691 cm.$^{-1}$.

It was slightly soluble in water. It was recovered (m. p. and mixed m. p.) after being refluxed with methyl iodide and (80%) after its solution in 5N-hydrochloric acid had been treated at 0° with sodium nitrite solution. It failed to give a precipitate with Brady's reagent.

It was warmed with phenyl isocyanate for a few minutes; light petroleum precipitated a (presumed) *phenylurea*, plates (from aqueous dimethylformamide) m. p. 193—195° (decomp.) (Found: C, 63·1; H, 5·05; N, 17·5. $C_{17}H_{16}N_4O_3$ requires C, 63·0; H, 5·0; N, 17·3%). The acid (0·5 g.) gave a *picrate* (283 mg.) in orange needles (from ethanol), m. p. 174° (decomp.) (Found: C, 44·0; H, 3·3; N, 19·3. $C_{16}H_{14}N_6O_9$ requires C, 44·2; H, 3·25; N, 19·35%).

(*c*) Crude α-guanidinocinnamic acid (0·5 g.), prepared as above, in ethanol was treated with ethanolic sulphuric acid (0·1 g.). A resulting precipitate afforded *α-guanidinocinnamoylguanidine sulphate hydrate* (cf. III) (122 mg., from aqueous ethanol), m. p. 228° (decomp.) after becoming red at 205° and sintering at 195° (Found: C, 36·7; H, 5·1; N, 22·6; S, 8·8. $C_{11}H_{18}N_6O_6S$ requires C, 36·5; H, 5·0; N, 23·2; S, 8·8%); $\lambda_{max.}$ (in 50% EtOH) 237 and 270 infl. (4·22, 2·81), changed by alkali to 238 and 270infl. (4·35, 2·91) ($\log_{10}$ ε in parentheses), $\nu_{max.}$ 3390s.sh, 3333s (νNH$_2$), 3142vs,br (νNH$_2^+$), 1735s, 1710vs (C:O, amide), 1667vs,br (δNH$_2$), 1615s,br (guanidine, ν), 1520w, 1467w, 1430sh, 1362, 1256, 1211s, 1177w, 1111, 1086, and 1064 triplet,vs (SO_4^{2-}), 1008w, 977w, 965, 884, 813br, 785w, 749ms (arom.), 735, 720br, 708br, 675ms,br cm.$^{-1}$.

(*d*) Guanidine carbonate and ethyl phenylglycidate did not react in boiling ethanol during 8 hr.

5-α-Ethoxybenzylhydantoin (XIV).—A solution of α-guanidinocinnamic acid (1·0 g.) in hot ethanol (70 ml.) was treated with concentrated sulphuric acid (0·5 ml.), set aside overnight, and then diluted with ammonia or sodium carbonate solution, giving the *hydantoin*, m. p. 232—235° (decomp.) (from 95% ethanol), as rods (Found: C, 61·4; H, 5·95; N, 12·0; O, 20·3; OEt, 18·1. $C_{12}H_{14}N_2O_3$ requires C, 61·5; H, 6·0; N, 12·0; O, 20·5; OEt, 19·2%); $\lambda_{max.}$ (in EtOH) 215 and 240infl. (4·41, 3·24), changed by acid to 215 (4·37) and 240 infl. mμ (3·17) and by alkali to log

ε_{210} 4·44, log ε_{250} 3·15) (no max. or infl.) (log ε in parentheses) $\nu_{max.}$ 3247s, 3167br (NH); 1736ms, 1665s,br (imide bands), 1600—1504broad, 1492w, 1402w, 1350, 1318, 1299, 1290, 1262s. 1227s, 1194ms, 1142s, 1120s; 1077 and 1075 doublet, 1033 and 1030 doublet, 1006 and 1000 doublet, antisym, 980w, 967ms, 963infl., 929, 881ms, 846w, 838w, 815, 793, 759ms, 724br,s, 698, 690sh, 672 cm.$^{-1}$.

