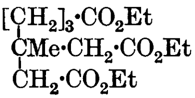
CCCCXXXVII.—*The Formation and Stability of Associated Alicyclic Systems. Part III. The Change from "Meta-" to "Para-" Bridged Rings.*

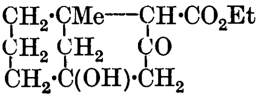
By ERNEST HAROLD FARMER and JOHN ROSS.

BY addition of esters to 1-methyl-Δ^1-*cyclo*hexen-3-one products of three types have been obtained. With ethyl sodiomalonate, the ketone yielded the ester (I) (Farmer and Ross, J., 1925, **127**, 2358), with ethyl sodioacetoacetate the dicyclic ester (II) (Rabe, *Ber.*, 1904, **37**, 1671), and with methyl cyanoacetate and piperidine the ester (III) (Farmer and Ross, this vol., p. 1570). Evidence concerning the formation of (I) by successive stages of addition, "para-" bridging, and fission has been recorded in Part II of this series (*loc. cit.*). Thus not only is the type of ester addition to a Δ^1-*cyclo*hexenone determined by the mode of carrying out the reaction, but the subsequent formation of "meta-" or "para-" bridged rings from "Michael" addition products would appear to be controlled by the specific reactivity of the addendum towards the $\cdot CH_2\cdot CO\cdot$ group of the ketone. The tendency, probably very diverse, to the formation of "meta" and "para" two-carbon bridges would then be compensated by differences in the nature of the added rings. On these grounds, it follows that where the addendum to the *cyclo*hexenone ring carries specific reactants for both methylene and carbonyl groups, as occurs with ethyl cyanoacetate, the type of bridged-ring produced depends on the conditions which exist during the initial addition. The stability of the bridged structures must, owing to their greatly differing constitutions, vary enormously. Working on this basis, we have been able to identify the numerous products derived directly and indirectly by the addition of ethyl sodiocyanoacetate to methyl*cyclo*hexenone.

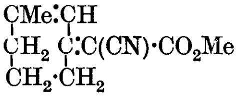


$$\begin{array}{l}[CH_2]_3\cdot CO_2Et\\ CMe\cdot CH_2\cdot CO_2Et\\ CH_2\cdot CO_2Et\end{array}$$

(I.)

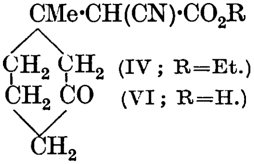


(II.)

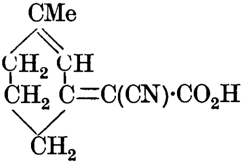


(III.)

The condensation product obtained by heating an alcoholic solution of the sodio-ester with the ketone gave ethyl methyl*cyclo*hexanonecyanoacetate (IV) (21% yield), and a viscous acidic material from which crystals of methyl*cyclo*hexenylidenecyanoacetic acid * (V) separated. The ester (IV) gave the corresponding acid (VI) on hydrolysis with sodium carbonate; both yielded semicarbazones. Thus the neutral conditions existing during the additive reaction had inhibited further cyclisation.



(IV; R=Et.)
(VI; R=H.)



(V.)

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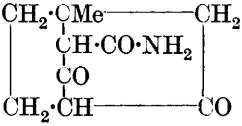
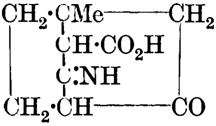
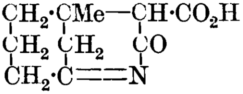
* This acid represents a single geometrical form (maleinoid or fumaroid; m. p. 183°), whereas the ester obtained by condensation of methyl*cyclo*hexenone with ethyl cyanoacetate in the presence of piperidine is a mixture of both forms (acid, m. p. 149°) (Farmer and Ross, *loc. cit.*).

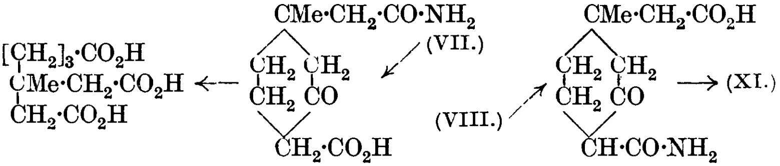
On short heating with hydrochloric acid, however, both ester (IV) and acid (VI) were quantitatively converted into a crystalline substance which gave an intense colour with ferric chloride and agreed in composition and basicity with the formulæ (VII) (enolic), (VIII), and (IX). Of these, (VII) and (VIII), derived by " Dieckmann " and " Thorpe " condensations, respectively, appear to be


(VII.)


