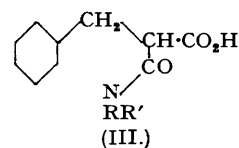
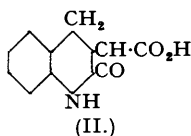
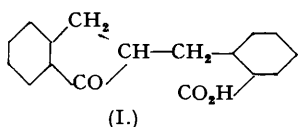


222. Asymmetric Transformations with Benzylmalonoanilic Acids.

By EDNA M. DAVIDSON and E. E. TURNER.

Second-order asymmetric transformations have been shown to occur with benzylmalonoanilic and benzylmalono-*o*-toluidic acids. First-order asymmetric transformations were not observed.

"FIRST-ORDER" asymmetric transformation, as re-defined by Jamison and Turner (J., 1942, 437) in modification of Kuhn's original definition (*Ber.*, 1932, 65, 49), embraces the experimental observations of several authors, notably those of Read and McMath (J., 1925, 1572; hydroxyhydrindamine salts of chlorobromomethanesulphonic acid) and of Mills and Elliott (J., 1928, 1291; brucine salts of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine). The generalisations made by Jamison and Turner (J., 1938, 1646; 1940, 264; 1942, 427) were the result of the discovery and examination of many examples of first-order asymmetric transformation of salts of alkaloids with acids the optical instability of which depended on the presence of restricted rotation within the molecule. A fairly comprehensive analysis has thus been made for first-order asymmetric transformation associated with restricted rotation. Optical instability can also arise by a tautomeric process for which experimental data are meagre. Thus, although two excellent examples of second-order asymmetric transformation were observed with the alkaloidal salts of 2-*o*-carboxybenzyl-1-hydrindone (I) (Leuchs and Wutke, *Ber.*, 1913, 46, 2420), and hydrocarbostyryl-3-carboxylic acid (II) (Leuchs, *Ber.*, 1921, 54, 830), no observations classifiable as first-order asymmetric transformation were made.



In selecting possible experimental material for such a study we rejected both of Leuchs' acids since the first proved to be very sparingly soluble in organic solvents and the second was an isolated member of a series and, moreover, difficult to obtain (Ingold and Wilson, J., 1934, 773). We eventually chose the benzylmalonoanilic acid series, which bears certain obvious structural relationships to the hydrocarbostyryl acid.

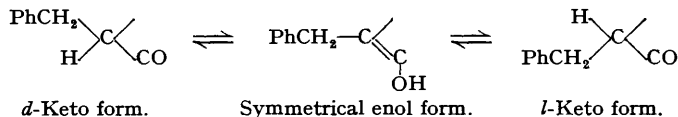
Benzylmalonoanilic acid itself (III; R = H, R' = Ph) is readily obtained by an adaptation of Chattaway's method (J., 1910, 97, 940). When a mixture of ethyl benzylmalonate and aniline (1.5 : 1 mols.) was boiled, 40% of the aniline was converted into the mono- and 60% into the di-anilide. These were readily separable and the purification of the anilic acid was facilitated owing to the sparing solubility of the sodium salt (IV, below). In alcoholic solution, the brucine salt of *dl*-benzylmalonoanilic acid underwent second-order asymmetric transformation; 83% of the material dissolved separating as optically pure brucine *l*-benzylmalonoanilate. This transformation, as might be expected, was accelerated by heating. A chloroform solution of the brucine salt showed mutarotation as a first-order change, for which *k* at 25.00° was approximately 0.078 (log₁₀ : mins.⁻¹; all values for *k* are in these units). *dl*-Benzylmalonoanilic acid being very sparingly soluble in chloroform, "activation" experiments could not be made using this solvent, but equimolecular mixtures of acid and brucine in acetone or in dioxan showed no mutarotation, and it may be concluded that the above mutarotation in chloroform represents conversion into the partial racemate and not into a mixture of unequal amounts of the two diastereoisomerides. No activation could be detected using strychnine in acetone solution. When equimolecular quantities of *dl*-benzylmalonoanilic acid and cinchonidine were dissolved in acetone, a 90% second-order asymmetric transformation took place, with separation of the optically pure cinchonidine *d*-benzylmalonoanilate. This salt showed mutarotation in chloroform but the change was too small for accurate rate measurements. The active forms of benzylmalonoanilic acid, obtained by removal of the alkaloids, showed no tendency to racemise in alcoholic solution at the ordinary temperature.

