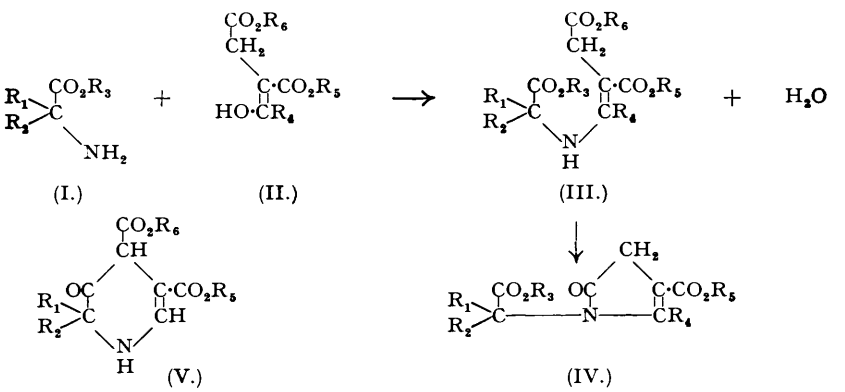
587. *Synthetical Experiments in the B Group of Vitamins. Part II.* Pyrrolinones Derived from the Condensation Products of Primary Amino-esters and Formyl- or Acetyl-succinic Acid Derivatives.*

By A. Cohen.

Condensation of some simple primary α-amino-esters with formyl- or acetyl-succinic esters yields carbalkoxyalkylaminoitaconic esters (III), which are cyclised by sodium or sodium alkoxide to derivatives of the pyrrolinone (IV). Cyclisation of the carbalkoxyalkylaminoitaconic acid derivative (IX) with a terminal nitrile group yields a bicyclic pyrrole derivative (X).

As a preliminary to the synthesis of 3-hydroxypyridine derivatives related to pyridoxin (vitamin B_6) (to be described in Part III, in preparation) the condensation of α-amino-esters with acylsuccinic esters and related compounds was studied as a means of providing suitable substituted aminoitaconic esters (III) which might be cyclised in a Dieckmann reaction to ketotetrahydropyridines (cf. V).



* Part I, *J.*, 1945. 165.

It was found that the aminoitaconic esters were only suitable for such a cyclisation if the nitrogen atom was completely substituted and did not carry a hydrogen atom [as it does in (III)], that is, if they were derived from secondary α-amino-esters (see Part III). The present communication concerns the aminoitaconic esters of type (III), derived from primary α-amino-esters, and their cyclisation products, the pyrrolinones (IV).

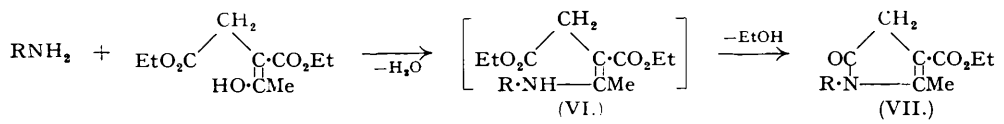
The reaction between esters (I) of glycine, DL-alanine, and α-amino*iso*butyric acid on the one hand, and α-formyl- or α-acetyl-succinic ester (II) on the other, yields quite readily the substituted aminoitaconic esters (III). The elimination of the elements of water is spontaneously exothermic with formylsuccinic ester, but with the acetylsuccinic ester heat is required; this difference may be attributed to the differing contents of enol form in these esters, which are 50% (Carrière, *Ann. Chim.*, 1922, [ix], **17**, 38) and 3·7% (K. H. Meyer, *Ber.*, 1912, **45**, 2854), respectively.