β-*Chloro*-α-*guanidino*-β-*phenylpropionic Acid Hydrochloride* (VI).—α-Guanidinocinnamic acid (1·0 g.) was treated with cold 5N-hydrochloric acid; an oil separated; next morning filtration afforded the *hydrochloride* (VI) in plates or, on occasion, needles (from ethanol–light petroleum), m. p. 187—189° (decomp.) (Found: C, 43·3; H, 4·8; N, 14·7; Cl, 25·2. $C_{10}H_{13}Cl_2N_3O_2$ requires C, 43·2; H, 4·7; N, 15·1; Cl, 25·5%), $\lambda_{max.}$ (in EtOH) 260infl. (2·88), log ε_{210} 4·25, changed by alkali to 238 and 271infl. mμ (4·30, 2·62) (log ε in parentheses), $\nu_{max.}$ 3335vs, 3203vs,br (νNH$_2$ asym., and sym.), 3133vs, 1733vs, 1695vs, asym (CO_2H), 1634s,asym (δNH$_2$), 1564br, 1524br, 1493, 1347, 1318w, 1304w, 1246w, 1189s, 1116asym, 1081sh,br, 1045, 1031w, 1025w, 933w, 853w, 789, 772, 742w, 721, 700s, 694sh, 673s, 668infl., and (KBr Infracord) 616s,br, 585sh, 530s, 509 cm.$^{-1}$. An aqueous solution of the hydrochloride was neutral to litmus.

2-*Acetamido*-5-*acetoxy*-4-*benzylidene*-4H-*imidazole* (IX).—(*a*) α-Guanidinocinnamic acid (5 g.) was heated in acetic anhydride (30 ml.) containing sodium acetate (2 g.) (*ca.* 2 min.) on the steam-bath for 0·5 hr., giving the diacetyl compound (3·1 g.) (from acetone or ethanol), m. p. 208—210° (decomp.) (cf. above) (Found: C, 62·1, 62·1; H, 4·8, 4·9; Ac, 29·1. Calc. for $C_{14}H_{13}N_3O_3$: C, 62·0; H, 4·8; 2Ac, 31·7%). In support of structure (IX), infrared absorption can probably be assigned as follows: 3250 (νNH, amide), 1748 (enolic acetate), 1704—1687 (NHAc), 1660 (C=C), 1600—1586 (C=N), and 1520 (amide II) cm.$^{-1}$. For comparison the monoacetyl derivative absorbed at 3344 (NH), 1716 (CO·NH), 1658 (C=C), 1617—1575 (C:N), 1531 (amide II), and the aminoimidazolone (VII) at 3333—3279 (νNH), 1711 (CO); 1680, 1656, 1650 (δNH$_2$, C=C) cm.$^{-1}$; absorption in the region 1500—1600 cm.$^{-1}$ was not strong in the absence of an amide II band.

(*b*) α-Guanidinoacetic acid (6 g.), fused sodium acetate (3 g.), benzaldehyde (20 ml.), and acetic anhydride (50 ml.) were refluxed for 4 hr. and set aside, then acetone was added giving the diacetyl compound (7·5 g.), m. p. 208—210° (decomp.) (Found: C, 62·25; H, 4·9; N, 15·2; O, 17·5%). Its infrared spectrum and mixed m. p. showed identity with the sample described in (*a*).

The proton magnetic resonance spectrum (see Fig. 4) might be assigned as follows (τ values are given and relative intensities were estimated fron an integrated curve): −0·57 (1 proton), to the acetamido-proton; 1·92, 1·97, 2·02, 2·05 quartet (total, 2 protons) to the *ortho*-aromatic protons of the phenyl group; 2·55, 2·60, 2·65 triplet (total, 3 protons) to the *meta*- and *para*-aromatic protons; 2·75 ($CHCl_3$); 2·98 sharp (1 proton) to the benzylidene proton (cf. 3·01 and 3·51 for *trans*- and *cis*-stilbene [9]); 7·33, 7·38 of equal intensity (6 protons) to the *N*- and *O*-acetyl protons.

(*c*) *Alkaline hydrolysis.* The ultraviolet spectrum of the acetyl derivative in alkali (after 5 min.) was virtually identical (slight differences in intensities being attributed to lack of control of the sodium hydroxide concentration) with that of the monoacetyl compound (below) in alkali. The alkaline solution absorbed appreciably at 420 mμ, where the optical density of the neutral solution was negligible in comparison. A plot of optical density with time (Carey spectrophotometer) at 420 mμ showed that the ethanolic solution had attained the final optical density within 25 sec. (time of insertion of cell) after the addition of alkali and was invariant thereafter; thus the hydrolysis is estimated to have a half-life of less than 6 sec. at room temperature.

