431. *A New Reaction Mechanism for the Marckwald Asymmetric Synthesis.*

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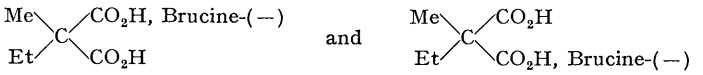
The alkaloidal salts of various optically active malonic acid derivatives have been found to yield optically inactive decarboxylation products. The formal resemblance of some of these experiments to the Marckwald asymmetric synthesis led to proposal of a new reaction mechanism for this reaction. According to this, decarboxylation of a dialkaloidal salt of a disubstituted malonic acid should yield an optically active decarboxylation product. Partial asymmetric syntheses of this type, where there is no possibility of an asymmetric transformation during the crystallisation process, have been carried out.

THE Marckwald asymmetric synthesis * (*Ber.*, 1904, **37**, 349) consisted in thermal decarboxylation of the monobrucine salt of ethylmethylmalonic acid to give, after purification,

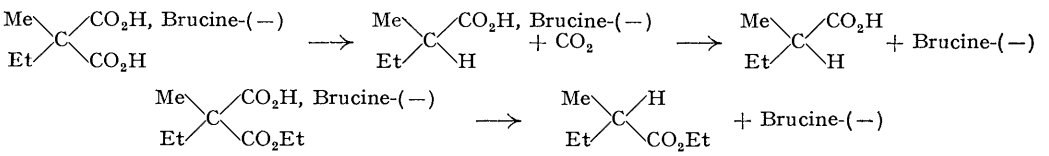
* The experiment should be described as a " partial asymmetric synthesis," but the name " Marckwald asymmetric synthesis " will be retained throughout when reference is made to the classical experiment.

an ethylmethylacetic acid about 10% enriched in the lævorotatory modification. To account for the success of this experiment numerous explanations have been advanced (Marckwald, *loc. cit.*; Cohen and Patterson, *ibid.*, p. 1012; Marckwald, *ibid.*, p. 1368; Euler, *Allgem. Chem. Enzyme*, 1907, **6**, 243, 1071; Erlenmeyer, *Biochem. Z.*, 1914, **64**, 366; Kortüm, *Samml. Chem. Vortr.*, 1932, **10**, 97; Eisenlohr and Meier, *Ber.*, 1938, **71**, 1004; Ritchie, *Adv. Enzymology*, 1947, **7**, 100). In all these theories it was either stated or implied that the success of the experiment depended upon either the crystallisation from solution of one of the two salts

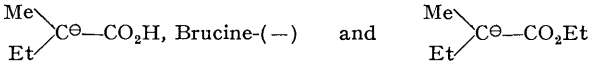


in excess of the other, or the differing rates of decarboxylation of these two molecules.

It was shown (Kenyon and Ross, *J.*, 1951, 3407) that the decarboxylation of optically active ethyl hydrogen ethylmethylmalonate, ethylmethylcyanoacetic acid, and α-benzyl-α-cyanopropionic acid gave rise to optically inactive decarboxylation products. The decarboxylation has now been studied of various alkaloidal salts of these optically active compounds. In all cases the products of decarboxylation were optically inactive. A formal resemblance between some of these experiments and the Marckwald asymmetric synthesis exists:



The interesting feature of a comparison between these two experiments is that whereas the optical purity of the molecule undergoing decarboxylation in the Marckwald asymmetric synthesis is indeterminate, it gives rise to a partially optically active decarboxylation product, whereas the optically pure alkaloidal salt in the second experiment gives rise to an optically inactive decarboxylation product. The most important chemical difference between the two decarboxylation experiments lies in the fact that the first decarboxylation product is an acid, and is isolated as the alkaloidal salt, whereas the second decarboxylation product is an ester and is therefore not in chemical combination with the alkaloid. The activity or inactivity of the products could be explained if it were to be assumed that the decarboxylation reactions occur with the intermediate formation of the two carbanions

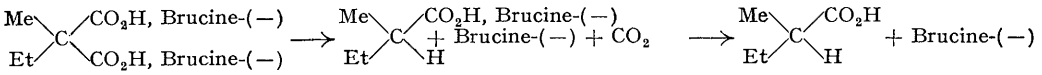


The combination of these two carbanions with a proton would, in the first case, produce diastereoisomerides, which in general have differing rates of formation, and in the second case lead to the formation of stereoisomers.