The condensations (I) + (II) ⟶ (III) ⟶ (IV) described in the Experimental section represent a limited number of examples of a reaction which is clearly of much wider scope. They are tabulated below with reference to the nature of the groups R_1—R_6, and include the

Reactants.	R_1.	R_2.	R_3.	R_4.	R_5.	R_6.
Glycine ethyl ester and ethyl α-formylsuccinate	H	H	Et	H	Et	Et
Glycine ethyl ester and ethyl α-acetylsuccinate	H	H	Et	Me	Et	Et
Glycine methyl ester and ethyl α-acetylsuccinate	H	H	Me	Me	Et	Et
DL-Alanine ethyl ester and ethyl α-formylsuccinate	Me	H	Et	H	Et	Et
DL-Alanine methyl ester and ethyl α-formylsuccinate	Me	H	Me	H	Et	Et
Methyl α-amino*iso*butyrate and ethyl α-formylsuccinate	Me	Me	Me	H	Et	Et
DL-Alanine ethyl ester and ethyl β-cyano-α-formylpropionate	Me	H	Et	H	Et	CN for CO_2R_6

condensation product of alanine ethyl ester and ethyl α-formylsuccinate, although this compound and the pyrrolinone formed by its cyclisation are described in a recent paper on " 4-Carbethoxy-2-pyrrolones " by Grob and Ankli (*Helv. Chim. Acta*, 1949, **32**, 2010). The work now reported was completed in 1942 (cf. B.P. 551,216/1941; the pyrrolinone cyclisations were reported to the XIth International Congress of Pure and Applied Chemistry, London, July 1947, Abstract No. 247/3, in the course of a communication on the synthesis of pyridoxin).

The condensation of primary arylamines with ethyl α-formylsuccinate has been found by Carrière (*loc. cit.*) to yield arylaminoitaconic esters, but Emery has recorded (*Annalen*, 1890, **260**, 137) that reaction of ammonia or primary aliphatic amines with ethyl acetylsuccinate leads to pyrrolinones (VII), presumably through the aminoitaconates (VI) from which the elimination of the elements of alcohol may be brought about by distillation.

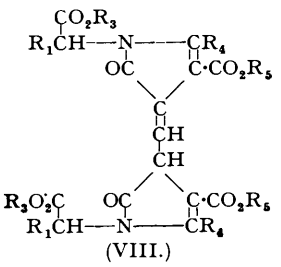


(VI.) (VII.)

By contrast, the substituted aminoitaconic esters now described distil under reduced pressure at fairly high temperatures with little or no decomposition and cyclisation by elimination of alcohol has not been observed. Grob and Ankli (*loc. cit.*) have explained the greater tendency for thermal cyclisation of the aminoethylidenesuccinic esters (cf. VI), compared with the analogous aminomethylene compounds (cf. III; R_4 = H), as being due to the higher electron density at the nitrogen atom of (VI) which is brought about by the compensatory effect of the methyl group on the electron shift caused by the ester carbonyl group. However, the condensation product (III; $R_1 = R_2$ = H, R_4 = Me, $R_3 = R_5 = R_6$ = Et) obtained from glycine ethyl ester and ethyl acetylsuccinate can be redistilled at about 180° at oil-pump vacuum without evidence of pyrrolinone formation (cf. IV). It therefore appears that the ester group of the amino-ester moiety exerts a further and inhibitory influence on the thermal cyclisation of these aminoitaconic esters.

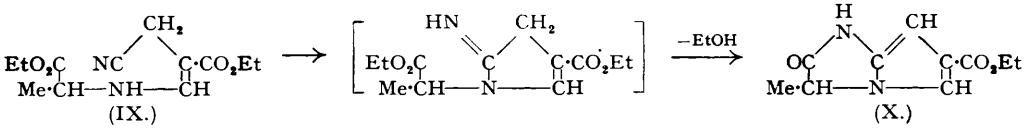
The substituted aminoitaconic esters derived from glycine and alanine esters have been cyclised by sodium or sodium alkoxide yielding derivatives (IV) of Δ^4-pyrrolin-2-one, isomeric with the hypothetical tetrahydro-3-ketopyridine derivatives (V). Formulation as (IV) is supported by analysis, lack of basic character (hydrochlorides are not formed in anhydrous media), failure to obtain 3-hydroxypyridine derivatives by a dehydrogenation procedure such as bromination (cf. Part III), and the presence of the reactive methylene group. In accord

with this, for example, 4-carbethoxy-1-carbethoxymethyl-5-methyl-Δ^4-pyrrolin-2-one (IV; $R_1 = R_2 = H$, $R_3 = R_4 = Me$, $R_5 = Et$) forms a yellow benzylidene derivative. The reactive methylene group is also demonstrated in condensations with ethyl orthoformate in the presence of acetic anhydride or acetyl chloride. This reaction yields red or orange-coloured crystalline methine derivatives, the composition of which is in agreement with the formulation (VIII) (R_2 is replaced by H in this formula since the compounds mentioned were derived from glycine and alanine respectively).