2-*Acetamido*-5-*benzylidene*-2-*imidazolin*-4-*one* (VIII).—(*a*) 2-Acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole was refluxed in acetic acid for 0·5 hr., and water was added, giving the *amide* (from aqueous acetic acid), m. p. 252—255° (decomp.) Found: C, 63·3; H, 5·05; N, 18·4. $C_{12}H_{11}N_3O_2$ requires C, 62·9; H, 4·8; N, 18·3%).

(*b*) The diacetyl compound was set aside in cold methanolic potassium hydroxide for 2 days, then acidified, giving the amide, m. p. 254° (decomp.) (Found: C, 62·3; H, 4·9; N, 18·7%), with an infrared absorption almost identical to that of samples described in (*a*).

(*c*) Glycocyamidine,[10] acetic acid (5 ml.), sodium acetate (1 g.; fused), and benzaldehyde (1·5 ml.) were refluxed for 1 hr. The cold mixture was diluted with water, ground under

[9] Ref. 8, p. 126.
[10] Schmidt, *Arch. Pharm.*, 1913, **251**, 557.

ethanol, and washed with water, giving the amide (from ethanol), m. p. 250—251° (decomp.) (Found: C, 62·7; H, 4·9; N, 18·0%), identified by its infrared absorption.

2-Acetamido-3,4-dihydro-4-oxo-6-phenylpyrimidine.—This compound, prepared from the 2-amino-compound in boiling acetic anhydride–sodium acetate (2·5 hr.), had m. p. 254—255° (lit.,[6] 248°) (Found: C, 62·35, 62·8; H, 4·9, 5·0; N, 18·3; O, 14·6; Ac, 17·9. Calc. for $C_{12}H_{11}N_3O_2$: C, 62·9; H, 4·8; N, 18·3; O, 14·0; Ac, 18·8%). It was insufficiently soluble in deuterochloroform for a useful proton magnetic resonance spectrum to be obtained. In sulphur dioxide solution it showed broad absorption at τ −0·04 (NHAc) (1 proton intensity); 2·08, 2·13, 2·19, and 2·27 (fine structure; 2 protons; *o*-aromatic, 2·39, 2·47, 2·52, and 2·61 (total intensity = 3 protons; *m*- and *p*-aromatic); 3·47 (1 proton) (the pyrimidone 5-*H*), 7·73 (intensity 3 protons; *N*-acetyl, and 9·01, 9·51 (spinning side bands). Absorption due to the heterocyclic NH was not observed, as expected (cf. pyrrole).

2-Amino-5-benzylidene-2-imidazolin-4-one (VII).—(*a*) 2-Acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole (0·5 g.) was treated with 10% sodium hydroxide solution (30 ml.) and was set aside for 3 hr., then acidified with acetic acid, giving (from ethanol containing a little water) the amine, m. p. 290—291° (decomp.) (red at *ca.* 287°) (lit.,[5] 297°, 295°) (Found: C, 64·3; H, 4·9; N, 22·4; O, 8·6. Calc. for $C_{10}H_9N_3O$: C, 64·2; H, 4·85; N, 22·45; O, 8·55%). When recrystallised from aqueous acetic acid it afforded the *hemiacetic acid solvate* in yellow spears which became cloudy on drying (Found: C, 60·1; H, 5·1; N, 19·2. $C_{10}H_9N_3O,0·5C_2H_4O_2$ requires C, 60·8; H, 5·1; N, 19·35%).

(*b*) α-Guanidinocinnamic acid (0·5 g.) was heated with 5% sodium hydroxide solution (20 ml.) on the steam-bath for 45 min. during which it afforded a yellow solution. This was acidified, giving a white solid, m. p. 294—296° (decomp.), which afforded (from acetic acid) the above hemiacetate solvate (infrared identification).