If such a carbanion is formed during a Marckwald asymmetric synthesis, clearly the effects of a partial asymmetric transformation during crystallisation and of the differing rates of decarboxylation of the two isomeric brucine salts would be nullified, at this stage of the experiment, by the formation of a common carbanion from both these forms. It should also be possible to carry out a new type of partial asymmetric synthesis by the decarboxylation of a neutral alkaloidal salt of a disubstituted malonic acid, provided that this can be achieved under comparably mild experimental conditions. In such an experiment, the symmetrical nature of the molecule makes an asymmetric transformation during crystallisation impossible.

Accordingly the dibrucine salt of ethylmethylmalonic acid was submitted to thermal decarboxylation. Decarboxylation occurred readily at the melting point of the salt (151—153°), and also after acidification, extraction, and purification an ethylmethylacetic

acid was obtained which contained about 10% excess of the lævorotatory modification (three experiments gave 8·5, 11·0, and 12·6%).



Lest the approximate agreement with the results from a Marckwald asymmetric synthesis was fortuitous, an experiment was performed with methylphenylmalonic acid, which had been shown by Eisenlohr and Meier (*loc. cit.*) to give a partially optically active hydratropic acid of a lower order of optical purity (0·2%) on thermal decarboxylation of its brucine salt. Dibrucine methylphenylmalonate was submitted to thermal decarboxylation. The isolated hydratropic acid was about 1·6% optically pure. This experiment shows that, although there need not in general be any relation between the optical purity of an acid obtained by a Marckwald asymmetric synthesis and that isolated after decarboxylation of a dialkaloidal salt, this second type of partial asymmetric synthesis may nevertheless be of general applicability.

Experimental

(+)-Ethyl quinine and (−)-ethyl cinchonidine ethylmethylmalonate, strychnine (−)-ethylmethylcyanoacetate, and brucine (±)- and (−)-α-benzyl-α-cyanopropionate were prepared as described previously (*J.*, 1951, 3409).

Decarboxylation of (+)-Ethyl Quinine Ethylmethylmalonate.—The salt (3·5 g.), m. p. 98—110°, was heated at 110—120° in a distillation flask until distillation ceased (about 1 hour). The distillate (ethyl α-methylbutyrate), n_D^{22} 1·3948 (1·1 g.), was devoid of optical activity in ether (*l*, 2; *c*, 5·2) and in the homogeneous state (*l*, 0·5) (Found: equiv., by saponification: 129. Calc. for $C_7H_{14}O_2$: equiv., 130).

Decarboxylation of Cinchonidine (−)-Ethyl Ethylmethylmalonate.—The salt (4·0 g.), m. p. 155—156°, was heated at 160—170° until distillation ceased. The distillate (1·2 g.) had n_D^{22} 1·3944 and α 0° in ether (*l*, 2; *c*, 5·0) and in the homogeneous state (*l*, 0·5) (Found: equiv., 130. Calc. for $C_7H_{14}O_2$: equiv., 130).

Decarboxylation of Strychnine (+)-Ethylmethylcyanoacetate.—The salt (8·0 g.), m. p. 127—130°, was heated at 150° until distillation ceased (about 1 hour). The colourless distillate (1·2 g.) was purified by extraction with dilute sodium hydrogen carbonate solution. The isolated nitrile, n_D^{25} 1·3897, micro-b. p. 124°, had α 0° in the homogeneous state (*l*, 0·5) and in ether (*l*, 2; *c*, 7·2).

Decarboxylation of Brucine (+)-α-Benzyl-α-cyanopropionate.—The salt (4·0 g.), m.p. 135—137°, was heated at 150°/18 mm. until distillation ceased (about 1 hour). The distillate of α-benzylpropionitrile (1·0 g.), n_D^{25} 1·5093, had α 0° in the homogeneous state (*l*, 0·5) and in ether (*l*, 2; *c*, 8·4). The nitrile (1·0 g.) was converted into (±)-benzylmethylacetamide [(±)-α-benzylpropionamide] by alkaline hydrolysis. Recrystallisation from aqueous alcohol gave needles (0·95 g.), m. p. 104·5—105·5°.

Decarboxylation of Brucine (−)-α-Benzyl-α-cyanopropionate.—The salt (4·0 g.), m. p. 127—129°, was heated at 150°/18 mm. until distillation ceased (about 1 hour). The distillate (1·0 g.), n_D^{25} 1·5094, had α 0° in the homogeneous state (*l*, 0·5) and in ether (*l*, 2; *c*, 8·7).

