*Derivatives of Acetoacetic Acid. Part VII.** α-*Acetyltetramic Acids.*†

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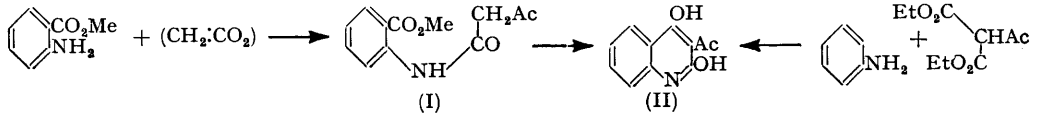
Methyl anthranilate was converted into the acetoacetyl derivative with diketen, and the product cyclised with sodium methoxide, giving 3-acetyl-2 : 4-dihydroxyquinoline. Esters of α-amino-acids (glycine, DL-alanine, and anilinoacetic acid) were similarly converted into the corresponding aceto-acetyl derivatives which, with sodium alkoxides, gave α-acetyltetramic acids (IV). By a similar sequence of reactions, ethyl β-aminopropionate was converted into 3-acetyl-1 : 2 : 5 : 6-tetrahydro-4-hydroxy-2-oxopyridine (V).

THE present paper is concerned with the preparation and properties of acetoacetamides from alkoxycarbonyl-amines and diketen. Methyl anthranilate reacts smoothly with diketen at 100—120°. Lyashenko and Sokolova (*J. Gen. Chem., U.S.S.R.*, 1947, **17**, 1868) found a parallel between the rate of reaction of diketen with an aromatic amine and the basic strength of the amine, and, since methyl anthranilate is a relatively weak base ($K = 1{\cdot}5 \times 10^{-12}$), the necessity for the high reaction temperature receives an explanation; aniline ($K = 5 \times 10^{-10}$) rapidly reacts with diketen at room temperature. However, the use of catalytic quantities of a *tert.*-amine led to a reduction of reaction temperature to 60—70° and a high yield of the expected acetoacetanilide (cf. Perekalin and Lerner, *J. Gen. Chem., U.S.S.R.*, 1951, **21**, 1995; Lacey and Connolly, B.P. Appln. 20198/1951). The success achieved is in contrast with the failure of diketen to react with methyl salicylate (Part IV).

It was shown in Part IV that the acetoacetates of α-hydroxy-carboxylates were readily cyclised to α-acetyltetronic acids by means of sodium or, in certain cases better, by alcoholic sodium alkoxide. Treatment of methyl *o*-acetoacetamidobenzoate (I) with sodium in toluene caused some conversion into 3-acetyl-2 : 4-dihydroxyquinoline (II) but better results were obtained by using sodium methoxide in methanol. Compounds similar to (II) had been prepared by Vaughan (*J. Amer. Chem. Soc.*, 1946, **68**, 324) by the condensation of *p*-methoxy- or *m*-chloro-aniline with acetylmalonic ester in refluxing nitrobenzene solution. Since (II) itself had not been prepared by Vaughan, aniline was condensed with acetyl-malonic ester, giving a product identical with that obtained by the above cyclisation. The quinoline (II) was remarkable in that, on treatment with phenylhydrazine in acetic acid solution, acetylation, presumably of the 4-hydroxyl, accompanied phenylhydrazone formation.



(I) (II)

Ethyl α-aminoacetate was liberated from its hydrochloride by treatment with alcoholic sodium ethoxide; the solution so obtained reacted rapidly with diketen at a low temperature, giving the expected acetoacetamide (III; R = R′ = H). When this was refluxed with sodium methoxide in methanol–benzene, self-condensation gave α-acetyl-tetramic acid (IV; R = R′ = H). The product liberated carbon dioxide from sodium hydrogen carbonate and gave a red colour with ferric chloride in close parallel with the strongly acidic properties of α-acetyltetronic acids (see Part IV).

Anschütz and Böcker (*Annalen*, 1909, **368**, 53) claimed to have prepared α-ethoxy-carbonyl-γ-phenyltetramic acid, but, since the substance did not possess acidic properties, it does not appear to be well characterised. Further references to pyrrolidine-2 : 4-diones include Benary (*Ber.*, 1911, **44**, 1763), Hoffmann-La Roche (G.P. 695,330), and three recent papers kindly pointed out by a referee (Cornforth and Huang, *J.*, 1948, 1958; King

* Part VI, preceding paper. † Patent pending: B.P. Appln. 2260/1951.

and McMillan, *J. Amer. Chem. Soc.*, 1950, **72**, 1236; and Larsen and Bernstein *ibid.*, p. 4447).

