369. *Polyene Acids. Part VII.* Half Methyl Esters and Amides of the Muconic Acids.*

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The half methyl esters, half amides, and mixed methyl ester amides of the three geometrically isomeric muconic acids have been prepared from the acids by standard methods. Light-absorption characteristics are given. The *cis-cis*- and *cis-trans*-derivatives are inverted to the *trans-trans*-compounds by ultra-violet light and iodine.

The derivatives of *cis-trans*-muconic acid are obtained in positionally isomeric forms, whilst in the *cis-cis*- and the *trans-trans*-series the two terminal positions show the expected equivalence.

Alkoxide ring-fission of the amide (VIII) of γ-carboxymethylbut-α-enolide provides an amide ester of β-ketoadipic acid and not a muconamic acid as would be expected by analogy with the behaviour of the lactonic ester (I).

The three geometrical isomers of muconic acid, and their methyl and diphenylmethyl esters, were described in Part I of this series (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235). Recently we have confirmed the configurations of the acids by semi-hydrogenation experiments (Elvidge, Linstead, and J. F. Smith, *J.*, 1953, 708). We now describe the half methyl esters, half amides, and mixed ester amides of the three muconic acids.

Positional isomerism is encountered in the derivatives of the *cis-trans*-acid, but not in the *cis-cis*- and the *trans-trans*-compounds. Furthermore, the equivalence of the two

* Part VI, *J.*, 1953, 1372.

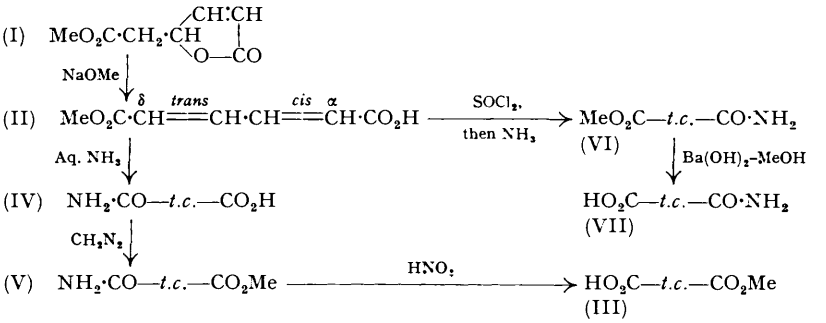
carboxyl groups in *cis-cis*-muconic acid, as well as in the *trans-trans*-acid, has been demonstrated by inversion and positional conversion of derivatives. The *cis-cis*- and *cis-trans*-compounds are easily inverted to the all-*trans*-isomers by ultra-violet light and iodine. These results fully accord with the geometrical configurations already assigned to the muconic acids.

Half Methyl Esters.—Methyl hydrogen *trans-trans*-muconate, m. p. 163°, was prepared in 25% yield by Karrer and Stoll (*Helv. Chim. Acta*, 1931, **14**, 1189) by partial hydrolysis of the diester with methanolic potassium hydroxide.

We attempted similarly to prepare the *cis-cis*-compound from the *cis-cis*-diester but obtained an equimolecular mixture of *cis-cis*-muconic acid and unchanged diester. However, partial esterification was successful, affording methyl hydrogen *cis-cis*-muconate, $C_7H_8O_4$, m. p. 80°, in 34% yield. Its structure was proved by hydrolysis to *cis-cis*-muconic acid and reaction with diazomethane to give methyl *cis-cis*-muconate. On distillation the half ester lactonised to γ-carbomethoxymethylbut-α-enolide (I). Irradiation, in the presence of iodine, inverted the half ester to methyl hydrogen *trans-trans*-muconate, which was hydrolysed to the *trans-trans*-acid. In contrast to *cis-cis*-muconic acid, the *cis-cis*-half ester was not inverted by brief treatment with boiling water or boiling dilute hydrochloric acid.