The sparing solubility of *dl*-benzylmalonoanilic acid led us to modify the molecule, and in *dl*-benzylmalono-*o*-toluidic acid [III, R = H; R' = C₆H₄Me(*o*)] prepared by the modified Chattaway method we found suitable material for a more extensive study. As in the case of the parent acid, the sodium salt was sparingly soluble in water. In warm acetone solution the cinchonidine salt of the *dl*-acid underwent second-order asymmetric transformation, an 83% yield of optically pure cinchonidine *d*-benzylmalono-*o*-toluidate crystallising out, unless prior inoculation with the base-*dl*-acid salt was permitted, when the latter separated. A solution of cinchonidine *d*-acid in chloroform exhibited mutarotation, which was observed as a first-order change for which *k* = 0.00635 (18.3°). No first-order asymmetric transformation could be detected. Evaporation of the mutarotated solution (a) followed by removal of cinchonidine gave *dl*-acid and (b) followed by crystallisation from alcohol gave the partial racemate, the specific rotation of which in chloroform was identical with a solution in chloroform of equivalent quantities of base and *dl*-acid, a solution which did not mutarotate.

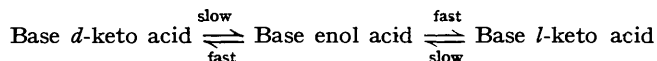
A point of importance is that base-*dl*-acid salt is less *l*-rotatory than base-*d*-acid salt in chloroform solution. In alcohol solution, on the other hand, base-*dl*-acid salt is more *l*-rotatory than base-*d*-acid salt. These facts probably express an essential difference between the non-ionised form of the salt and the ionically ethanolsed salt. An alcoholic solution of base-*d*-acid salt showed mutarotation of the first order type, *k* = 0.0044 (18.3°). This change must represent partial racemisation, since an alcoholic solution of equimolecular proportions of

cinchonidine and the *dl*-acid did not mutarotate. Removal of cinchonidine from base-*d*-acid salt gave *d*-benzylmalono-*o*-toluidic acid, which did not racemise at a measurable rate in alcohol at the ordinary temperature and racemised slowly in formic acid solution ($\frac{1}{2}$ -life period 381 mins. at 18.3°).

The essential mechanism permitting second-order asymmetric transformation in the above examples is clearly :



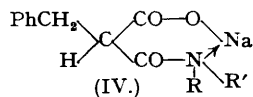
and it seems probable therefore that the absence of first-order asymmetric transformation even in chloroform solution is due to the following conditions :



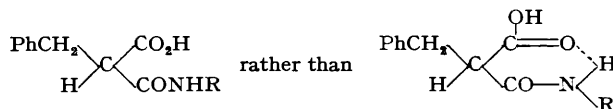
so that, in fact, there is no real equilibrium between the active salts. For first-order asymmetric transformation to be observable, the fast and slow changes would have to be interchanged.

Although *d*-benzylmalono-*o*-toluidic acid is itself difficult to racemise, immediate loss of optical activity occurs when its alcoholic solution is titrated with alcoholic sodium hydroxide or alcoholic potassium hydroxide, the disappearance of optical activity being precisely proportional to the alkali added, becoming complete when one equivalent of alkali has been added. Since ionisation of the carboxyl group cannot of itself promote the relevant keto-enol change and in fact would tend to hinder the initial removal of the α -proton, some other process must operate.

