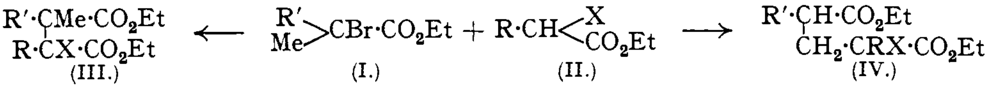
312. *The Condensation of Ethyl α-Bromo*iso*butyrate with* n-*Alkylmalonic Esters. A Note on the Structure of the Lupin Alkaloids.*

By H. N. Rydon.

Bone and Sprankling (J., 1899, **75**, 839) showed that, when α-bromo-esters (I) were condensed with sodioalkylmalonic esters (II; $X = CO_2Et$) in alcoholic solution, the product contained not only the expected carbethoxysuccinic ester (III; $X = CO_2Et$), but also, and sometimes in preponderating amount, the isomeric carbethoxyglutaric ester (IV; $X = CO_2Et$).



$$\begin{array}{c} R'\cdot\overset{|}{C}Me\cdot CO_2Et \\ R\cdot\underset{}{C}X\cdot CO_2Et \end{array} \longleftarrow \begin{array}{c} R' \\ Me \end{array}\!\!>CBr\cdot CO_2Et + R\cdot CH\!\!<\!\!\begin{array}{l} X \\ CO_2Et \end{array} \longrightarrow \begin{array}{l} R'\cdot\overset{|}{C}H\cdot CO_2Et \\ CH_2\cdot CRX\cdot CO_2Et \end{array}$$

(III.) (I.) (II.) (IV.)

Reactions of this type have been extensively employed in synthetic work for the production of compounds of type (III) and Ing (J., 1933, 504) employed the reaction for the synthesis of a compound of type (IV). Owing to the possibility of confusion arising from the use of this process it appeared desirable to inquire more deeply into the structural factors governing its course. Particular attention has been paid to the effect of variations in R.

Bone and Sprankling (*loc. cit.*) estimated the proportion of (III) and (IV) in their products by hydrolysis and decarboxylation to the corresponding dibasic acids, which were readily separated by means of their calcium salts, that of the substituted succinic acid (from III) being considerably the less soluble. This method has been found to be fairly satisfactory and the results are summarised in the following table :

(II.)	% " Succinic " (III).*	% " Glutaric " (IV).*	Observer.†
Ethyl malonate	66	33	B.S.
Ethyl methylmalonate	0 0 } 0	100 100 } 100	B.S. ; R.
Ethyl ethylmalonate	0	100	R.
Ethyl *n*-propylmalonate	9	91	R.
Ethyl *n*-butylmalonate	35	65	R.
Ethyl *n*-amylmalonate	47, 43 53, 49 } 48	53, 57 47, 51 } 52	R.

* These percentages are calculated on the total dicarboxylic acid isolated.
† B.S. = Bone and Sprankling, *loc. cit.*; R. = this paper.

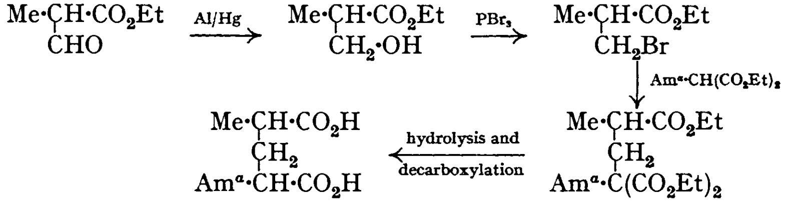
Consideration of these results together with the other results of Bone and Sprankling (*loc. cit.*) leads to three main conclusions regarding the influence of the nature of R, R′ and X on the relative proportion of (III) and (IV). First, the proportion of (IV) increases as X becomes successively CO·CH$_3$, CN, and CO$_2$Et. Secondly, when R = Me the formation of (IV) is favoured more than when R = H; but, as R becomes successively Et, Pr^a, Bu^a, and Am^a, the proportion of (IV) diminishes in a tolerably regular manner. Thirdly, when R′ = Me, (IV) is formed to a greater extent than when R′ = H.

Owing to the complex nature of the reactions involved, it is not possible to put forward, with any degree of certainty, a theoretical explanation of the phenomena outlined above. From the practical point of view, however, it is evident that reactions of this type must be used in synthetic work with some caution; the results of Lawrence (P., 1901, **16**, 154) suggest that they may be employed with more confidence when carried out in hydrocarbon solvents.