5-Benzylidenehydantoin.—2-Acetamido-5-acetoxy-4-benzylidene-4*H*-imidazole (1 g.) was refluxed in acetic acid for 0·5 hr., then diluted with water; the solid, on successive recrystallisations from acetic acid, gave the benzylidenehydantoin of melting points, 202°, 205—224°, 224—226°, 224—225° (209 mg.) (lit.,[11] *cis*-, 220°; *trans*-, 246°), the last product being a hydrate (Found: C, 58·4; H, 5·0; N, 13·7; O, 22·9; Ac, <0·2. Calc. for $C_{10}H_{10}N_2O_3$: C, 58·3; H, 4·9; N, 13·6; O, 23·3%). The compound differed in its infrared absorption from the related compounds above; in Nujol mull it had $\nu_{max.}$ at 3268sh,s, 3205br,s (νNH), 3032sh,s,br, 1795infl., 1772infl.; 1770vs (C:O; imide), 1763infl.,vs, 1716vs,br (C:O; imide), 1684infl., 1667sh, 1647vs,asym (C=C); 1600w, 1515, 1362sh,s, 1312, 1292w, 1256ms,asym, 1197, 1185, 1158, 1099s,asym, 1030, 1008s, 1000, 931, 881, 877infl., 839, 833w, 770vs, 758infl., 737ms, 708s, 694s cm.$^{-1}$.

However, the outcome of the above reaction was variable; in one instance a substance of m. p. 205° (Found: C, 60·7; H, 4·7; N, 14·8; O, 20·1; Ac, 5·5%) was obtained of composition and infrared absorption appropriate to a mixture of the hydantoin and the monoacetyl derivative (VIII).

1-Amidinopiperidine Phenylglycidate.—1-Amidinopiperidine (6 g.) and ethyl phenylglycidate (3 g.) in ethanol (50 ml.) were kept at 40—50° for 6—8 hr. and then at 5° for several days, giving the *salt* (1·4 g.), m. p. 207—209° (from ethanol) (Found: C, 61·4; H, 7·4; N, 14·45. $C_{15}H_{21}N_3O_3$ requires C, 61·8; H, 7·3; N, 14·4%), $\lambda_{max.}$ 261, 256 mμ (log ε 2·52, 2·46), $\nu_{max.}$ 3320ms,br, 3215ms,br (νNH$_2$), 1701sh,infl., 1671s, (δNH$_2$), 1621sh; 1600vs, br (CO_2^-), 1429, 1318, 1305, 1282, 1264w, 1230w, 1200, 1144w, 1124sh, 1104br, 1068w, 1027w, 979, 897s, 865w, 853w, 824w, 763, 741br, 712br, 695 cm.$^{-1}$. Lower yields were obtained by reaction at 0—5°. The salt gave an oil with hydrochloric acid, and the aqueous layer afforded 1-amidinopiperidine picrate, m. p. 258—260° (infrared identification). The salt gave a precipitate with Brady's reagent.

A mixture of potassium phenylglycidate and 1-amidinopiperidine sulphate in approximately equimolar proportion had an infrared spectrum (Nujol mull) similar to that of the salt, but with differences attributable to such a mixture.

NN-*Dimethylguanidinium Phenylglycidate.*—*NN*-Dimethylguanidine (3 g.) in ethanol (30 ml.), when treated with ethyl phenylglycidate (6 g.) at room temperature, afforded the *salt* (7 g.), m. p. 206—208° (from ethanol) (Found: C, 57·4; H, 6·9; N, 16·2. $C_{12}H_{17}N_3O_3$ requires C, 57·35; H, 6·8; N, 16·7%), $\nu_{max.}$ 3333infl., 3226vs,br, 3060vs,br, 1688s, 1623vs,sh, 1607vs,br, 1425, 1315, 1302, 1277, 1118br, 1086w, 1067, 1020, 961w, 918w, 894, 863, 825, 780infl.,

[11] Johnson and Bates, *J. Amer. Chem. Soc.*, 1915, **37**, 385.

759ms,br, 718ms, 695ms cm.$^{-1}$. This gave a crystalline precipitate with Brady's reagent; it afforded *NN*-dimethylguanidinium picrate, m. p. and mixed m. p. 229—230° (Found: C, 34·2; H, 4·1. Calc. for $C_9H_{12}N_6O_7$: C, 34·2; H, 3·8%). The phenylglycidate was treated with 5N-hydrochloric acid and extracted with benzene, giving a product (from light petroleum), m. p. 119—127°, as plates (Found: C, 53·9; H, 4·8; O, 23·3; N, 0. Calc. for $C_9H_9ClO_3$: C, 53·8; H, 4·5; O, 23·8%). This is probably a mixture of isomers of β-chloro-α-hydroxy-β-phenylpropionic acid (lit.,[12] 141—142°).