(VIII.)

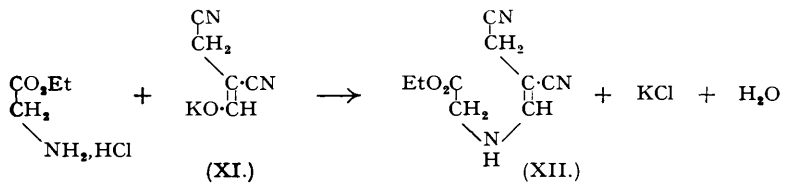
The aminoitaconic ester obtained from methyl α-amino*iso*butyrate was only available in small amount and its cyclisation was not carried out. The condensation product (IX) obtained from DL-alanine ethyl ester and ethyl β-cyano-α-formylpropionate was cyclised with sodium or sodium ethoxide, yielding a non-basic compound, $C_{10}H_{12}O_3N_2$, which is soluble in dilute alkali and gives a positive test with Ehrlich's reagent. It is therefore formulated as the bicyclic pyrrole derivative (X) and it is considered to be formed by additive cyclisation of –NH– to the nitrile group followed by isomerisation and elimination of alcohol as depicted.



(IX.) (X.)

Although hydroxymethylenesuccinonitrile is unstable under ordinary distillation conditions and could not be prepared in a pure state, its potassium salt (XI) was obtained by treatment of succinonitrile with ethyl formate in the presence of potassium ethoxide. The same compound, obtained with the aid of potassium *tert.*-amyloxide was recently reported by Grob and Ankli (*Helv. Chim. Acta*, 1950, **33**, 273), who have apparently overlooked the author's earlier preparation (B.P. 551,216; U.S.P. 2,384,068) while acknowledging its use in condensations with amino-esters.

When (XI) is heated with glycine ethyl ester hydrochloride, neutralisation and condensation yield *N*-(carbethoxymethyl)aminoitaconodinitrile (XII). These experiments were not



(XI.) (XII.)

pursued as it was realised at the time that the main objective, *viz.*, synthesis of keto-tetrahydropyridine derivatives, required condensation products derived from secondary amino-esters, to which attention was then directed.

Experimental.

(M. p.s are uncorrected.)

4-Carbethoxy-1-(1-carbethoxyethyl)-Δ^4-pyrrolin-2-one (IV; $R_1 = Me$, $R_3 = R_5 = Et$, $R_2 = R_4 = H$).—DL-Alanine ethyl ester (33 g.) and ethyl α-formylsuccinate (44 g.) were mixed, with immediate development of heat. After 1 hour, the mixture was freed from water and fractionally distilled. After removal of a small fore-run (2 g.), *ethyl N-(1-carbethoxyethyl)aminoitaconate* (III; $R_1 = Me$, $R_2 = R_4 = H$, $R_3 = R_5 = R_6 = Et$) was obtained as a yellow oil, b. p. 156—159°/0·1 mm. (94%) (Found: C, 55·95; H, 7·6. $C_{14}H_{23}O_6N$ requires C, 55·8; H, 7·6%).