Application of the partial esterification conditions to *cis-trans*-muconic acid yielded the known methyl hydrogen *trans-cis*-muconate (II),* m. p. 101°, previously obtained (Part I) by methoxide ring-fission of the lactonic ester (I). The structure of (II) follows from that method. Partial hydrolysis of methyl *cis-trans*-muconate, on the other hand, afforded (in poor yield) a new half ester, m. p. 105°, which was therefore the positional isomer (III), methyl hydrogen *cis-trans*-muconate.* The melting point of a mixture of the two *cis-trans*-half esters was strongly depressed. The new half ester (III) with diazomethane gave the known *cis-trans*-dimethyl ester, and on hydrolysis *cis-trans*-muconic acid : hydrogenation and hydrolysis gave adipic acid. In conformity with the assigned configurations, the acid ester (II) lactonised on distillation to γ-carbomethoxymethylbut-α-enolide (I), whereas the acid ester (III) did not, being geometrically unfavourable (cf. Elvidge, Linstead, and Sims, *J.*, 1951, 3386). Each of the half esters (II) and (III) was inverted on irradiation in the presence of iodine to methyl hydrogen *trans-trans*-muconate, and at about the same rate, which was slightly slower than for the *cis-cis*-half ester. The inversions of (II) and (III) to a single *trans-trans*-half ester is a demonstration of the equivalence of the two carboxyl groups in *trans-trans*-muconic acid.

Light-absorption data for the half esters which confirm the open-chain structures are recorded in the Table.



Half Amides and Methyl Ester Amides.—Methyl hydrogen *trans-trans*-muconate with aqueous ammonia gave in good yield *trans-trans*-muconamic acid, m. p. 284°. This has previously been isolated from the urine of rabbits fed with sorbamide (Kuhn, Köhler, and Köhler, *Z. physiol. Chem.*, 1937, **247**, 197). Alkaline hydrolysis of the half amide yielded

* The terms *cis* and *trans* are given in positional order; see *J.*, 1951, 3386. Fully unambiguous names for (II) and (III) are, respectively, (δ)-methyl (α)-hydrogen *cis-trans*-muconate and (α)-methyl (δ)-hydrogen *cis-trans*-muconate.

trans-trans-muconic acid, whilst reaction with diazomethane afforded methyl *trans-trans*-muconamate, m. p. 177°.

cis-cis-Muconamic acid, m. p. 152°, was prepared analogously from the *cis-cis*-half methyl ester and ammonia. Hydrolysis of the half amide with alkali gave *cis-cis*-muconic acid, further characterised as the dimethyl ester, and irradiation in the presence of iodine yielded *trans-trans*-muconamic acid. With diazomethane the *cis-cis*-half amide yielded methyl *cis-cis*-muconamate, m. p. 105°, and an identical product resulted from treatment of methyl hydrogen *cis-cis*-muconate with thionyl chloride (to yield the ester acid chloride) and then ammonia. These syntheses, which produce the same muconamate by conversion of opposite muconic carboxyl groups into amide and ester functions, demonstrate the symmetry of *cis-cis*-muconic acid. Irradiation of the *cis-cis*-muconamate gave the all-*trans*-ester amide.

From the readily available methyl hydrogen *trans-cis*-muconate (II) with ammonia, *cis-trans*-muconic (α)-acid (δ)-amide (IV), m. p. 153°, resulted. This was hydrolysed with hot alkali to *cis-trans*-muconic acid (characterised as the dimethyl ester), and with diazomethane yielded *cis-trans*-muconic (α)-methyl ester (δ)-amide (V), m. p. 116°. Treatment of the latter with nitrous acid afforded methyl hydrogen *cis-trans*-muconate (III), a result which confirmed the geometry of the double bonds as well as the orientation of the ester and amide groupings in (V).

The positionally isomeric half amide ester, *cis-trans*-muconic (α)-amide (δ)-methyl ester (VI), m. p. 114° [depressed by 30° by (V)], was also prepared from methyl hydrogen *trans-cis*-muconate (II) by conversion of this into the ester acid chloride and then reaction with ammonia. Cautious hydrolysis of (VI) with methanolic barium hydroxide provided the second *cis-trans*-half amide, *cis-trans*-muconic (δ)-acid (α)-amide (VII), m. p. 199°. Each of the half amides (IV) and (VII) was inverted, on irradiation, to *trans-trans*-muconamic acid, and each of the ester amides (V) and (VI) similarly gave methyl *trans-trans*-muconamate.