The sodium salt of the acid is sparingly soluble in water and therefore it probably has the cyclic structure (IV); this contains a modified β -diketone grouping which would be expected to exhibit relatively high tautomeric mobility resulting, we think, in almost complete enolisation, corresponding to optical inactivity. From the fact that the free acid has a high degree of optical stability in ethyl-alcoholic and in formic acid solutions it seems probable that in these circumstances the acid is

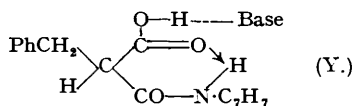
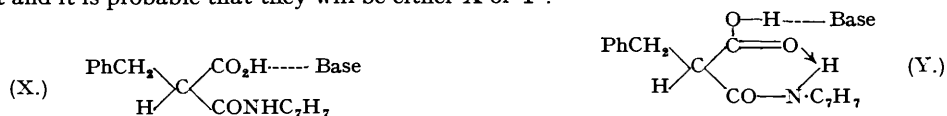


rather than



which is not surprising in view of the solvatory properties of these two solvents.

The pyridine and piperidine salts of benzylmalono-*o*-toluidic acid cannot be represented analogously to the sodium salt and it is probable that they will be either X or Y :



although, of course, other possibilities exist. Y would tend to racemise much more quickly than X and considerably more quickly than the acyclic free acid itself. Quantitative measurements of the rate of racemisation of the pyridine salt were made in the solvents chloroform, ethyl acetate, ethyl alcohol and methyl cyanide. With the first three solvents at 25.00°, racemisation was preceded by an induction period of 12, 25 and 75 minutes, respectively, but thereafter proceeded normally, the rate constants for the first order changes being 0.015, 0.0016 and 0.0040 in the order named. With methyl cyanide the rate constant was 0.0051 and there was no induction period. On one occasion a chloroform solution also began to racemise without an observable period of induction.

One point of considerable interest is that the solution of the pyridine salt of the *d*-acid in chloroform was *l*-rotatory, whereas the solutions in alcohol, ethyl acetate and methyl cyanide were *d*-rotatory. A second point of interest is that mixtures in alcohol of the *d*-acid with 0 to 1.0 equivalent of pyridine had identical rotations.

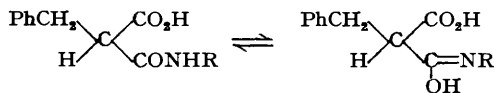
On the other hand an alcoholic solution of the *d*-acid, having $\alpha = +1.34^\circ$, had $\alpha = -0.20^\circ$ after the addition of 1 molecule of piperidine. In a series of rate determinations the following observations were made with varying proportions of piperidine and *d*-acid in alcohol at 18.3° :

<i>c</i> , acid.	Equivs. of piperidine.	Initial α .	<i>k</i> .	<i>c</i> , acid.	Equivs. of piperidine.	Initial α .	<i>k</i> .
1.3707	1.26	-0.35°	0.0029	1.4673	0.50	+0.68°	0.0035
1.4180	1.00	-0.34	0.0030	1.4107	0.50	+0.68	0.0032

all mutarotating to zero.

These results are surprising, for although at first sight it appears that in presence of only 0.5 equivalent of piperidine one is following the racemisation of only half the *d*-acid present, this, in fact, cannot be the case, since the free acid does not racemise at an appreciable rate in alcohol, and yet in both experiments with a defect of piperidine complete racemisation occurred, the rate constant being the same as that for 1 or 1.26 equivalents of base (period of $\frac{1}{2}$ change about 94 mins.). As a comment on these facts it may be recorded that an ethyl-alcoholic solution of the *d*-acid containing the neutral salt, tetraethylammonium chloride (selected as likely to have an effect similar to that of the above piperidine salt), showed no tendency to racemise at 18.3°.