Dibrucine Ethylmethylmalonate.—Ethylmethylmalonic acid, prepared from ethyl malonate in 61% yield and twice recrystallised from ether–light petroleum, formed needles, m. p. 116—118° (decomp.) (0·2259 g. required 31·00 ml. of 0·1N-NaOH. Calc. for $C_6H_{10}O_4$: 30·94 ml.). To the acid (10·2 g.) in aqueous acetone (150 c.c. of 50%) was added brucine (55·1 g.; dried at 105° for 6 hours), and the whole warmed until dissolution was complete. After 3 days at room temperature the *salt* (42 g.) was deposited as colourless needles. After drying *in vacuo* over phosphoric oxide for 6 hours it had m. p. 151—153° (decomp.), $[\alpha]_D^{20·5}$ −51·8° (*l*, 2; *c*, 5·41 in chloroform). Recrystallisation from aqueous acetone gave needles (40 g.), m. p. 151—153° (decomp.), and $[\alpha]_D^{20·5}$ −52·7° (*l*, 2; *c*, 5·51 in chloroform), after drying (Found: C, 63·8; H, 7·0; N, 5·7. $C_{52}H_{62}O_{12}N_4$ requires C, 64·2; H, 6·7; N, 6·0%).

Decarboxylation of Dibrucine Ethylmethylmalonate.—(i) The salt (50 g.), heated at 160—180° in a flask fitted with an air-condenser, melted with evolution of carbon dioxide which was complete in 2 hours. The product, a pale brown, glassy solid, was dissolved in dilute hydrochloric acid, and the solution extracted four times with ether. The combined ethereal extracts were washed twice with dilute hydrochloric acid and once with water. Evaporation of the dried

(Na_2SO_4) ethereal solution gave a liquid residue (4·7 g.), $\alpha_D^{21\cdot5}$ −0·70° (*l*, 0·5), n_D^{25} 1·4029. Distillation (b. p. 173—175°) gave a product, $\alpha_D^{21\cdot5}$ −0·74° (*l*, 0·5), n_D^{25} 1·4029 (0·2453 g. required 24·05 ml. of 0·1N-NaOH. Calc. for $C_5H_{10}O_2$: 24·05 ml.). The acid (0·5 g.) was converted into the *p*-bromophenacyl ester (0·9 g.), needles (from aqueous alcohol), m. p. 54—55°, alone or mixed with the authentic ester of ethylmethylacetic acid. The alkaloid was recovered unchanged from the hydrochloric acid extracts of the product by treatment with ammonia. Prolonged drying of the product, first *in vacuo* over phosphoric oxide and finally in an air oven at 105°, gave a slightly discoloured product (42 g.), characterised by m. p., mixed m. p., and specific rotation.

(ii) The decarboxylation was repeated with 50 g. of the salt, but at > 156° (vapour of boiling *cyclo*hexanone). The salt slowly melted with effervescence, which was complete after 6 hours. The decarboxylation products, isolated and identified as before, gave an acid, b. p. (after distillation) 173—175°, α_D^{22} −0·96° (*l*, 0·5), n_D^{25} 1·4026, or, in a third experiment, b. p. 76—77°/15 mm., α_D^{21} −1·10° (*l*, 0·5), n_D^{25} 1·4028.

Dibrucine Methylphenylmalonate.—Methylphenylmalonic acid (18·2 g.), needles, m. p. 155—157° (decomp.) (0·2209 g. required 22·75 ml. of 0·1N-NaOH. Calc. for $C_{10}H_{10}O_4$: 22·77 ml.), and brucine (dried at 105° for 6 hours; 73·9 g.) in aqueous methanol were warmed until dissolution was complete. After several weeks at room temperature the salt (73 g.) had been deposited as colourless needles, m. p. 82—85° (decomp.). Recrystallisation from the same solvent gave needles, m. p. 88—89° (decomp.) after drying *in vacuo* at 61°.

Decarboxylation of Dibrucine Methylphenylmalonate.—The salt (48 g.), heated at 140° in a flask fitted with an air-condenser, melted with evolution of carbon dioxide which was complete in 4 hours. The acidic component (6·7 g.) and the alkaloid (40·0 g.) were recovered and purified as in the previous experiment. The isolated hydratropic acid, after distillation (b. p. 153—155°/20 mm.), had α_D^{20} +0·85° (*l*, 0·5; homogeneous), +1·65° (*l*, 2; *c*, 2·9 in ether) (optical purity 1·6%, calc. on figures of Arcus and Kenyon, *J.*, 1939, 916) (0·2036 g. required 13·48 ml. of 0·1N-NaOH. Calc. for $C_9H_{10}O_2$: 13·57 ml.). A portion of the acid (1·0 g.) was converted by the usual method into the amide, colourless plates (0·95 g.) (from chloroform–light petroleum), m. p. 92—93°.

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