Ing (*loc. cit.*) had to a large extent based his structures for anagyrine, lupanine and sparteine on the supposed identity of his synthetic " α-methyl-α′-*n*-amylglutarimide " with the imide, $C_{11}H_{19}O_2N$, obtained by the degradation of anagyrine, and Clemo and Raper (J., 1933, 644) advanced alternative formulæ for the last two alkaloids which were also, in principle, based on this identity. Since the work here described demonstrated that Ing's synthetic material was not homogeneous, it appeared desirable to synthesise the isomeric αα-dimethyl-α′-*n*-amylsuccinic and α-methyl-α′-*n*-amylglutaric acids and their imides for direct comparison with the material obtained from anagyrine.

To this end ethyl α-cyano-α′α′-dimethylsuccinate, of the homogeneity of which there is no doubt (Bone and Sprankling, *loc. cit.*; E. H. Ingold, J., 1925, **127**, 470), was condensed with *n*-amyl bromide, and the resulting ***ethyl* α*-cyano-*α′α′*-dimethyl-*α-n*-amylsuccinate*** hydrolysed and decarboxylated to ***αα-dimethyl-α′-*n*-amylsuccinic acid***, m. p. 119°, which was identical with that separated from the mixture obtained from ethyl α-bromo*iso*butyrate and ethyl *n*-amylmalonate. ***αα-Dimethyl-α′-*n*-amylsuccinimide***, prepared from the synthetic acid, had m. p. 64—65° and this was depressed to 53—57° on admixture with the imide obtained from anagyrine (which melted at 58—60° *), a specimen of which was kindly provided by Dr. Ing.

cis-***α-Methyl-α′-*n*-amylglutaric acid*** was synthesised by the following series of reactions :



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* Dr. Ing (*loc. cit.*, p. 509) records m. p. 52—54°; he has since confirmed the amended m. p. given above.

The product was identical with that isolated from the mixture obtained from ethyl *n*-amylmalonate and ethyl α-bromo*iso*butyrate, having m. p. 74—75°. cis-α-*Methyl*-α′-n-*amylglutarimide*, prepared from this acid, had m. p. 71—72° and on admixture with the imide from anagyrine, raised its m. p. to 59—64°. Although, owing to the apparent non-homogeneity of the imide from anagyrine, the evidence is not wholly satisfactory, it may be concluded that this is, in all probability, α-methyl-α′-*n*-amylglutarimide, and, hence, that the constitutions assigned to the lupin alkaloids by Ing and by Clemo and Raper (*loc. cit.*) are well founded in this particular.*

EXPERIMENTAL.

Ethyl α-bromo*iso*butyrate, prepared from *iso*butyric acid, was redistilled; b. p. 58°/12 mm.

Condensations (1)—(5) were carried out in the following manner: 0·05 G.-mol. of the alkylmalonic ester was added to sodium ethoxide (sodium, 1·15 g.; absolute alcohol, 15 c.c.), and 0·05 g.-mol. of ethyl α-bromo*iso*butyrate added to the mixture. After refluxing for 48 hours, the product was poured into water, acidified, and extracted with ether. After removal of the ether from the dried extract the residue was fractionated. The low fractions were in all cases identified as mainly unchanged initial materials.

(1) *Condensation with Ethyl Methylmalonate.*—The principal product was an oil, b. p. 150—154°/11 mm., 8 g. (61%). A low fraction consisted of ethyl α-bromo*iso*butyrate (35%), containing, presumably, some ethoxy-ester (Found: Br, 30·2. Calc. for $C_6H_{11}O_2Br$: Br, 41·0%).

8 G. of the condensation product were refluxed for 15 hours with 10 g. of potassium hydroxide in 35 c.c. of water. Extraction of the acidified solution with ether and evaporation of the dried extract left an oil which readily solidified in a vacuum; 5·7 g. (100%), m. p. (tiled) 157—160° (decomp.). 5 G. of this tricarboxylic acid were heated at 160—180° for 30 minutes, copious evolution of carbon dioxide taking place. The residue readily solidified in a vacuum desiccator; 3·5 g. (95%), m. p. (tiled) 94—98°. After being converted into the ammonium salt, it gave no precipitate with hot calcium chloride solution, indicating the absence of trimethylsuccinic acid. Furthermore, treatment with acetyl chloride (Auwers and Thorpe, *Annalen*, 1895, **285**, 311) yielded only *cis*-αα′-dimethylglutaric anhydride, m. p. 94°, and *trans*-αα′-dimethylglutaric acid, m. p. 140°.