In order to study the effect of preventing the second tautomeric change to which benzylmalonoanilic acids are subject, viz.,



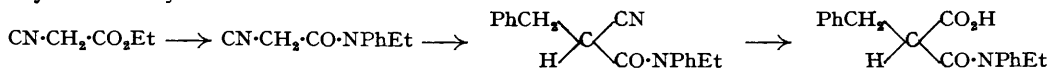
benzylmalonopiperidinic and benzylmalonoethylanic acids were prepared. These acids are very soluble in organic solvents, suggesting a cyclic structure, and both form sparingly soluble sodium salts which are doubtless analogous to (IV).

The cinchonidine salt of *dl*-benzylmalonopiperidinic acid gave rise to no second-order asymmetric transformation in either acetone or alcohol. A very high yield of one and the same crystalline salt was formed with both these solvents. Its chloroform solution did not mutarotate, nor was its optical composition essentially altered after prolonged digestion with insufficient boiling acetone to dissolve it, conditions under which second-order asymmetric transformation, had it been favoured, would have been accelerated. Removal of the cinchonidine gave the *dl*-acid. Clearly in this case, the partial racemate (a mono-hydrate) is the least soluble form.

Benzylmalono-ethylanic acid could not be made by Chattaway's method; the only product isolated after heating ethyl benzonate with methylaniline or ethylaniline was 2:4-diketo-3-benzyl-1-methyl-1:2:3:4-tetrahydroquinoline and the corresponding ethyl compound respectively.

Reisert (*Ber.*, 1892, 25, 1193) obtained 2:4-diketo-1-methyl-1:2:3:4-tetrahydroquinoline from ethyl malonate and methylaniline. It was found possible to isolate small amounts of the intermediate compound, ethyl malonomethylanilate, by heating with a large excess of methylaniline for 12 hours at 120°. Malono-methylanilic acid was obtained from the ester on hydrolysis.

A successful synthesis for benzylmalono-ethylanic acid from ethyl cyanoacetate was finally achieved using cyanoacetophenylethylamide, made from ethyl cyanoacetate according to the method of Guareschi (*Atti R. Accad. Scienze Torino*, XXVII, 1017). This with benzyl chloride in presence of sodium ethoxide condensed to give cyanobenzylacetophenylethylamide, which was partially hydrolysed with alcoholic potassium hydroxide to give benzylmalonoethylanic acid.



EXPERIMENTAL.

All polarimetric measurements were carried out in a 2 dm. tube and refer to λ 5461; k is expressed in Briggsian logarithms and min.^{-1} .

dl-Benzylmalonoanilic Acid.—Adapting a method of Chattaway (*J.*, 1910, 97, 940), benzylmalonoanilic acid was obtained in 40% yield.* Benzylmalonodianilide was also formed (yield 60%) and crystallised from alcohol in needles, m. p. 218°. Sodium benzylmalonoanilate crystallised from water in clusters of long needles, m. p. 220° (decomp.). It is soluble in alcohol (Found: Na, 7.0; M, 329. $\text{C}_{16}\text{H}_{14}\text{O}_2\text{NNa}\cdot 2\text{H}_2\text{O}$ requires Na, 7.0%; M, 327).

Brucine 1-Benzylmalonoanilate.—The *dl*-acid (2.69 g.) and brucine (3.94 g.) were dissolved together with gentle warming in alcohol (150 c.c.). The solution was filtered and the filtrate, on standing, or more quickly on warming, deposited *brucine 1-benzylmalono-anilate* (5.5 g., 83%) in fine silky needles, m. p. 128° (decomp.) (Found: C, 68.7; H, 6.7; N, 6.1. $\text{C}_{35}\text{H}_{41}\text{O}_7\text{N}_3\cdot \text{H}_2\text{O}$ requires C, 68.7; H, 6.4; N, 6.2%).

Cinchonidine d-Benzylmalono-anilate.—The *dl*-acid (1.34 g.) and cinchonidine (1.42 g.) were dissolved together in acetone (30 c.c.) with gentle warming. The solution was filtered and, on warming the filtrate, *cinchonidine d-benzylmalonoanilate* (2.4 g., 90%) rapidly separated in needles, m. p. 165° (decomp.) (Found: C, 71.9; H, 6.4. $\text{C}_{35}\text{H}_{37}\text{O}_4\text{N}_3$ requires C, 72.6; H, 6.4%).