NN-Dimethylguanidinium sulphate and potassium phenylglycidate had $\nu_{max.}$ 3577, 3286s,br, 3112s,br, 1686infl., 1621vs,br, 1610vs, 1550, 1429sh, 1397w, 1317w, 1301w, 1275, 1237w, 1183w, 1167w, 1090, and 1069vs (SO_4^{2-}), 881br, 854, 845w, 816, 750vs, 724w, 710, 695ms cm.$^{-1}$.

Cyclohexylguanidinium Phenylglycidate.—This *salt*, m. p. 199—200° (decomp.) (from propan-1-ol) (Found: C, 62·2; H, 7·45; N, 14·4. $C_{16}H_{23}N_3O_3$ requires C, 62·9; H, 7·6; N, 13·8%), was obtained from ethanolic cyclohexylguanidine and ethyl phenylglycidate.

2-Amino-2-imidazoline Phenylglycidate.—This *salt*, prepared from ethanolic 2-amino-2-imidazoline and ethyl phenylglycidate, had m. p. 173—174° (Found: C, 57·7; H, 6·0; N, 17·0. $C_{12}H_{15}N_3O_3$ requires C, 57·8; H, 6·1; N, 16·9%).

NN-*Dimethylguanidinium 2,1′-Epoxy-2-cyclohexylacetate.*—This *salt*, m. p. 236—238° (from ethanol) (Found: C, 54·1; H, 8·6; N, 17·2. $C_{11}H_{21}N_3O_3$ requires C, 54·3; H, 8·7; N, 17·3%), was obtained from *NN*-dimethylguanidine and ethyl 2,1′-epoxy-2-cyclohexylacetate.

Reaction of Ethyl 2,1′-Epoxy-2-cyclohexylacetate with Guanidine.—These components in ethanol afforded a compound, possibly α-guanidinocyclohexylideneacetic acid, m. p. 170° with bubbling (Found: C, 54·2; H, 7·85; N, 20·4. Calc. for $C_9H_{15}N_3O_2$: C, 54·8; H, 7·7; N, 21·3%), $\nu_{max.}$ 3405 doublet, s 3313s (νNH_2), 3115s,br; 1679s (δNH_2), 1615vs (C=C), 1600sh,vs (CO_2^-), 1542s,br, 1343, 1325, 1289s, 1274, 1243w, 1205w, 1133w, 1115w,br, 1083w, 1053w, 1017w, 981, 953, 918, 904sh,w, 833, 811ms, 794, 765, 737w, 721w cm.$^{-1}$, and with rising absorption from 702 to 667 cm.$^{-1}$. This spectrum in the 2·5—6 μ region is similar to that of α-guanidinocinnamic acid and, in the 1500—1550 cm.$^{-1}$ region, different from those of the salts.

Sodium α-NN-*Dimethylguanidino-*β-*hydroxy-*β-*methylbutyrate* (cf. XV; $R^1 = R^2 = Me$).—Reaction of ethyl dimethylglycidate with ethanolic *NN*-dimethylguanidine containing an excess of sodium ethoxide afforded the named *salt*, m. p. 177—178° (from ethanol) (Found: C, 42·6; H, 7·8; N, 19·4. $C_8H_{16}N_3O_3Na$ requires C, 42·7; H, 7·2; N, 18·7%), $\nu_{max.}$ 3333infl., 3270s, 3093s,br, 1703infl., 1685, 1626, 1608, 1443infl., 1408, 1289s, 1245vs, 1122vs,br, 1070ms, 1041, 1027, 974w, 936, 914s, 832sh, 788infl, 772s,br, 722ms,br, 671v.br cm.$^{-1}$. A similar salt, possibly (XV; $R^1R^2 = [CH_2]_5$), was obtained by reaction of ethyl dimethylglycidate with 1-amidinopiperidine; it had m. p. 178—180° (depressed on admixture with the previous salt) (Found: N, 15·6; O, 18·8. $C_{11}H_{20}N_3NaO_3$ requires N, 15·8; O, 18·1%; poor carbon analyses were obtained).