(2) *Condensation with Ethyl Ethylmalonate.*—8·5 G. (63%) of condensation product, b. p. 158—161°/13 mm., were obtained. 8 G. of it, treated (48 hours) with potassium hydroxide solution as described under (1), afforded 5·8 g. (100%) of an oil which readily solidified in a vacuum. This, heated at 160—180° for 30 minutes, lost carbon dioxide; the product readily solidified in a vacuum, m. p. (tiled) 65—70°; 4·05 g. (88%). As ammonium salt it gave no precipitate with boiling calcium chloride solution, thus being free from αα′-dimethyl-α′-ethylsuccinic acid.

1·39 G. of the acid were heated on the steam-bath for 30 minutes with 1·5 c.c. of acetyl chloride. The excess of acetyl chloride was removed in a vacuum over sodium hydroxide, and the residue heated at 200° with 0·5 g. of urea for 15 minutes. The cooled product was triturated with sodium bicarbonate solution, and the insoluble material filtered off; on recrystallisation from petroleum (b. p. 80—100°) cis-α-*methyl*-α′-*ethylglutarimide* was obtained in long hair-like needles, m. p. 116° (Found: C, 62·0; H, 8·5; N, 9·2. $C_8H_{13}O_2N$ requires C, 61·9; H, 8·4; N, 9·0%). This was refluxed overnight with concentrated hydrochloric acid; on cooling, pure *cis*-α-methyl-α′-ethylglutaric acid crystallised in needles, m. p. 63°. The sodium bicarbonate filtrate from the crude imide was acidified and extracted with ether. Evaporation of the dried extract yielded *trans*-α-methyl-α′-ethylglutaric acid, which, crystallised from light petroleum (b. p. 60—80°), had m. p. 107°. The *cis*- and the *trans*-isomer appeared to be present in about equal amounts.

(3) *Condensation with Ethyl* n-*Propylmalonate.*—9·5 G. (60%) of condensation product were obtained, b. p. 163—166°/14 mm. 8·5 G. of it, by the treatment (7 days) with potassium hydroxide solution, gave an oil which readily solidified, m. p. (tiled) 143—145°. This was decarboxylated by heating at 160° for 30 minutes. The product became only semi-solid in a vacuum desiccator after 10 days. 2·14 G. were dissolved in water, made alkaline with aqueous ammonia, and boiled with excess of 25% calcium chloride solution. The precipitated calcium salt was collected hot and dissolved in hydrochloric acid; ether then extracted 0·17 g. (8·0%)

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* Since this paper was submitted for publication this conclusion has been amply confirmed by the synthesis of *dl*-oxysparteine (Clemo, Morgan, and Raper, this vol., p. 1025).

of an oil which solidified in a vacuum; crystallisation from water yielded αα-dimethyl-α′-*n*-propylsuccinic acid, m. p. 145°.

The filtrate from the calcium salt was acidified and extracted with ether. Evaporation of the dried extract left 1·88 g. (87·5%) of a sticky mass. 1·19 G. of this were refluxed for 20 minutes with 2 c.c. of acetyl chloride. After exposure to sodium hydroxide in a vacuum desiccator the residue was heated at 150—200° for 50 minutes with 0·5 g. of urea. The cooled material was triturated with sodium bicarbonate solution; the filtered liquid, on acidification and extraction with ether, afforded a small amount of impure *trans*-α-methyl-α′-*n*-propylglutaric acid, m. p. 95°. The insoluble material was recrystallised from light petroleum (b. p. 60—80°), cis-*α-methyl-α′-*n-*propylglutarimide*, m. p. 78° (Found: N, 8·2. $C_9H_{15}O_2N$ requires N, 8·3%), being obtained in good yield. The imide was refluxed with concentrated hydrochloric acid for 10 hours; extraction with ether afforded *cis*-α-methyl-α′-*n*-propylglutaric acid, m. p. 53° after one crystallisation from light petroleum.