A solution of this oil (6·3 g.) in dry " AnalaR " benzene (20 ml.) was refluxed with powdered sodium (0·45 g.) in an atmosphere of dry nitrogen for 1 hour. The cooled liquid was made just acid to litmus with dilute hydrochloric acid and ice. The benzene extract was combined with a further ethereal extract and washed with sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). After removal of solvents, the residue was distilled *in vacuo*, yielding 1·75 g. of 4-carbethoxy-1-(1-carbethoxyethyl)-Δ^4-pyrrolin-2-one, b. p. 136—140°/0·4 mm. It crystallised from light petroleum in colourless feathery needles, m. p. 40—42° (Found: C, 56·6; H, 6·9; N, 5·8. Calc. for $C_{12}H_{17}O_5N$: C, 56·5; H, 6·7; N, 5·5%). Grob and Ankli (*loc. cit.*) give m. p. 42—43° (corr.). This compound absorbs bromine (no crystalline product could be isolated), and gives with ferric chloride a greenish-yellow colour, gradually darkening to magenta. When the ester (5·1 g.) was mixed with ethyl orthoformate

(3·0 g.) and acetyl chloride (1·6 g.) a vigorous reaction ensued. After some hours the mixture was freed from volatile liquids at water-pump vacuum on the water-bath. The residue crystallised from benzene–light petroleum or alcohol, yielding *ethyl* 1-(*carbethoxyethyl*)-4-[4-*carbethoxy*-1-(1-*carbethoxyethyl*)-2-*keto*-Δ^4-*pyrrolin*-3-*ylmethylene*]-5-*keto*-Δ^2-*pyrroline*-3-*carboxylate* (VIII; R_1 = Me, R_4 = H, R_3 = R_5 =Et), red needles, m. p. 143° (Found: C, 57·2; H, 5·95; N, 5·7. $C_{25}H_{32}O_{10}N_2$ requires C, 57·7; H, 6·15; N, 5·4%).

In an early experiment in which it was intended to demonstrate the direction of cyclisation by employing different ester groups in the initial reactants, alanine methyl ester (4·5 g.) and ethyl α-formylsuccinate (8·5 g.) were allowed to react as described above, yielding *ethyl* N-(1-*carbomethoxyethyl*)*aminoitaconate* (III; R_1 = R_3 = Me, R_2 = R_4 = H, R_5 = R_6 = Et) (12·4 g.), a yellow oil, b. p. 173°/0·4 mm. (Found: C, 54·4; H, 7·6; N, 5·1. $C_{13}H_{21}O_6N$ requires C, 54·4; H, 7·3; N, 4·9%).

When this was cyclised with powdered sodium in benzene (cf. above), some trans-esterification occurred and the distilled product (2·6 g.), b. p. *ca.* 155°/0·2 mm., could not be crystallised. Analysis gave results which were intermediate between those for a methyl and those for an ethyl ester (IV; R_1 = Me, R_2 = R_4 = H, R_5 = Et, R_3 = Me or Et) (Found: C, 55·4; H, 6·4. Calc. for $C_{12}H_{17}O_5N$: C, 56·5; H, 6·7%. Calc. for $C_{11}H_{15}O_5N$: C, 54·8; H, 6·2%).

4-*Carbethoxy*-1-*carbethoxymethyl*-Δ^4-*pyrrolin*-2-*one*.—Condensation of glycine ethyl ester (5·5 g.) with ethyl α-formylsuccinate (10·1 g.) as already described yielded *ethyl* N-(*carbethoxymethyl*)-*aminoitaconate* (11·2 g., 78%), b. p. 175—178°/0·6 mm. (Found: C, 54·0; H, 7·0; N, 5·0. $C_{13}H_{21}O_6N$ requires C, 54·3; H, 7·3; N, 4·9%). This was cyclised with sodium in benzene solution yielding the *pyrrolinone*, b. p. 155°/0·2 mm., which crystallised from light petroleum (b. p. 60—80°) in feathery needles, m. p. 86° (Found: C, 54·8; H, 6·3; N, 5·8. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·2; N, 5·8%). Ferric chloride is first decolorised by this compound in alcoholic solution, but in excess causes a purple-red colour.