Conductivities.—Resistivities were determined at room temperature on a Phillips bridge GM4249 at 1000 c./sec. with a cell as supplied (this was marked 1·37, the reciprocal of the cell constant as usually defined). The specific conductivity of a solution of 1-amidinopiperidine sulphate containing 0·00700 equivalent per l. in water at 25·1° was determined by Professor R. H. Stokes; it had equivalent conductance of 98·4 cm.^{2} ohm^{-1} equiv.$^{-1}$. This solution was used shortly thereafter to check (at 25°) the cell constant, giving 0·765; in spite of this calibration the measured conductivities given in the Table are probably not better than ±2%; concentrations were in the range 0·001—0·005M.

Compound	Equiv. conductivity cm.^{2} ohm^{-1} equiv.$^{-1}$	Temp.
1-Amidinopiperidine sulphate	96·2	20°
Potassium phenylglycidate	91·6	20
α-Guanidinocinnamic acid	8·0	19
Cyclohexylguanidinium phenylglycidate	45·5	19
2-Amidino-2-imidazoline phenylglycidate	56·3	19
1-Amidinopiperidinium phenylglycidate	46·2	19
Sodium α-*NN*-dimethylguanidino-β-hydroxy-β-methylbutyrate	67·0	19
NN-Dimethylguanidinium phenylglycidate	55·5	19
Potassium sulphate	140	22
α-Guanidinocinnamoylguanidine sulphate hydrate (III)	106	22
β-Chloro-α-guanidino-β-phenylpropionic acid hydrochloride (VI)	101	22

[12] Erlenmeyer, *Annalen*, 1892, **271**, 150.

As the sum of equivalent conductivities of potassium phenylglycidate and 1-amidinopiperidine sulphate (187·8) is in reasonable agreement with the sum of the conductivities of potassium sulphate and 1-amidinopiperidine phenylglycidate (186·2), the constitution of the last compound is established.

The low conductivity of α-guanidinocinnamic acid, about one-eigth of that expected for a salt of analogous equivalent weight, is in accord with the proposed zwitterionic constitution, the maximum conductivity of a zwitterionic compound being expected to be rather less than a quarter of that of a comparable salt. [For acidic and basic dissociation constants not too disparate, hydrolysis will result in ionisation of approximately equal numbers of acidic and basic groups. For non-interacting groups the probability that a given function in the molecule is ionised is here defined as a. The probability that both functions are simultaneously ionised is a^2, that neither is ionised is $(1 - a)^2$, the remaining molecules with a net charge will be $1 - a^2 - (1 - a)^2 = 2a(1 - a)$ which is a maximum for $a = 0{\cdot}5$. Thus the fraction 0·25 of each charged (conducting) species will at most be present.]

The conductivity of compound (VI) excludes a dihydrochloride constitution.

Compound from Guanidine Cyanide and Benzaldehyde.—A solution of guanidine nitrate (100 g.) and sodium cyanide (50 g.) in water (500 ml.) was warmed to 50°, then benzaldehyde (200 ml.) was added and sufficient methanol to give a homogeneous solution. A viscous red oil separated from the cold solution; it was triturated with ethanol–ether (partial crystallisation); then crystallisation from a little anisole gave crude material (62 g.), m. p. 190—194° (decomp.). An analytical specimen of the *compound* (from anisole, then from acetone) had m. p. 224—226° (decomp.) (Found: C, 76·7; H, 5·3; N, 18·3. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6; N, 17·9%). However, other samples prepared differently had different compositions; thus samples of m. p. 226—228° (decomp.) (from acetone, then ethanol) (Found: C, 72·45; H, 5·5; N, 17·7; O, 4·9%), m. p. 225—226° (decomp.) (from acetone, then acetone–light petroleum) (Found: C, 74·5; H, 5·1; N, 18·2%), and m. p. 224—226° (decomp.) (from anisole, then ethanol) (Found: C, 74·0; H, 5·25; N, 17·9; O, 1·96%), were also obtained. Differences in the infrared spectra of the samples were consistent either with different degrees of solvation and/or with decomposition. Thus the first-mentioned analytical sample appeared to have undergone slight decomposition on drying, and its infrared absorption was not quite as sharp as before. After drying (16 hr. at 100—120°/0·01 mm.) it had $\nu_{max.}$ (in Nujol), 3470, 3058sh, 1667vs, 1602, 1574w, 1567w, 1542infl., 1539vs, 1521sh, 1511infl., 1495w, 1478sh,s, 1417vs, 1341, 1316, 1305, 1205, 1121w,br, 1068w, 1027w, 936, 914w, 870, 824w, 765s,asym., 753s, 745s, 741s,sh, 714, 702s, 694s, 690infl., 681 cm.$^{-1}$.