1-Benzylmalonoanilic Acid.—The *brucine l*-acid salt, in chloroform solution at 0°, was treated with hydrochloric acid and the precipitation of the liberated acid completed by addition of ligroin (b. p. 40–60°). The acid was freed from traces of brucine by dissolving it in alcohol and precipitating with water. The acid (0.067 g.) was dissolved in alcohol (to 20 c.c.); α 0.92°, $[\alpha]$ 13.73° at 14°. No racemisation was observed.

d-Benzylmalonoanilic acid was obtained as for the *l*-acid by decomposing the cinchonidine *d*-acid salt. The acid (0.1449 g.) was dissolved in alcohol (to 20 c.c.); α 1.38° at 18°, $[\alpha]$ 9.52°.

dl-Benzylmalono-*o*-toluidic acid and benzylmalonodi-*o*-toluidide were prepared by the general method. Ethyl benzylmalonate (37 g.) and *o*-toluidine (10.7 g.) gave benzylmalono-*o*-toluidic acid (8 g.) and benzylmalonodi-*o*-toluidide (10.5 g.). *dl*-Benzylmalono-*o*-toluidic acid crystallised from alcohol in needles, m. p. 154° (decomp.) (Found: C, 72.0; H, 6.2; N, 4.9. $\text{C}_{17}\text{H}_{17}\text{O}_3\text{N}$ requires C, 72.1; H, 6.0; N, 4.9%). Benzylmalonodi-*o*-toluidide crystallised from alcohol, in which it is only sparingly soluble, in small needles, m. p. 190° (Found: C, 77.8; H, 6.3; N, 7.6. $\text{C}_{24}\text{H}_{24}\text{O}_2\text{N}_2$ requires C, 77.4; H, 6.4; N, 7.5%). Sodium benzylmalono-*o*-toluidate crystallised, on cooling a solution in hot water, in long flat needles, which lost water of crystallisation at 100° and had m. p. 283° (decomp.) (Found: Na, 6.6. $\text{C}_{17}\text{H}_{16}\text{O}_3\text{NNa}\cdot 2\text{H}_2\text{O}$ requires Na, 6.8%).

* M. p. 180° (decomp.); Dieckmann, Hoppe and Stein, *Ber.*, 1904, 37, 4633, who obtained the anilide from the ethyl ester of benzylacetymalonoanilic acid, gave no melting point.

Cinchonidine d-Benzylmalono-o-toluidate.—(i) The *dl*-acid (4.25 g.) and cinchonidine (4.41 g.) were dissolved together with gentle stirring in acetone (200 cc.). The solution was filtered and then heated under reflux at 70° for 4 hours.

Time in mins. after 1st addn. of piperidine.	Equivs. of piperidine added.	α .	Time in mins. after 1st addn. of piperidine.	Equivs. of piperidine added.	α .
0	0	1.34°	36—39	1.22	-0.20°
4—9	0.03	0.84	41—48	1.62	-0.19
10—16	0.056	0.39	49—52	2.0	-0.165
18—23	0.068	0.19	83	2.0	-0.11
24—29	0.082	0.00	720	2.0	0.00
30—34	1.00	-0.20			

Racemisation of the Piperidine Salt of d-Benzylmalono-o-toluidic Acid.—In Alcohol. Temp. 18.3°. (i) Acid : base ratio, 1 : 1.26; c (acid) = 1.3707; readings were begun 12 mins. after adding the piperidine and changed from -0.35° to zero; k = 0.0029 (limits, 0.0025 and 0.0034).

(ii) Acid : base ratio, 1 : 1; c (acid) 1.4180; readings were begun 10 mins. after adding the piperidine and changed from -0.34° to zero; k = 0.0030 (limits, 0.0027 and 0.0033).