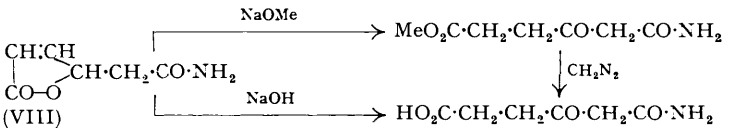
The light-absorption properties of the half amides and their esters, recorded in the Table, agree with the open-chain structures.

Light absorption of muconic derivatives, $R'\cdot CO\cdot \overset{\delta}{C}H{:}CH\cdot CH{:}\overset{\alpha}{C}H\cdot CO\cdot R$, *in ethanol.*

		cis-cis		*cis(αβ)-trans(γδ)*		*trans-trans*	
R	R′	$\lambda_{max.}$, Å	ε	$\lambda_{max.}$, Å	ε	$\lambda_{max.}$, Å	ε
OMe	OH	2580	20,900	2580	22,400	2570	29,400
		2640 *	19,000	2640	23,700		
OH	OMe			2570 *	24,800		
				2640	25,800		
NH_2	OH	2510	19,000	2510 *	27,500	2510	27,500
		2570	23,100	2570	29,000	2580	31,000
		2640	23,100	2640	29,000	2640	31,000
OH	NH_2			2510 *	18,900		
				2570	21,300		
				2640	21,300		
OMe	NH_2	2510 *	22,300	2490 *	19,400	2510	25,500
		2580	25,900	2570	23,400	2570 *	28,600
		2640	25,900	2640	23,400	2650	30,600
		2780 *	14,700				
NH_2	OMe			2560	22,500		
				2650	26,500		

* Inflection.

In extension of the above work, the action of sodium methoxide on the unsaturated lactonic amide (VIII) was examined, but this reaction did not yield a *cis-trans*-muconic half amide, as expected by analogy with the ring-fission behaviour of the lactonic ester (I).



The lactonic amide (VIII) was best obtained from the corresponding αβ-unsaturated lactonic acid (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228) *via* the acid chloride and mild treatment with ammonia. It was also formed by thermal cyclisation of the geometrically suitable *cis-trans*-muconamic acid (IV). The Δ^{α}-structure of (VIII) was supported by the light absorption (inflection at 2250 Å., $\varepsilon = 3100$). With 1 mol. of sodium methoxide in methanol, (VIII) afforded a neutral ketonic product, isolated as the 2 : 4-dinitrophenylhydrazone, the analysis of which corresponded with that of β-ketoadipic (α)-amide (δ)-methyl ester. Aqueous sodium hydroxide gave the corresponding acid, β-ketoadipic (δ)-acid (α)-amide, also isolated as the 2 : 4-dinitrophenylhydrazone. The latter amide with diazomethane gave the previously encountered neutral derivative.

The double bond in (VIII) is evidently so easily mobile in presence of alkaline reagents that ring-fission yields the enolate ion of a β-ketoadipic derivative even with cold alkoxide. The lactonic acid, γ-carboxymethylbut-α-enolide gave lævulic acid with hot alkali (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*), presumably *via* β-ketoadipic acid and decarboxylation. In the present case the α-carboxyl group of the product is protected (as an amide) and is not therefore eliminated.

Experimental

M. p.s marked * were taken by immersion of the sample in a bath at 165°, with the temperature rising at 10°/min. Other m. p.s were taken normally.

Methyl hydrogen *trans-trans*-muconate had m. p. 163° (Karrer and Stoll, *loc. cit.*).