(VIII.)

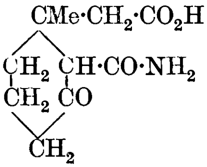

(IX.)

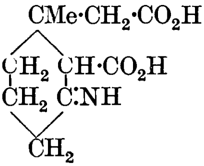
excluded on the grounds of stability and unsuitability of the condensing agent. On the other hand, prolonged boiling with caustic alkali caused quantitative conversion of the crystalline substance into the open-chain acid (XI)—a change which is readily explicable on the dihydroresorcinol formula (VII) (compare Part II, *loc. cit.*), possible with (VIII), but difficult to reconcile with (IX).

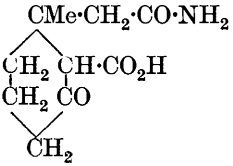


(XI.) (X.) (XII.)

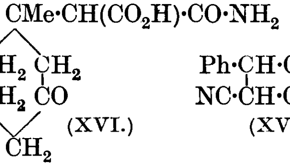
When hydrolysis was interrupted after proceeding for only a few minutes, two substances were obtained—a crystalline, nitrogenous acid (A) and an acidic, nitrogenous gum (B). The latter passed almost entirely into a crystalline, nitrogenous acid (C) on short heating with dilute hydrochloric acid. The two crystalline acids agreed in composition and basicity with the formulæ (X), (XII), (XIII), and (XIV), the last two derivable by an alternative, but less probable fission of (VII) and (VIII). Since neither of the acids gave a colour with ferric chloride, structures (X), (XII), and (XIII) are excluded along with an isomeride (XV) not derivable by fission.

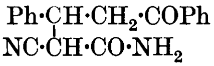

(XIII.)

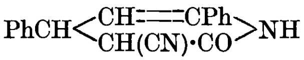

(XIV.)


(XV.)

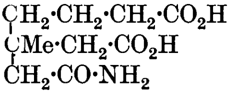
The remaining improbable fission formula (XIV) is an unsuitable representation of either acid. The only alternative formula in which the *cyclo*hexanone ring is preserved is (XVI), and this, not reasonably derivable from (VII) or (VIII) by fission, adequately represented the properties of the acid (A). It appeared, therefore, that (A) must arise by fission of the dicyclic acid (IX), or some other associated ring compound. Concerning (IX), the production of ketonic tetrahydropyridine rings has been brought about by the action of cyanoacetic ester or cyanoacetamide on open-chain ketones. For example, Kohler and Souther (*J. Amer. Chem. Soc.*, 1922, **44**, 2544, 2907), by the interaction of cyanoacetamide with benzylideneacetophenone, obtained the compound (XVII), which passed on treatment with hydrochloric or hydrobromic acid into a substance represented by them as (XVIII). Whilst this and similar substances are regarded by these authors, contrary to the opinion held by Knoevenagel (*Ber.*, 1903, **36**, 2813), as capable of displaying in full the potential tautomeric capacity expressed by the formula, the occurrence of fission by alkali at a nitrogen–carbon double bond, as in (XVIII), does not appear to have been observed. Indeed the main features of these substances are their formation and stability in the presence of halogen acids and their capacity for undergoing simultaneous oxidation and reduction to pyridine and piperidine derivatives.

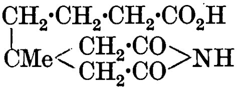

(XVI.)


$$\begin{array}{l} Ph\cdot CH\cdot CH_2\cdot COPh \\ \quad | \\ NC\cdot CH\cdot CO\cdot NH_2 \end{array}$$
(XVII.)


$$PhCH{<}\begin{array}{l} CH{=}CPh \\ CH(CN)\cdot CO \end{array}{>}NH$$
(XVIII.)

If (IX) correctly represents the structure of the dicyclic compound under consideration, hydrolytic fission at the double bond would lead to reversal of the intramolecular condensation and would account for the production of the acid A (XVI) by the use of alkali. Further fission would be brought about only after further intramolecular condensation, and since caustic alkali is the reagent, the latter would probably be of the Dieckmann type, leading to (VII). This would pass on fission into (X) and (XIX) successively, and finally by prolonged hydrolysis to the open-chain tricarboxylic acid (XI). The intermediate compounds which escape complete fission and hydrolysis by alkali should then be obtained in the gum B (above). This consisted almost entirely of a substance agreeing

(XIX.)

$$\begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO_2H \\ | \\ CMe\cdot CH_2\cdot CO_2H \\ | \\ CH_2\cdot CO\cdot NH_2 \end{array}$$


$$\begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO_2H \\ | \\ CMe{<}\begin{array}{l} CH_2\cdot CO \\ CH_2\cdot CO \end{array}{>}NH \end{array}$$
(XX.)

in properties with the formula (XIX); the acid C (above), derived therefrom by short treatment with dilute hydrochloric acid, was the glutarimide (XX). (This imide could not arise from a dicyclic substance of formula VIII.)