(iii) Acid : base ratio, 0.5 : 1; c (acid) 1.4673; readings were begun 10 mins. after adding the piperidine and changed from 0.68° to zero.

(iv) Acid : base ratio, 0.5 : 1; c (acid) 1.4107; readings were begun 5 mins. after adding the piperidine and changed from 0.68° to zero; k = 0.0032 (limits, 0.0028 and 0.0034).

In dioxan. On addition of 1 equivalent of piperidine to a solution of the acid, c = 1.2927, in dioxan, the piperidine salt crystallised out, m. p. 155° (decomp.) (Found : N, 7.6. $C_{22}H_{29}O_3N_2$ requires N, 7.6%).

Neutralisation of d-Benzylmalono-o-toluidic Acid in Alcohol with Alkalis.—(A). *Alcoholic potassium hydroxide.* (1) Alkali added in successive portions. Rotation diminished at once in exact proportion to the potassium hydroxide added, becoming zero just before 1 equivalent had been added, showing that slight racemisation of the acid present as such accompanies salt formation. c (acid) = 1.0235.

Time in mins. after 1st addn. of KOH.	Equivs. of KOH added.	α .	Time in mins. after 1st addn. of KOH.	Equivs. of KOH added.	α .
0	0	1.12°	33—36	0.7619	0.12°
3—12	0.1982	0.80	43—52	0.9523	0.00
13—20	0.3862	0.635	53—60	1.00	0.00
23—30	0.5608	0.345	—	—	—

(ii) Acid : alkali, 1 : 1 (initially); α 0.00°, first reading within 4 mins. of adding the alkali.

(B). Similar results were obtained using alcoholic sodium hydroxide.

Effect of the Neutral Sodium Salt on the Racemisation of d-Benzylmalono-o-toluidic Acid in Alcohol.—Temp. 18°. Acid : base ratio, 2 : 1; readings changed from 0.22° to zero; k = 0.00095 \pm 0.00005.

Racemisation of the Ammonium Salt.—Temp. 18°. (A) Alcohol. Acid : base ratio, 1 : 1; α 0.00° within 5 mins. (B) Water. Acid : base, 3 : 1; readings changed from 0.215 to zero; k is of the order 0.00015; i.e., $\frac{1}{2}$ -life period is about 33 hours.

d-Benzylmalono-o-toluidic Acid in Presence of the Neutral Salt, Tetraethylammonium Chloride.—Temp. 18.3°. Alcohol. Acid : salt, 1 : 1; no racemisation was observed within 24 hours.

Synthesis of Benzylmalonoethylamyllic Acid.—Benzylcyanoacetophenylethylamide. Cyanoacetophenylethylamide (18.8 g., 1 mol.; prepared according to Guareschi, *loc. cit.*) was added to sodium (2.3 g., 1 atom) dissolved in alcohol (50 c.c.). Benzyl chloride (12 g., 1 mol.) was run in with shaking so that all had been added within 5 mins.; the mixture became hot and sodium chloride separated. The reaction was completed by heating under reflux on a water-bath for 30 mins., after which time the mixture reacted neutral to moist litmus. Some of the alcohol was distilled away; on pouring the remainder of the solution into water (1 litre), benzylcyanoacetophenylethylamide separated as a solid which crystallised from alcohol in needles, m. p. 110—112°; yield, 93% (Found : C, 77.5; H, 6.7; N, 10.2. $C_{18}H_{18}ON_2$ requires C, 77.7; H, 6.5; N, 10.1%).