Methyl Hydrogen cis-cis-*Muconate.*—*cis-cis*-Muconic acid (5 g.) was kept for 48 hr. in the dark with methanol (50 c.c.) containing 0·5% of hydrogen chloride. The solvent was evaporated under reduced pressure, and the portion of the residue soluble in boiling benzene (2 × 25 c.c.) was shaken with aqueous sodium hydrogen carbonate and ether. The aqueous layer was acidified with hydrochloric acid (Congo-red), and the precipitate crystallised from benzene, affording *methyl hydrogen* cis-cis-*muconate* (1·9 g., 34%) as needles, m. p. 80° (Found: C, 53·8; H, 5·3. $C_7H_8O_4$ requires C, 53·9; H, 5·2%.

Hydrogenation of the half ester (220 mg.) in ethanol (5 c.c.) over Adams's catalyst (H_2 uptake at 755 mm./23°: 76·5 c.c. Calc. for 2 double bonds: 70 c.c.) afforded an oil, which was heated under reflux with concentrated hydrochloric acid (2 c.c.). Evaporation of the hydrolysate gave adipic acid (155 mg.), m. p. and mixed m. p. 146—148°.

Methyl hydrogen *cis-cis*-muconate (100 mg.) was dissolved in 10% aqueous sodium hydroxide (1 c.c.), and after 30 min. the solution was acidified. From ethanol, the precipitate (50 mg.) formed prisms, m. p. 185—187° * undepressed by *cis-cis*-muconic acid.

The *cis-cis*-half ester (50 mg.) was treated with an excess of ethereal diazomethane. The product, isolated by evaporation of the solution, was crystallised from aqueous methanol, affording needles, m. p. 73—73·5° undepressed by methyl *cis-cis*-muconate, but depressed to 50—55° by the *cis-trans*-dimethyl ester.

Distillation of methyl hydrogen *cis-cis*-muconate (2 g.) (bath-temp., 190°) afforded γ-carbomethoxymethylbut-α-enolide (I) (0·85 g., 42%), b. p. 155°/12 mm., n_D^{18} 1·4743, and a residue of a neutral, brittle resin.

After being heated in boiling water (1 c.c.) for 2 min., methyl hydrogen *cis-cis*-muconate (100 mg.) was recovered (90 mg.), m. p. and mixed m. p. 79°, and was unchanged by similar treatment with boiling 2N-hydrochloric acid.

Methyl hydrogen *cis-cis*-muconate (0·2 g.) in benzene (2 c.c.), containing a trace of iodine, was irradiated with ultra-violet light from a Hanovia lamp for 15 min. Recrystallisation of the precipitate (yield, almost quantitative) from benzene gave needles, m. p. 163°, of methyl hydrogen *trans-trans*-muconate.

(δ)-*Methyl* (α)-*Hydrogen* cis-trans-*Muconate* (II).—This, m. p. 101°, was prepared by Elvidge, Linstead, Sims, and Orkin (*loc. cit.*) from (I), and was also obtained by treating *cis-trans*-muconic acid (10 g.) with methanol (150 c.c.) containing 0·5% of hydrogen chloride for 16 hr. (cf. *cis-cis* case, above) [yield, 5·2 g. (47%); m. p. 90—95°, raised to 99—100° (undepressed by the previous sample) by crystallisation 3 times from benzene].

Distillation of the half ester (1·8 g.) (bath-temp. 190°) gave γ-carbomethoxymethylbut-α-enolide (0·65 g., 36%), b. p. 154°/11 mm., n_D^{15} 1·4738, together with a residue of a neutral, brittle resin.

(α)-*Methyl* (δ)-*Hydrogen* cis-trans-*Muconate* (III).—Methyl *cis-trans*-muconate (3 g.) in methanol (10 c.c.) was added to methanolic barium hydroxide (22 c.c.; 0·79N). Next day, the

precipitate was washed with methanol (10 c.c.), and its solution in water (20 c.c.) acidified. Isolation with ether (3 × 25 c.c.) yielded an oil, which was taken up in hot benzene (25 c.c.). (α)-*Methyl* (δ)-*hydrogen* cis-trans-*muconate* (220 mg., 8·3%) separated from benzene as needles, m. p. 105—106° (Found: C, 53·7; H, 5·3%; equiv., 156·2. $C_7H_8O_4$ requires C, 53·9; H, 5·2%; equiv., 156·1). A mixture with (δ)-methyl (α)-hydrogen *cis-trans*-muconate (II) (m. p. 101°) had m. p. 80—85°.