It appears certain, therefore, that change from the " meta- " bridged compound (IX) to the " para- " bridged compound (VII) takes place rapidly in alkaline solution. Whilst (IX), however, is extremely stable in acid or neutral solution, the temporary existence of (VII) can only be argued from the nature of its fission products. It is hoped to deal with further factors concerning " meta "-bridging in a subsequent paper.

EXPERIMENTAL.

Condensation of Ethyl Sodiocyanoacetate with 1-*Methyl*-Δ^1-cyclo*hexen*-3-*one*.—The ketone (1 mol.) was added to a cold alcoholic suspension of ethyl sodiocyanoacetate (1 mol.), and the mixture heated for 16 hours on the steam-bath. The cooled product was poured on to ice, acidified with dilute hydrochloric acid, and extracted with ether. The extract was separated into neutral and acidic portions in the usual way.

Ethyl 1-*Methyl*cyclo*hexan*-3-*one*-1-*cyanoacetate* (IV).—The neutral product so obtained yielded on fractionation a small amount of unchanged ketone, but mainly a material, b. p. 160—210°/2 mm. This, on refractionation, gave the pure *ester* as a colourless liquid, b. p. 197°/2 mm. (yield, 21%) (Found: C, 64·3; H, 7·8; N, 6·3. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·6; N, 6·3%). The *semicarbazone* crystallised from aqueous alcohol in long needles, m. p. 166° (Found: C, 57·5; H, 7·3. $C_{13}H_{20}O_3N_4$ requires C, 57·4; H, 7·15%).

Methyl 1-*methyl*cyclo*hexan*-3-*one*-1-*cyanoacetate* was prepared in a similar way and obtained, though in poorer yield, as a viscous, colourless liquid, b. p. 185°/2 mm. (Found: C, 63·15; H, 7·3; N, 6·9. $C_{11}H_{15}O_3N$ requires C, 63·15; H, 7·3; N, 6·7%). The *semicarbazone* crystallised from aqueous alcohol in colourless plates, m. p. 183° (Found: C, 53·8; H, 6·7. $C_{12}H_{18}O_3N_4$ requires C, 54·1; H, 6·8%).

1-*Methyl*cyclo*hexenylidene*-3-*cyanoacetic Acid* (V).—The acidic condensation product was a thick red syrup. Occasional scratching over a period of several weeks promoted partial crystallisation and the semi-solid mass was then ground with acetone–petroleum. The brownish crystals were dissolved in acetone and decolorised by boiling with animal charcoal. From the filtered solution the *acid* crystallised in colourless prisms, m. p. 183° with evolution of gas (Found: C, 67·7; H, 6·3; N, 8·1; *M*, 180; equiv., 179. $C_{10}H_{11}O_2N$ requires C, 67·7; H, 6·3; N, 7·9%; *M*, 177). The acid gave no coloration with ferric chloride and was decomposed on boiling for 1 hour with 10% caustic potash solution into methyl*cyclo*hexenone (semicarbazone, m. p. 199°) and malonic acid.

The methyl ester, obtained from the silver salt and methyl iodide, solidified after distillation (b. p. 165—170°/2 mm.) and crystallised from petroleum in large, flat, colourless prisms (m. p. 60°) which were found by direct comparison to be identical with one form of methyl methyl*cyclo*hexenylidenecyanoacetate (J., 1925, **127**, 2358). Equilibration leading to the mixture of hexenylidene and hexadienyl forms (m. p.'s 74°, 60°, 42°) previously described (*loc. cit.*) was effected with sodium methoxide. The acid which separated from the acidic portion of the condensation product thus represented a single geometrical form.

1-*Methyl*cyclo*hexan*-3-*one*-1-*cyanoacetic acid* was obtained from the corresponding esters by boiling for 2 hours with 10% sodium carbonate solution. Unchanged ester was removed by extraction with ether. By acidification and further extraction, the acid was obtained as a sticky mass which slowly solidified. Recrystallisation from chloroform–petroleum yielded colourless prisms, m. p. 106° (Found: C, 61·3; H, 6·6; N, 7·5. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·6; N, 7·2%).