(4) *Condensation with Ethyl* n-*Butylmalonate*.—A 64% yield of condensation product, b. p. 173°/14 mm., was obtained. 10 G. were refluxed for 11 days with a solution of 20 g. of potassium hydroxide in 20 c.c. of water. From the acidified solution, ether extracted an oil, which was decarboxylated by heating at 140—160° for 25 minutes. Separation of 4·03 g. of the decarboxylation product by means of the calcium salts in the usual manner afforded 1·34 g. (33%) of *αα-dimethyl-α′-*n-*butylsuccinic acid* [Found: equiv. (by titration), 102·2. $C_{10}H_{18}O_4$ (dibasic) requires equiv., 101·1] and 2·51 g. (62%) of *α-methyl-α′-*n-*butylglutaric acid* [Found: equiv. (by titration), 102·0. $C_{10}H_{18}O_4$ (dibasic) requires equiv. 101·1]. Both substances were thick oils which neither solidified nor gave solid derivatives.

(5) *Condensation with Ethyl* n-*Amylmalonate*.—11 G. (64%) of condensation product, b. p. 140—145°/1—2 mm. were obtained. 11 G. were refluxed for 100 hours with a solution of potassium hydroxide (12 g.) in water (40 c.c.). Extraction of the acidified solution and evaporation of the dried extract afforded an oil, which solidified in a vacuum; m. p. 105—115°. This was decarboxylated by heating at 150° for an hour. The product, after standing in a vacuum for some weeks, deposited leaflets, m. p. 70—72°. These were recrystallised from light petroleum and identified as *cis*-α-methyl-α′-*n*-amylglutaric acid, m. p. and mixed m. p. 76°.

1·15 G. of the decarboxylation product were dissolved in 100 c.c. of boiling water and submitted to the ammonia–calcium chloride treatment. The precipitated calcium salt was collected hot and dissolved in dilute hydrochloric acid; ether extracted 0·52 g. (45%) of " succinic " acid. The filtrate was acidified and treated similarly, 0·57 g. (50%) of " glutaric " acid being obtained. Four independent separations gave 45 and 50, 53 and 47, 43 and 56, 48 and 49% of " succinic " and " glutaric " acid respectively. The " succinic " acid readily solidified in a vacuum and, on recrystallisation from water containing a little alcohol, αα-dimethyl-α′-*n*-amylsuccinic acid was obtained in flattened needles, m. p. 119°, unchanged on admixture with the synthetic product (below). The " glutaric " acid solidified in a vacuum and, on recrystallisation from water, afforded cis-*α-methyl-α′-*n-*amylglutaric acid* [Found: C, 61·0; H, 9·3; equiv. (by titration), 108·4. $C_{11}H_{20}O_4$ (dibasic) requires C, 61·1; H, 9·3%; equiv., 108·1] in feathery aggregates of plates, m. p. 76°. No *trans*-acid was detected in the product.

(6) *Synthesis of αα-Dimethyl-α′-*n-*amylsuccinic Acid*.—Ethyl-α′-cyano-αα-dimethylsuccinate (Bone and Sprankling, J., 1899, **75**, 839) (16 g.) was added to sodium ethoxide (from sodium, 1·6 g., and absolute alcohol, 20 c.c.), followed by 11 g. of *n*-amyl bromide. The mixture was refluxed overnight and worked up in the usual manner, 13 g. (60%) of *ethyl α-cyano-α′α′-dimethyl-α-*n-*amylsuccinate* being obtained as a viscous oil, b. p. 187—191°/22 mm., 137°/0·9 mm. (Found: N, 4·9. $C_{16}H_{27}O_4N$ requires N, 4·7%). 13 G. of this ester were refluxed for 48 hours with a solution of 30 g. of potassium hydroxide in 30 c.c. of water. Extraction of the acidified solution afforded 8 g. of a sticky nitrogenous material; this was refluxed overnight with 50 c.c. of concentrated hydrochloric acid. On cooling, 5·9 g. (62%) of crude acid separated, and on recrystallisation from water containing a little alcohol afforded *αα-dimethyl-α′-*n-*amylsuccinic acid* in flattened needles, m. p. 119° [Found: C, 61·5; H, 9·5; equiv. (by titration), 108·5. $C_{11}H_{20}O_4$ (dibasic) requires C, 61·1; H, 9·3%; equiv., 108·1].