Benzylmalonoethylamyllic acid. To a solution of potassium hydroxide (1.3 g.) in water (3 c.c.) and alcohol (11 c.c.) benzylcyanoacetophenylethylamide (5.5 g.) was added and the mixture heated on a water-bath under reflux for 1 hour. The alcohol was evaporated off, leaving a solid residue which was dissolved in water and extracted three times with ether to remove unchanged starting material (0.53 g.). The aqueous layer was heated for a few minutes to drive off traces of ether and acidified with dilute hydrochloric acid; an oily liquid separated which showed no tendency to solidify. On adding sodium hydroxide to the oil sodium benzylmalono-ethylamyllic acid separated. The salt was readily soluble in benzene, but sparingly soluble in cold water, from which it crystallised in shining plates, m. p. 180° (decomp.) (Found : Na, 4.6. $C_{18}H_{18}O_2NNa \cdot 10H_2O$ requires Na, 4.6%). The pure salt was acidified with hydrochloric acid and benzylmalono-ethylamyllic acid again separated as a semi-solid, which crystallised from carbon tetrachloride and ligroin (b. p. 60—80°), m. p. 106—107° (decomp.); yield, 48% (Found : C, 73.0; H, 6.9. $C_{18}H_{18}O_2N$ requires C, 72.7; H, 6.5%). From 30 g. of cyanide 22 g. of salt were obtained. Attempts to prepare active brucine, strychnine, morphine, cinchonine, cinchonidine, quinine and quinidine salts were unsuccessful.

2 : 4-Diketo-3-benzyl-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline.—Ethyl benzylmalonate (37 g., 1.5 mols.) and methyl-aniline (10.5 g., 1 mol.) were heated together to gentle boiling for 1 hour. The mixture solidified on cooling and the only product isolated was 2 : 4-diketo-3-benzyl-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline which crystallised from alcohol in needles, m. p. 218°; yield, 14 g. (Found : C, 76.7; H, 5.7; N, 5.3. $C_{17}H_{15}O_2N$ requires C, 76.8; H, 6.1; N, 5.3%).

2 : 4-Diketo-3-benzyl-1-ethyl-1 : 2 : 3 : 4-tetrahydroquinoline.—By heating ethyl benzylmalonate similarly with ethyl-aniline, 2 : 4-diketo-3-benzyl-1-ethyl-1 : 2 : 3 : 4-tetrahydroquinoline was obtained, and crystallised from alcohol in plates, m. p. 228—230° (Found : N, 5.0. $C_{18}H_{17}O_2N$ requires N, 5.0%).

Malonomethylamyllic Acid.—Ethyl malonate (40 g., 2.5 mols.) was heated with methyl-aniline (10.7 g., 1 mol.) at 120° for 12 hours. The resulting liquid was distilled under reduced pressure. Unchanged ethyl malonate and methyl-aniline were recovered in a first fraction (42 g.) but a small fraction (6 g.) boiling above 165°/7 mm. was collected, although considerable decomposition occurred. The product was hydrolysed by boiling for a few minutes with 10% sodium hydroxide solution. On acidifying with hydrochloric acid malonomethylamyllic acid separated. Crystallisation from a small amount of alcohol, in which it is easily soluble, gave needles, m. p. 120° (decomp.) (Found : C, 62.2; H, 6.0; N, 7.7. $C_{16}H_{11}O_2N$ requires C, 62.1; H, 5.7; N, 7.3%). On heating, malonomethylamyllic acid decomposes to give acetophenyl-methylamide, m. p. 101—102°.

Reaction between Benzaldehyde and Cyanoacetophenylmethylamide.—(i) *Leading to α -dicyano- β -phenyl-glutarodiphenylmethylamide.* Benzaldehyde (12 g., 1.1 mol.) and cyanoacetophenylmethylamide (17.4 g., 1 mol.; as prepared by Guareschi, *loc. cit.*) were mixed with piperidine (3 drops) and left at 0° for some hours. α -Dicyano- β -phenyl-glutarodiphenylmethylamide (15 g.) separated, crystallising from alcohol in flat polyhedra, m. p. 180° (Found :

C, 73.7; H, 5.5; N, 12.1. $C_{27}H_{24}O_2N_4$ requires C, 74.3; H, 5.5; N, 12.8%. Complete hydrolysis with 70% sulphuric acid gave β -phenylglutaric acid, m. p. 138° (Knoevenagel, *Ber.*, 1902, **35**, 393).