4-*Carbethoxy*-1-*carbethoxymethyl*-5-*methyl*-Δ^4-*pyrrolin*-2-*one*.—A mixture of glycine ethyl ester (7·3 g.) and ethyl α-acetylsuccinate (17 g.) was heated on a boiling water-bath for 2 hours and left cooling overnight. The viscous oily mixture was dissolved in ether, washed with aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Ether was removed, and the residue (*ca.* 18 g.) crystallised on cooling. Recrystallisation from a mixture of a small volume of benzene and a large volume of light petroleum yielded colourless silky needles of *ethyl* α-(1-N-*carbethoxymethylaminoethylidene*)*succinate* (III; R_1 = R_2 = H, R_4 = Me, R_3 = R_5 = R_6 = Et), m. p. 56—57° (Found: C, 55·8; H, 7·75; N, 4·8. $C_{14}H_{23}O_6N$ requires C, 55·8; H, 7·7; N, 4·65%). A portion of the crude compound (13·5 g.) was distilled *in vacuo*. A low-boiling fraction (3·2 g.) of unchanged ethyl acetylsuccinate was obtained, followed by the purified condensation product (8 g.), b. p. 175—178°/0·5 mm., a non-volatile residue (*ca.* 1 g.) being left. The distilled product crystallised spontaneously, was identical with the above undistilled material (m. p. and mixed m. p. 55—57°), and depressed the m. p. of the cyclisation product (61°) described below to 35—40°.

For cyclisation, this compound (10·5 g.) was treated in benzene (35 ml.) solution with sodium powder (0·77 g.) as described for the first example above, yielding the *pyrrolinone*, b. p. 160°/0·2 mm. (4·4 g., 51%). It crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 61° (Found: C, 56·6; H, 6·7; N, 5·7. $C_{12}H_{17}O_5N$ requires C, 56·5; H, 6·7; N, 5·5%).

The *benzylidene* derivative, obtained by briefly heating an equimolecular mixture of the compound, benzaldehyde, and a trace of piperidine on a boiling water-bath, crystallised from methanol in bright yellow needles, m. p. 100° (Found: C, 66·6; H, 6·0; N, 4·1. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1; N, 4·1%).

Methine derivative (VIII; R_1 = H, R_3 = R_5 = Et, R_4 = Me). A mixture of the pyrrolinone (1·0 g.) and equal quantities of ethyl orthoformate and acetyl chloride reacted vigorously, evolving hydrogen chloride. Volatile material was removed (water-bath and water-pump) and the residue of *ethyl* 1-*carbethoxymethyl*-4-(4-*carbethoxy*-1-*carbethoxymethyl*-2-*keto*-5-*methyl*-Δ^4-*pyrrolin*-3-*ylmethylene*)-5-*keto*-2-*methyl*-Δ^2-*pyrroline*-3-*carboxylate* recrystallsed from alcohol, forming orange-red needles, m. p. 176—178° (Found: C, 58·3; H, 6·2; N, 5·45. $C_{25}H_{32}O_{10}N_2$ requires C, 57·7; H, 6·15; N, 5·4%).

4-*Carbethoxy*-1-*carbomethoxymethyl*-5-*methyl*-Δ^4-*pyrrolin*-2-*one*.—A mixture of glycine methyl ester (6 g.) and ethyl acetylsuccinate (12·5 g.) was heated on the water-bath for 2 hours. On distillation the condensation product was obtained as a yellow oil (9·8 g.), b. p. 175°/0·3 mm. A solution of this material (9 g.) in dry benzene (36 ml.) was refluxed under nitrogen with powdered sodium (0·72 g.) for 1 hour. The cyclisation product was isolated as described above, the *pyrrolinone* (4·5 g.) distilling at 155—158°/0·2 mm. and crystallising from benzene–light petroleum in fine needles, m. p. 86° (Found: C, 54·8; H, 6·2; N, 5·9. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·2; N, 5·8%).

When treated with ethyl orthoformate and acetic anhydride as already described, this pyrrolinone yielded *ethyl* 1-(*carbomethoxymethyl*)-4-[4-*carbethoxy*-1-(*carbomethoxymethyl*)-2-*keto*-5-*methyl*-Δ^4-*pyrrolin*-3-*ylmethylene*]-5-*keto*-2-*methyl*-Δ^2-*pyrroline*-3-*carboxylate* (VIII; R_1 = H, R_3 = R_4 = Me, R_5 = Et) which formed orange-red needles, m. p. 190—192°, on crystallisation from alcohol (Found: C, 56·7; H, 5·8; N, 5·4. $C_{23}H_{28}O_{10}N_2$ requires C, 56·1; H, 5·7; N, 5·7%).