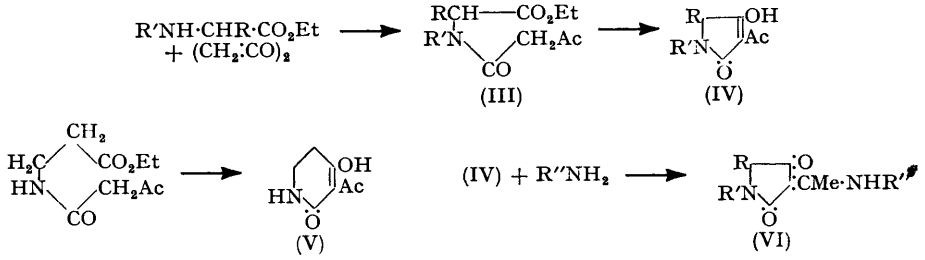
Similarly, DL-α-alanine ethyl ester was liberated from its hydrochloride as above or by Hillman's method (*Z. Naturforsch.*, 1946, **1**, 682) and treated with diketen in the cold. The acetoacetamide (III; R = Me, R′ = H) was obtained as an oil which decomposed when heated, but treatment of the crude product with sodium ethoxide in ethanol–benzene gave α-acetyl-γ-methyltetramic acid (IV; R = Me, R′ = H). Ethyl anilinoacetate was converted into (III; R = H, R′ = Ph) by reaction with diketen in boiling benzene. The reaction was slower than with the two amino-esters previously studied, the phenyl group greatly reducing the basicity of the amino-group. Cyclisation of the acetoacetamide with sodium ethoxide in ethanol–benzene gave the tetramic acid (IV; R = H, R′ = Ph) in 85% overall yield.

Attempts to effect the self-condensation of the acetoacetate of ethyl β-hydroxybutyrate (Part IV) were unsuccessful, but, by the above methods β-alanine ethyl ester was converted into the acetoacetamide, which, on treatment with sodium ethoxide in ethanol–toluene followed by prolonged refluxing, gave a small yield of 3-acetyl-1 : 2 : 5 : 6-tetrahydro-4-hydroxy-2-oxopyridine (V), which was not rigorously characterised although it was shown to be soluble in sodium hydrogen carbonate solution, insoluble in dilute mineral acid, to give the expected red colour with ferric chloride, and to exhibit light-absorption properties closely similar to those of the α-acetyltetramic acids described above (see Table).

Light-absorption data (in ethanol solution).

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(IV; R = R′ = H)	2390	9,550	2770	13,500
(IV; R = Me, R′ = H)	2400	5,250	2800	10,850
(IV; R = H, R′ = Ph)	2580	14,500	2820	26,050
(V)	2300 (infl.)	6,300	2750	15,000
(VI; R = Me, R′ = H, R″ = Ph)	2650	15,900	3300	27,600
(VI; R = H, R′ = R″ = Ph)	2650	16,000	3300	27,600
(VI; R = H, R′ = Ph, R″ = CH_2Ph)	2660	17,800	3200	26,300

α-Acetyltetramic acids reacted with primary amines, giving the "amides" which possess the α-enamine structure (VI) found in the "amides" of α-acetyltetronic acids (cf. Part IV), as shown by the light-absorption properties (see Table). The acids were resistant to alkaline hydrolysis and both α-acetyl-γ-methyltetramic acid and α-acetyl-*N*-phenyltetramic acid were substantially unchanged after several hours' boiling with 10% sodium hydroxide. Clutterbuck, Raistrick, and Reuter (*Biochem. J.*, 1935, **29**, 300) showed that α-acetyltetronic acids may be hydrogenated to α-ethyltetronic acids over a



palladium on charcoal catalyst. However (IV; R = Me, R′ = H) and (IV; R = H, R′ = Ph) resisted hydrogenation under these conditions which, in confirmation of the work of Clutterbuck *et al.* (*loc. cit.*), were found adequate for the reduction of α-acetyltetronic acids. The bromination of α-acetyltetramic acids did not proceed analogously to that of α-acetyltetronic acids (Clutterbuck *et al.*, *loc. cit.*) (cf. Part IV), but gave only intractable products.