Hydrogenation of the *cis-trans*-half ester (III) (200 mg.) in ethanol (5 c.c.) over Adams's catalyst (30 mg.) (H_2 uptake at 755 mm./23°: 69 c.c. Calc. for 2 double bonds: 63 c.c.) and hydrolysis of the oily product with boiling concentrated hydrochloric acid (2 c.c.) for 30 min. yielded adipic acid (130 mg.), m. p. 147—149° and mixed m. p. 148—149°.

The *cis-trans*-half ester (III) with diazomethane in ether gave methyl *cis-trans*-muconate, which crystallised from aqueous methanol as needles, m. p. and mixed m. p. 73—74°. The m. p. of a mixture with methyl *cis-cis*-muconate was depressed to 60—65°.

The half ester (III) (120 mg.) was kept for 1 hr. with 10% sodium hydroxide (2 c.c.). On acidification, *cis-trans*-muconic acid was precipitated (70 mg., 82%), m. p. 180—184°* and mixed m. p. 181—185°.* The product, with diazomethane, gave methyl *cis-trans*-muconate as needles, m. p. and mixed m. p. 74—75°.

When heated at 190°/11 mm., the half ester (III) failed to distil but in part sublimed. The sublimate (30 mg.) had m. p. 105° undepressed by the starting material. The residue was a neutral, brown resin.

Comparison of the Rates of Inversion of the cis-*Half Esters.*—100-Mg. samples of the esters in benzene (3-c.c. portions) containing a trace of iodine were simultaneously irradiated with light from a 100-w filament lamp, and the times (in min.) for appearance of a precipitate noted: methyl hydrogen *cis-cis*-muconate, 7; (III), 8; (II), 8. In each case the precipitate had m. p. 163° alone and when mixed with methyl hydrogen *trans-trans*-muconate.

trans-trans-*Muconamic Acid.*—Methyl hydrogen *trans-trans*-muconate (100 mg.) was kept with aqueous ammonia (3 c.c.; *d* 0·88) for 4 days, and the solution then acidified. The precipitated *trans-trans*-muconamic acid (80 mg., 88%) crystallised from water as needles, m. p. 284—285° (decomp.) (Found: C, 51·0; H, 4·9; N, 9·7. Calc. for $C_6H_7O_3N$: C, 51·1; H, 5·0; N, 9·9%). Kuhn, Köhler, and Köhler (*loc. cit.*) record m. p. 281—282°.

Hydrolysis of the *trans-trans*-half amide (100 mg.) with boiling 10% aqueous sodium hydroxide (1·5 c.c.) for 1 hr., and acidification, yielded *trans-trans*-muconic acid (80 mg., 80%), m. p. and mixed m. p. 298—300° (decomp.).

Methyl trans-trans-*muconamate*, obtained in high yield from the muconamic acid and diazomethane, crystallised from benzene as needles, m. p. 177—178° (Found: N, 9·3. $C_7H_9O_3N$ requires N, 9·0%).

cis-cis-*Muconamic Acid.*—Prepared analogously to the all-*trans*-compound, cis-cis-*muconamic acid* (48% yield) crystallised from ethanol–light petroleum (b. p. 40—60°) as needles, m. p. 152—153° (Found: C, 51·35; H, 5·0; N, 9·9. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

Hydrolysis of the *cis-cis*-half amide (100 mg.) (as for the all-*trans*-isomer) gave *cis-cis*-muconic acid (80 mg.), m. p. 185—187°*, converted by diazomethane into methyl *cis-cis*-muconate, m. p. 73°, undepressed by authentic material, but depressed to 53—58° by methyl *cis-trans*-muconate.

Irradiation of the *cis-cis*-half amide (100 mg.), in ethanol (5 c.c.) containing a trace of iodine with light from a 100-w filament lamp for 30 min., gave a precipitate of *trans-trans*-muconamic acid, which crystallised from water as needles (85 mg., 85%), m. p. and mixed m. p. 285—286° (decomp.).