Propane-$^{1:3}$II$^{2:4}$-6-*keto*-4-*methyl*-3 : 4 : 5 : 6-*tetrahydropyridine*-5-*carboxylic Acid* (IX).—Methyl*cyclo*hexanonecyanoacetic acid dissolved on boiling with 15% hydrochloric acid, but within 15 minutes a bulky, crystalline mass of the dicyclic compound was precipitated. The same compound was also obtained directly from the monocyclic cyanoacetic ester by boiling with a mixture of equal volumes of hydrochloric acid, water, and alcohol for 1½ hours; large, needle-shaped crystals separated which were freed from traces of unchanged ester by washing with ether. In both cases the yields were almost quantitative. The *acid*, which gave a deep purple colour with ferric chloride, melted at 181° after recrystallisation from ethyl acetate (Found: C, 61·5; H, 6·6; N, 7·5; *M*, cryoscopic in acetic acid, 196; equiv., 197. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·6; N, 7·2%; *M*, 195).

Bromination. Bromine (2 mols.) and the dicyclic acid (1 mol.) in chloroform gave a *bromo*-derivative which crystallised in fine needles, m. p. 186°, and developed no colour with ferric chloride (Found: Br, 45·4. $C_{10}H_{13}O_3NBr_2$ requires Br, 45·2%).

Hydrolytic Fission of the Dicyclic Compound (IX).—(a) *Complete fission.* The dicyclic acid was boiled for 20 hours with 10% caustic potash solution (2 equivs.), ammonia being evolved. By extracting the cooled, acidified solution with ether, an oil was obtained which rapidly solidified (yield, almost quantitative); this, m. p. 125°

after recrystallisation, was identified with β-methylpimelic-β-acetic acid by direct comparison.

(b) *Partial fission.* The acid (10 g.) was boiled for 5 minutes only with 10% caustic potash solution (2 equivs.). The solution was immediately cooled, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. From the extract an acid syrup was obtained which, on slight dilution with acetone and vigorous scratching, partly crystallised. The crystals (acid A) were removed, and the acetone was evaporated from the filtrate; the residue was a syrup (acid B).

1-*Methyl*cyclo*hexan*-3-*one*-1-*malonamic Acid* (XVI).—The acid A, which crystallised in stout prisms (yield, 5·8 g.), m. p. 151° with evolution of carbon dioxide, gave no coloration with ferric chloride. It reverted completely to the dicyclic acid (m. p. 181°) on boiling for 15 minutes with 15% hydrochloric acid. By prolonged hydrolysis with caustic potash, it was converted into β-methylpimelic-β-acetic acid (Found: C, 55·95; H, 7·1; N, 7·0; *M*, monobasic, 212·5. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1; N, 6·6%; *M*, 213).

β-*Methylpimelic Acid* β-*Acetamide* (XIX).—The syrup (acid B) consisted almost entirely of this compound. It still contained a very small amount of the above malonamic acid (acid A), but its constitution follows from its basicity (dibasic), the loss of ammonia on heating it with caustic potash, its conversion into the corresponding imide (below), and the production of β-methylpimelic-β-acetic acid on further hydrolysis with caustic potash.

β-*Methylglutarimide*-β-*butyric Acid* (XX).—When the syrup (acid B) was boiled for 1 hour with 15% hydrochloric acid, a few crystals of the dicyclic acid (IX), formed from the malonamic acid (acid A) which had escaped separation, were deposited. They were removed and the solution was evaporated almost to dryness on a steam-bath. The residue slowly deposited crystals which recrystallised from ethyl acetate in colourless, flat needles, m. p. 139° (yield, 4 g.). This substance gave no coloration with ferric chloride and was unchanged on further boiling with hydrochloric acid. Prolonged boiling with caustic potash caused complete conversion into β-methylpimelic-β-acetic acid. The constitution was confirmed by direct comparison with synthetically prepared β-methylglutarimide-β-butyric acid (Found: C, 56·4; H, 7·1; N, 6·9; *M*, monobasic, 212. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1; N, 6·6%; *M*, 213).

Synthesis of β-*Methylglutarimide*-β-*butyric Acid.*—Dry ammonia was bubbled through the molten anhydride of β-methylpimelic-β-acetic acid (Farmer and Ross, *loc. cit.*) at 135°. When the mass became very viscous and absorbed no more gas, it was cooled, dissolved in water, and boiled for 1 hour with 10% hydrochloric acid;

the imide, which crystallised on cooling, separated from ethyl acetate in long, colourless prisms (Found: C, 56·25; H, 7·1; N, 6·7%; *M*, monobasic, 213); these, alone or mixed with the imide obtained by fission (acid C), melted at 139°.

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