(ii) *Leading to benzylidenecyanoacetophenylmethylamide.* Cyanoacetophenylmethylamide (20 g.) and benzaldehyde (100 g.) with piperidine (3 drops) were heated for 15 hours on a water-bath. The excess benzaldehyde was distilled off under reduced pressure and the crude residue of *benzylidenecyanoacetophenylmethylamide* was crystallised from alcohol, m. p. 92°; yield, 93% (Found: C, 77.6; H, 5.5; N, 10.9. $C_{17}H_{14}ON_2$ requires C, 77.8; H, 5.4; N, 10.7%).

Benzylidenecyanoacetic Acid.—Benzylidenecyanoacetophenylmethylamide (8 g.) was heated under reflux on a water-bath with potassium hydroxide (2 g.) in water (2 c.c.) and alcohol (20 c.c.). The solid which rapidly separated was filtered off and acidified with hydrochloric acid; the product, benzylidenecyanoacetic acid, crystallised from glacial acetic acid in prisms, m. p. 180° (decomp.); yield 3.7 g. (Figuet, *Ann. Chim. Phys.*, 1893, **29**, 442).

Benzylmalonopiperidinic acid was prepared by the general method, but in this case no dipiperide was isolated. Ethyl benzylmalonate (15.3 g.) with piperidine (12 g.) gave *benzylmalonopiperidinic acid* (14 g.) which crystallised from alcohol in prisms, m. p. 135° (decomp.) (Found: C, 68.7; H, 7.6; N, 5.5. $C_{15}H_{19}O_3N$ requires C, 68.9; H, 7.3; 5.4%). *Sodium benzylmalonopiperidinate* crystallised on cooling a solution in hot water, in small needles, m. p. 260° (decomp.) (Found: Na, 7.0. $C_{15}H_{18}O_3NNa, 2H_2O$ requires Na, 7.0%).

Cinchonidine Benzylmalonopiperidinate.—(i) The *dl*-acid (0.26 g.) was dissolved in acetone (3 c.c.) and mixed with cinchonidine (0.29 g.) in acetone (17 c.c.). On gentle warming *cinchonidine benzylmalonopiperidinate* (0.54 g.) was deposited, m. p. 161° (decomp.) (Found: C, 71.6; H, 7.6; N, 7.9. $C_{34}H_{41}O_4N_3, H_2O$ requires C, 71.2; H, 7.5; N, 7.4%). (ii) The *dl*-acid (0.26 g.) and cinchonidine (0.2 g.) were dissolved together with gentle warming in alcohol (6 c.c.). Cinchonidine benzylmalonopiperidinate separated in long needles, m. p. 161° (decomp.); yield, 18.1%.

In each case no mutarotation of the salt was observed in chloroform solution; $[\alpha] -60.6^\circ$. The rotation of the chloroform solution was unaffected by adding excess of the *dl*-acid. Cinchonidine benzylmalonopiperidinate (0.3 g.) in acetone (10 c.c., insufficient solvent to dissolve the salt completely) was heated under reflux for 5 hours and the mixture cooled and filtered. Both the residue and the filtrate were examined polarimetrically. (a) A portion of the residue (0.1590 g.) was dissolved to 20 c.c. in chloroform and the first reading taken within 3 mins. of wetting the salt; $\alpha - 0.94^\circ$; $[\alpha] - 59.1^\circ$. No mutarotation was observed within 24 hours. (b) The filtrate was evaporated to dryness under reduced pressure and a portion of the residue (0.0988 g.) was dissolved in chloroform (to 20 c.c.); $\alpha - 0.61^\circ$, $[\alpha] - 61.7^\circ$. No mutarotation was observed within 24 hours. The benzylmalonopiperidinic acid liberated from the salt was inactive.

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