Methyl cis-cis-*muconamate*, from *cis-cis*-muconamic acid and ethereal diazomethane, crystallised from benzene as needles (yield 60%), m. p. 104—105° (Found: C, 54·4; H, 5·9; N, 8·9; $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%). In an alternative preparation, methyl hydrogen *cis-cis*-muconate (400 mg.) was heated under reflux with thionyl chloride (5 c.c.) for 15 min. Excess of the reagent was removed under reduced pressure, and the product added slowly to aqueous ammonia (2 c.c.; *d* 0·88) cooled in ice. Crystallisation of the product from benzene afforded fine needles, m. p. 105° undepressed by the preceding preparation.

Irradiation under the previous conditions gave methyl *trans-trans*-muconamate (75%), m. p. and mixed m. p. 176—177°.

cis-trans-*Muconic* (α)-*Acid* (δ)-*Amide* (IV).—(δ)-Methyl (α)-hydrogen *cis-trans*-muconate (II) (0·4 g.) was kept with aqueous ammonia (5 c.c.; *d* 0·88) for 4 days. The solution was concentrated under reduced pressure and acidified, and the precipitate was crystallised from hot water. cis-trans-*Muconic* (α)-*acid* (δ)-*amide* (0·28 g., 77%) formed needles, m. p. 152—153° (Found:

C, 51·2; H, 5·2; N, 9·65. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). The m. p. was depressed to 143—145° by *cis-cis*-muconamic acid (m. p. 152—153°).

Hydrolysis of (IV) with alkali (as in previous cases) for 60 min. produced *cis-trans*-muconic acid (55%), m. p. and mixed m. p. 184—186°,* which with diazomethane gave methyl *cis-trans*-muconate, m. p. and mixed m. p. 73—74°, depressed to 52—56° by methyl *cis-cis*-muconate.

cis-trans-*Muconic* (α)-*Methyl Ester* (δ)-*Amide* (V).—Obtained from the *cis-trans*-muconamic acid (IV) with diazomethane, this *compound* crystallised from benzene as needles, m. p. 116° (Found: C, 54·3; H, 5·95; N, 9·4. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%), depressed to 75—82° by methyl *cis-cis*-muconamate.

A suspension of this (α)-methyl ester (δ)-amide (200 mg.) in 2N-hydrochloric acid (10 c.c.) was treated at room temperature with 10% aqueous sodium nitrite (2 c.c.), and after 5 hr. the solution was extracted with ether (3 × 10 c.c.). Evaporation of the extract gave (α)-methyl (δ)-hydrogen *cis-trans*-muconate (45 mg., 22%), which crystallised from water as needles, m. p. 103—104° and mixed m. p. 104—105°.

cis-trans-*Muconic* (α)-*Amide* (δ)-*Methyl Ester* (VI).—(δ)-Methyl (α)-hydrogen *cis-trans*-muconate (0·5 g.) was heated under reflux with thionyl chloride (10 c.c.) for 10 min. Excess of reagent was distilled off under reduced pressure and the residue added slowly to aqueous ammonia (2 c.c.; *d* 0·88) at 0°. From benzene, cis-trans-*muconic* (α)-*amide* (δ)-*methyl ester* (0·39 g., 77%) separated as fine needles, m. p. 114—115° (Found: C, 54·1; H, 5·8; N, 8·9. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%), depressed to 74—80° by methyl *cis-cis*-muconamate.

cis-trans-*Muconic* (α)-*Amide* (δ)-*Acid* (VII).—The amide ester (VI) (0·1 g.) was dissolved in methanolic barium hydroxide (1 c.c.; 0·8N). After 30 min., the solution was diluted with water (1 c.c.), acidified, and kept at 0° for several hr. The cis-trans-*muconic* (α)-*amide* (δ)-*acid* (58 mg., 63%), which separated crystallised from water as needles, m. p. 199—200° (decomp.) (Found: C, 51·3; H, 5·4; N, 10·0. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

Inversion of the cis-trans-*Muconic Amides.*—Solutions of the *cis-trans*-amides, containing traces of iodine, were irradiated with light from a 100-w filament lamp, and the precipitates recrystallised, and identified by mixed m. p.s.