A crude sample (1·0 g.) was dissolved in warm acetone (200 ml.), and 20% sodium hydroxide solution was added; a red upper layer and a colourless lower layer were formed. The mixture was cooled and acetic anhydride (10 ml.) was added in small portions; dilution with water gave crystals that, purified from ethanol, yielded an acetyl derivative in yellow needles (421 mg.), m. p. 192—193·5° [Found: C, 70·6; H, 5·4; N, 13·3; O, 10·6; Ac (Wenzel's H_2SO_4), 26·0. Calc. for $C_{19}H_{17}N_3O_2$: C, 71·45; H, 5·4; N, 13·2; O, 10·0; 2Ac, 27·0. Calc. for $C_{26}H_{24}N_4O_3$: C, 70·9; H, 5·5; N, 12·7; O, 10·9%]. In Nujol it had $\nu_{max.}$ 1737vs, 1720vs, 1609, 1582ms, 1568ms, 1559infl., 1494sh,w, 1481infl., 1448s, 1421s, 1348ms, 1310, 1292sh, 1271vs,asym., 1226vs, 1212s, 1192s, 1168, 1158, 1140, 1072, 1052w, 1036w, 1031, 1020, 999w, 985w, 976w, 966, 959sh, 901, 797w, 777ms, 767, 764, 760, 717, 702ms, 697s, 687w, 678ms cm.$^{-1}$. In ethanol it had $\lambda_{max.}$ 229, 273, 283, $\lambda_{infl.}$, 255 mμ ($\log_{10} \varepsilon$ 4·19, 4·35, 4·07, 4·31, calc. for $C_{26}H_{24}N_4O_3$), practically unchanged by addition of a drop of acetic acid. The proton magnetic resonance spectrum of this compound in deuterochloroform gave peaks as follows [frequencies are given as τ values with integrated intensities (arbitrary scale) in parentheses]: five peaks centred at 1·93 (11·5); 2·43 (6·0); 2·62 (32), a group (34) consisting of one weak peak at 2·78 and one strong peak at 2·72 with flanking shoulders; 6·97 (13·0); 7·70 (28·5). A few minor peaks, a quartet centred at 6·33 (6), and a triplet at 8·80 (8) suggest the presence of ethanol (*ca.* 0·5 mol.), possibly derived from ethanol of solvation.

Spectra.—Frequencies and estimates of the intensities of the main absorption bands for Nujol mulls were estimated from spectra determined on a Grubb-Parsons double-beam GS2 spectrometer. Potassium phenylglycidate had $\nu_{max.}$ 3049vw, sharp, (νCH, epoxide), 1606vs, (CO_2^-], 1575 (arom.), 1396, 1318, 1304, 1275s, 1240, 1191, 1168, 1105, 1093, 1069s, 1026, 954br, 882s, 849ms, 845, 816s, 749vs (arom. δ CH), 710s, 693br,s cm.$^{-1}$

Spectra for other compounds will be submitted to the D.M.S. scheme.

Correction to Part IV.[1] In this paper, two corrections of the nomenclature are required. Compound "*N'*-acetylguanidino-2-acetylimino-5-*N*-ethyl-3,4-diphenyl-2*H*-pyrrole" is a transposition of the correct name: 5-*N*-acetyl-*N'*-ethylguanidino-2-acetylimino-3,4-diphenyl-2*H*-pyrrole. The compound named as 2-acetylimino-5-*N*-cyclohexylguanidino-3,4-diphenyl-2*H*-pyrrole is, of course, the diacetyl compound, 2-acetylimino-5*N*-acetyl-*N'*-cyclohexylguanidino-3,4-diphenyl-2*H*-pyrrole, as shown by the analyses there given.

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