(7) *Synthesis of α-Methyl-α′-*n-*amylglutaric Acid*.—40 G. of ethyl α-formylpropionate (Wheeler and McFarland, *Amer. Chem. J.*, 1910, **43**, 22) were dissolved in 300 c.c. of wet ether, and 10 g. of aluminium amalgam added. After 12 hours, the alumina was removed and washed with ether. Evaporation of the dried filtrate and washings left an oil which, on distillation, yielded 30 g. (60%) of ethyl β-hydroxy*iso*butyrate, b. p. 81—82°/12 mm. 14 G. of this ester were dissolved in 10 c.c. of chloroform, 21 g. of phosphorus tribromide in 15 c.c. of chloroform added dropwise, with shaking, during 45 minutes, and the mixture heated on the steam-bath for 2

hours and poured into water. Extraction with chloroform, followed by drying and distillation, yielded 6 g. (30%) of *ethyl* β-*bromo*iso*butyrate*, b. p. 91—93°/19 mm. (Found: Br, 40·8. $C_6H_{11}O_2Br$ requires Br, 41·0%). 7 G. of ethyl β-hydroxy*iso*butyrate were dissolved in 14 c.c. of dry ether, and 11 g. of phosphorus pentachloride added slowly to the ice-cooled solution. The mixture was refluxed on the steam-bath overnight, poured on ice, and extracted with ether. Distillation of the dried extract afforded 3 g. (40%) of *ethyl* β-*chloro*iso*butyrate*, b. p. 56—58°/10 mm. (Found: Cl, 23·6. $C_6H_{11}O_2Cl$ requires Cl, 23·6%).

7 G. of ethyl *n*-amylmalonate were added to sodium ethoxide (from sodium, 0·7 g., and absolute alcohol, 10 c.c.), followed by 6 g. of sodium iodide and 6 g. of ethyl β-bromo*iso*butyrate, and the whole was refluxed overnight. Ethyl α'-carbethoxy-α-methyl-α'-*n*-amylglutarate (4 g.; 40%), isolated in the usual manner, had b. p. 140—145°/3 mm. Use of the chloro-ester gave even poorer yields. 4 G. of the tricarboxylic ester were refluxed with 5 g. of potassium hydroxide in 20 c.c. of water for 70 hours. The product was acidified and extracted with ether. The gummy material obtained by evaporation of the dried extract was heated at 160—180° for 30 minutes. The product contained much tar but partly solidified on long standing in a vacuum desiccator. Recrystallisation of the solid from water afforded a small amount of α-methyl-α'-*n*-amylglutaric acid, m. p. 74—75°.

(8) *Preparation of Imides.—αα-Dimethyl-α'-*n*-amylsuccinimide.* 0·5 G. of αα-dimethyl-α'-*n*-amylsuccinic acid was refluxed for 30 minutes with 2 c.c. of acetyl chloride. After exposure to sodium hydroxide in a vacuum the product was heated at 160—200° for 1 hour with 0·2 g. of urea and then triturated with sodium bicarbonate solution. Recrystallised from light petroleum, *αα-dimethyl-α'-*n*-amylsuccinimide* was obtained in felted masses of prismatic needles, m. p. 64—65° (Found: N, 7·2. $C_{11}H_{19}O_2N$ requires N, 7·1%).

*α-Methyl-α'-*n*-amylglutarimide.* Similar treatment of 0·5 g. of *cis*-α-methyl-α'-*n*-amylglutaric acid (45 minutes; 1 c.c. of acetyl chloride) gave a product, which was heated at 180—190° for 20 minutes with 0·1 g. of urea and dried in a vacuum. Crystallisation from light petroleum yielded *α-methyl-α'-*n*-amylglutarimide* in felted masses of hair-like needles, m. p. 71—72° (Found: N, 7·3. $C_{11}H_{19}O_2N$ requires N, 7·1%).

A mixture of the two imides had m. p. 52—56°.

*Imide from the condensation product of ethyl α-bromo*iso*butyrate and ethyl *n*-amylmalonate.* The crude dicarboxylic acid (p. 1447) was converted as described above into the imide, m. p. 53—57°. No effective separation was brought about by fractional crystallisation from light petroleum, five final fractions having m. p. 56—62°, 50—55°, 50—54°, 55—57°, and 51—58°. The initial product was mechanically separated into stout prismatic needles, m. p. 64—65°, and thin hair-like needles, m. p. 69°. A mixture of the two had m. p. 57—60°.

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