Compound	Solvent	Time (min.)	Product (all-*trans*)	Solvent for recrystn. and yield (%)	M. p.
(IV) (0·1 g.)	H_2O (5 c.c.)	15	Muconamic acid	H_2O, 90	284—285° (decomp.)
(VII) (0·2 g.)	EtOH (30 c.c.)	60	,, ,,	,, 95	285—286 (decomp.)
(V) (0·1 g.)	C_6H_6 (10 c.c.)	20	Methyl muconamate	C_6H_6, 85	177—178
(VI) (50 mg.)	,, (2 c.c.)	60	,, ,,	,, 70	,,

Amide of γ-*Carboxymethylbut-*α*-enolide* (VIII).—(*a*) γ-Carboxymethylbut-α-enolide (*J.*, 1950, 2228) (1 g.) was heated under reflux with thionyl chloride (10 c.c.) for 15 min. Excess of reagent was removed under reduced pressure and the residue added slowly to aqueous ammonia (2 c.c.; *d* 0·88) at 0°. From ethanol the *amide* of γ-carboxymethylbut-α-enolide (0·25 g.) crystallised as needles, m. p. 146—147° (Found: C, 50·9; H, 4·9; N, 10·2. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). Light absorption in ethanol: inflection at 2250 Å, ε = 3100.

(*b*) *cis-trans*-Muconic (α)-acid (δ)-amide (180 mg.) was kept at 155—165° for 2 hr., and the red melt was cooled and extracted with saturated aqueous sodium hydrogen carbonate (2 c.c.). Crystallisation of the residue from ethanol afforded needles (30 mg., 16%), m. p. 145—146°, and mixed m. p. 146—147° with the preparation (*a*). The m. p. of a mixture with the starting material (m. p. 152—153°) was depressed to 137—142°.

Reaction of (VIII) *with Sodium Methoxide.*—The lactonic amide (220 mg.) in methanol (5 c.c.) was kept with methanolic sodium methoxide (0·8 c.c.; 2·4N) for 20 min. The solution was then evaporated to small bulk under reduced pressure, diluted with water (2 c.c.), acidified with hydrochloric acid, and treated with aqueous 2:4-dinitrophenylhydrazine hydrochloride. After several days at 0°, the neutral precipitate (280 mg., 50%) was crystallised from aqueous ethanol, affording β-*ketoadipic* (α)-*amide* (δ)-*methyl ester* 2:4-*dinitrophenylhydrazone* as yellow needles, m. p. 169—170° (Found: C, 43·65; H, 4·4; N, 19·6. $C_{13}H_{15}O_7N_5$ requires C, 44·2; H, 4·3; N, 19·8%).

Reaction of (VIII) *with Sodium Hydroxide.*—The lactonic amide (200 mg.) was dissolved in 10% aqueous sodium hydroxide (2 c.c.), and after 20 min. the solution was acidified and kept at 0° with aqueous 2:4-dinitrophenylhydrazine hydrochloride. β-*Ketoadipic* (δ)-*acid* (α)-

amide 2 : 4-*dinitrophenylhydrazone* (310 mg., 72%) crystallised from aqueous ethanol as yellow needles, m. p. 191—192° (decomp.) (Found : C, 42·5; H, 3·95; N, 20·6. $C_{12}H_{13}O_7N_5$ requires C, 42·5; H, 3·9; N, 20·6%).

Treatment of a suspension of the acid derivative (200 mg.) in ether with diazomethane afforded the ester derivative (yield, almost theoretical), m. p. and mixed m. p. 167—169°.

Analyses were performed in the microanalytical laboratory (Mr. F. H. Oliver) and measurements of light absorption in the spectrographic laboratory (Mrs. A. I. Boston) of this Department. Grateful acknowledgment is made to the Ministry of Education for a grant (to P. S.).

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[*Received, February 3rd*, 1953.]