The absorption spectra of the α-acetyltetramic acids (see Table) were closely similar to those recorded for α-acetyltetronic acids (cf. Part IV). Two bands were exhibited, ascribed to (*a*) the αβ-unsaturated carboxyl group ($\lambda_{max.}$ 2300—2600 Å) and (*b*) the system

C(OH):CAc ($\lambda_{max.}$ 2650—2850 Å). Comparison of these values with those for α-acetyltetronic acids showed that both bands were shifted to higher wave-lengths ($\Delta\lambda \sim 100$—150 Å) by the replacement of the ester O of the α-acetyltetronic acids by NH, and replacement of O by NPh caused a larger shift (280 Å) in band (*a*), as would be expected, with only a small shift in band (*b*) over that obtained by replacement with NH. The facts support the above explanation of the form of the absorption curves, although the shift in band (*b*) would indicate that the band is not attributable to the C(OH):CAc system in isolation, for the introduction of NH would be expected, on the basis of the above simple reasoning, to affect only band (*a*). The " amides " of α-acetyltetramic acids (VI) also exhibit two absorption bands as did the " amides " of α-acetyltetronic acids (cf. Part IV). Very large auxochromic shifts of the absorption maxima ($\Delta\lambda \sim 300$—400 Å) were observed between the " amides " of tetronic acids and those of tetramic acids.

Attempts to prepare the sulphur analogue of α-acetyltetronic acid by the reaction of diketen with methyl thioglycollate followed by treatment with sodium in toluene were unsuccessful, giving only dehydroacetic acid.

Experimental

M. p.s were determined on a Kofler block and are corrected.

Methyl o-Acetoacetamidobenzoate (I).—(*a*) Diketen (21 g.) was added to methyl anthranilate (38 g.) with stirring during 20 min. The product was then heated at 110—120° for 0·5 hr., cooled, and triturated with light petroleum, giving a solid (51·5 g., 86·5%), m. p. 71·5—73°. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the *amide* (I) as prisms, m. p. 79—80° (Found: C, 61·1; H, 5·65. $C_{12}H_{13}O_4N$ requires C, 61·25; H, 5·55%).

(*b*) To an agitated solution of methyl anthranilate (76 g.) in benzene (100 c.c.) containing triethylamine (1 c.c.) at 60—70° diketen (43 g.) was added during 0·75 hr. After a further 0·5 hr. at 70° removal of solvent gave the amide (104 g., 88·5%), m. p. 74°.

3-Acetyl-2 : 4-dihydroxyquinoline (II).—(*a*) The amide (I) (59 g.) in toluene (100 c.c.) was added to a suspension of finely-divided sodium (6 g.) in toluene (100 c.c.), and the mixture heated with stirring for 3 hr., and then set aside overnight. The mixture was acidified with dilute sulphuric acid, and the product (7·2 g.) crystallised from acetic acid giving the *quinoline* (II), m. p. 259° (Found: C, 64·8; H, 4·7. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·45%). From the solvent layer after acidification starting material (19·8 g.) was obtained.

(*b*) A solution of sodium methoxide (from 6 g. of sodium in 100 c.c. of methanol) was added to an agitated solution of the above amide (59 g.) in ether (100 c.c.) and methanol (50 c.c.) during 0·5 hr. After being refluxed overnight, the mixture was acidified as before, giving the above quinoline (48·6 g., 96%), m. p. 255°. Refluxing of a mixture of the quinoline (II) (1 g.) and phenylhydrazine (2 g.) in acetic acid (10 c.c.) for 0·5 hr., followed by the addition of water, gave the *phenylhydrazone acetate*, as red micro-crystals, m. p. 206—207° (from aqueous methanol) (Found: C, 68·55; H, 5·35; N, 12·5. $C_{19}H_{17}O_3N_3$ requires C, 68·05; H, 5·1; N, 12·55%).