Ethyl N-(2-*Carbomethoxy*iso*propyl*)*aminoitaconate*.—This *ester* was obtained on mixing equivalent quantities of methyl α-amino*iso*butyrate and ethyl α-formylsuccinate (development of heat). Distillation yielded an almost colourless oil (87% yield), b. p. 155—158°/0·1 mm. (Found: C, 56·1; H, 7·6; N, 4·9. $C_{14}H_{23}O_6N$ requires C, 55·8; H, 7·6; N, 4·65%).

Bicyclic Pyrrole Derivative (X).—Ethyl β-cyano-α-formylpropionate (16 g.) and DL-alanine ethyl ester (16 g.) were allowed to react and the mixture distilled *in vacuo* after a few hours, yielding *ethyl* β-1-*carbethoxyethylamino*-α-*cyanomethylacrylate* (IX) (20·5 g.), as a pale yellow oil, b. p. 160°/0·02 mm.

(Found : C, 56·8; H, 7·3. $C_{12}H_{18}O_4N_2$ requires C, 56·7; H, 7·1%). A solution of this material (20 g.) in dry benzene (70 ml.) was added to a benzene suspension of powdered sodium (1·84 g.) and refluxed for 1 hour in a nitrogen atmosphere. The mixture was cooled to 0° and acidified with acetic acid and ice. The precipitated solid was collected, dried (15·5 g.), and recrystallised from alcohol, yielding *ethyl* 2 : 3 : 4 : 5-*tetrahydro*-4-*keto*-5-*methylpyrrolo*(1′ : 2′-1 : 2)*glyoxaline*-4′-*carboxylate* (X) as colourless leaflets, m. p. 187° (Found : C, 57·9; H, 5·8; N, 13·4. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%). Light absorption (in alcohol) : Max., 2300 and 2600 A.; ε = 21,000 and 9000, respectively. The substance is insoluble in dilute hydrochloric acid and does not form a hydrochloride when treated with hydrogen chloride in anhydrous alcohol–ether. It is soluble in dilute sodium hydroxide and warm sodium carbonate solution, and gives a red colour when warmed with Ehrlich's reagent. This cyclisation can also be effected by refluxing (IX) with an absolute alcoholic solution of one equivalent of sodium for 15 minutes under nitrogen.

Potassium Salt of Hydroxymethylenesuccinonitrile (XI).—A solution of succinonitrile (16 g.) and ethyl formate (16 g.) in anhydrous ether (32 ml.) was gradually added at 0° under an atmosphere of dry nitrogen to a stirred solution prepared from potassium (7·8 g.), absolute ethanol (25 ml.), and anhydrous ether (50 ml.). A yellow precipitate was soon formed, more anhydrous ether (50 ml.) was added, and the mixture allowed to reach room temperature during a few hours. The precipitated cream-yellow *potassium* salt (23 g., 78%) was filtered off, washed with anhydrous alcohol–ether (1 : 3), and dried *in vacuo* (Found : N, 18·5; K, 25·7%; N : K = 2·01 : 1. $C_5H_3ON_2K$ requires N, 19·2; K, 26·7%; N : K = 2 : 1). It may be recrystallised from alcohol by addition of ether, but the solution darkens in spite of operating under nitrogen; the product has m. p. 199°.

N-(*Carbethoxymethyl*)*aminoitaconodinitrile* (XII).—A mixture of the above potassium salt (1·5 g.) and a slight excess of glycine ethyl ester hydrochloride (2 g.) was heated on a boiling water-bath for 1 hour. The melt was extracted with ether and washed with ice-cold dilute alkali and water. The ethereal solution was dried and evaporated, and the residue warmed in oil-pump vacuum to remove volatile material. Distillation of the residual light-brown oil (1·1 g.) was not attempted but it consisted essentially of the desired product (XII) (Found : N, 22·2. Calc. for $C_9H_{11}O_2N_3$: N, 21·75%). Grob and Ankli (*Helv. Chim. Acta*, 1950, **33**, 273) report m. p. 57°.

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