(*c*) (cf. Vaughan, *loc. cit.*) Aniline (4·5 g.), acetomalonic ester (20 g.; Lund, *Ber.*, 1934, **67**, *B*, 935), and nitrobenzene (150 c.c.) were heated beneath a short distillation column, ethanol being removed as formed. The precipitate formed on cooling was washed with ether and crystallised from acetic acid; it had m. p. 259° undepressed with material obtained by methods (*a*) or (*b*).

Ethyl Acetoacetamidoacetate (III; R = R′ = H).—Ethyl aminoacetate hydrochloride (42 g.), in warm ethanol (80 c.c.), was treated with ethanolic sodium ethoxide (from 6·9 g. of sodium and 80 c.c. of ethanol) with agitation and rapid cooling. The precipitated sodium chloride was filtered off and the alcoholic ethyl aminoacetate thus obtained treated with diketen (26 g.) added during 20 min. at <5°. After 1 hr. at room temperature, the solvent was removed at reduced pressure, and the residue extracted with ether, leaving a small amount of sodium chloride. Evaporation of the ether gave the *amide* (49 g., 87%), m. p. 45°, readily soluble in ethanol, water and ether, but insoluble in light petroleum. Crystallisation from ether gave needles, m. p. 49—50° (Found: C, 51·1; H, 6·95; N, 7·3. $C_8H_{13}O_4N$ requires C, 51·35; H, 7·0; N, 7·5%).

α-Acetyltetramic Acid (IV; R = R′ = H).—Ethyl acetoacetamidoacetate (49 g.) in benzene (100 c.c.) was refluxed with agitation with a solution of sodium methoxide (from 7 g. of sodium and 80 c.c. of methanol) for 3 hr. and set aside overnight. Water (100 c.c.) was added and the solvent layer extracted with water (2 × 50 c.c.). The aqueous extracts were carefully acidified

with concentrated sulphuric acid (16 g.) and repeatedly extracted with ether, giving, after washing, drying, and evaporation, *α-acetyltetramic acid* (IV; R = R′ = H) (crude yield: 28·2 g., 76%) which formed micro-crystals, m. p. 155°, from ethyl acetate (Found: C, 51·4; H, 5·1; N, 10·2. $C_6H_7O_3N$ requires C, 51·05; H, 5·0; N, 9·95%). Light absorption: see Table.

The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as dark red prisms, m. p. 229° (decomp.) (Found: C, 45·1; H, 3·7; N, 21·4. $C_{12}H_{11}O_6N_5$ requires C, 44·85; H, 3·45; N, 21·8%). The *phenylhydrazone* formed golden needles, m. p. 191—192°, from aqueous methanol (Found: C, 62·55; H, 5·6; N, 17·8. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·65; N, 18·15%).

Ethyl α-Acetoacetamidopropionate (III; R = Me, R′ = H).—(*a*) Ethyl DL-α-aminopropionate hydrochloride (25 g.) in warm ethanol (50 c.c.) was treated with a solution of sodium ethoxide (from 3·7 g. of sodium and 50 c.c. of ethanol). The product was rapidly cooled, filtered, and treated with diketen (14·5 g.), added to the agitated solution during 1 hr. at <10°. After 1 hr. at room temperature, the product was evaporated at reduced pressure, giving a pale yellow oil (28 g., 85·5%).

(*b*) Ethyl DL-α-aminopropionate hydrochloride (20 g.) was stirred at room temperature with a solution of ammonia (2·4 g.) in chloroform (90 c.c.) for 3 hr. The ammonium chloride was filtered off and the solution concentrated somewhat in a stream of air at reduced pressure to remove the excess of ammonia. Diketen (11·5 g.) was added to the agitated solution at room temperature during 0·5 hr. and, after a further 0·5 hr., the solvent was removed, giving the amide (24 g., 91·5%), which decomposed on attempted distillation at 12 mm.

α-Acetyl-γ-methyltetramic Acid (IV; R = Me, R′ = H).—The above crude amide (28 g.), benzene, and alcoholic sodium ethoxide (from 3·75 g. of sodium and 50 c.c. of ethanol) were refluxed with agitation and then set aside overnight. Water (150 c.c.) was added to dissolve the sodium salts, and the benzene layer was extracted with water (2 × 25 c.c.). The combined extracts were carefully neutralised (concentrated sulphuric acid) and concentrated *in vacuo* at 20—25° (to about 100 c.c.), some solid separating. Thorough extraction with ether gave, on removal of solvent, the *tetramic acid* (11·5 g., 53·5%), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 115—116° (Found: C, 54·0; H, 5·55; N, 9·2. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·05%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as red microcrystals, m. p. 223° (decomp.) (Found: N, 21·2. $C_{13}H_{13}O_6N_5$ requires N, 20·9%).

α-Acetyl-γ-methyltetramic acid (1 g.) and aniline (1 g.) were refluxed in ethanol for 30 min., and water then added, giving the *anilide* (VI; R = Me, R′ = H, R″ = Ph) (crude yield: 1·3 g.), needles, m. p. 165°, from aqueous ethanol (Found: C, 67·7; H, 6·25; N, 12·1. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·15; N, 12·15%).

α-Acetyl-N-phenyltetramic Acid (IV; R = H, R′ = Ph).—Ethyl anilinoacetate (33·4 g.; cf. Gault, *Bull. Soc. chim.*, 1908, **3**, 370) in boiling benzene (50 c.c.) was treated during 0·5 hr. with diketen (17·6 g.), refluxing continued for a further 1·5 hr., and the solvent then removed. To a solution of the resulting oil (51 g.) in benzene (100 c.c.) was added alcoholic sodium ethoxide (from 5 g. of sodium in 50 c.c. of ethanol). The mixture was refluxed with agitation for 5 hr. and then set aside overnight. The sodium salts were extracted with water and the aqueous extract shaken with ether. Acidification with dilute sulphuric acid and crystallisation of the precipitate from ethanol gave the *tetramic acid* (37 g., 85% overall), m. p. 145°. Crystallisation from ethyl acetate gave pale brown plates, m. p. 148° (Found: C, 66·6; H, 5·25; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1; N, 6·45%).

The 2 : 4-*dinitrophenylhydrazone* was prepared in ethanol and formed a red precipitate, m. p. 263° (decomp.), practically insoluble in most solvents (Found: C, 54·5; H, 3·9; N, 17·0. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8; N, 17·65%). The *phenylhydrazone* crystallised as pale brown plates, m. p. 198—199°, from aqueous acetic acid (Found: C, 70·35; H, 5·9; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·35; H, 5·6; N, 13·7%).

α-Acetyl-*N*-phenyltetramic acid (1 g.), aniline (0·5 g.), and ethanol (10 c.c.) were refluxed for 5 min. Water was added, giving the *anilide* (VI; R = H, R′ = R″ = Ph) (1·1 g.), which crystallised from aqueous ethanol as needles, m. p. 142—143° (Found: C, 73·85; H, 5·5; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·45; N, 9·6%). Light absorption: see Table.

The tetramic acid (1 g.), benzylamine (1 g.), water (2 c.c.), and methanol (5 c.c.) were refluxed for 10 min. and allowed to cool. The *benzylamide* (VI; R = H, R′ = Ph, R″ = CH_2Ph) crystallised from aqueous methanol as needles, m. p. 114—115° (Found: C, 74·4; H, 6·05; N, 9·1. $C_{19}H_{18}O_2N_2$ requires C, 74·45; H, 5·95; N, 9·15%). Light absorption: see Table.

3-*Acetyl*-1 : 2 : 5 : 6-*tetrahydro*-4-*hydroxy*-2-*oxopyridine* (V).—A solution of β-alanine ethyl ester hydrochloride (46 g.) in ethanol (50 c.c.) was treated with sodium ethoxide (from 6·9 g. of sodium and 80 c.c. of ethanol), and the product was cooled and filtered. Diketen (26 g.) was added with agitation at 5—10° during 0·5 hr. after which the mixture was stirred at 20° for a further 0·5 hr. Evaporation of the solvent afforded the acetoacetamide as a pale yellow oil (44 g.) which was used directly for the next stage.

The crude acetoacetamide (42 g.) in toluene (100 c.c.) and a solution of sodium ethoxide (from 7 g. of sodium and 80 c.c. of ethanol) was refluxed for 20 hr. The product was acidified with dilute hydrochloric acid and thoroughly extracted with ether, giving an oil (4·1 g.) from which, on being rubbed with methanol, the *pyridone* (1·3 g.) separated; this formed needles, m. p. 192°, from methanol (Found: C, 54·1; H, 6·05; N, 8·85. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·05%). Light absorption: see Table.

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