Tetrahedron Vol. 29, pp. 4251 to 4258. Pergamon Press 1973 Printed in Great Britain

NATURALLY OCCURING LACTONES AND LACTAMES—V[1]

HALOGENATED β-KETO ESTERS AS STARTING MATERIALS FOR THE SYNTHESIS OF TETRONIC ACIDS

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(*Received in UK* 30 *July* 1973; *Accepted for publication* 30 *August* 1973)

Abstract—In an effort to improve and simplify the synthetic route to tetronic acids 15 differently substituted β-keto esters were investigated as potential starting materials. The β-keto esters were brominated and cyclised with 2·5 N KOH as cyclising agent. Tetronic acid and seven derivatives including the naturally occuring carolinic acid were obtained. In a number of cases products arising from a Favorskii rearrangment were isolated. The NMR spectroscopic data are discussed.

INTRODUCTION

Tetronic acids may be prepared by cyclisation of halogenated acylmalonic esters to 3-ethoxycarbonyltetronic acids and subsequent alkaline hydrolyses to remove the ethoxycarbonyl group.[2-7] With one exception[6] the yields are rather low. In a recent paper[8] an improved synthesis of tetronic acid and three analogues was described. The difficulties of the original route were circumvented with the use of triethylamine as cyclising agent.

Replacement of acylmalonic esters by derivatives of ethyl acetoacetate have been used in a few cases. Thus 3-bromotetronic acid[9] and some 3-alkyltetronic acids[10,11] have been obtained by pyrolysis of ethyl 2,4-dibromoacetoacetate and ethyl 2-alkyl-4-bromoacetoacetate, respectively, just as (±)-carolinic acid[4] could be obtained from cyclisation of the condensation product of 2-chloropropionyl chloride with the ethoxymagnesio-derivative of diethyl 3-oxohexanedioate. Recently the synthesis of carolinic acid has been repeated using a modified procedure.[12] It appears that tetronic acid itself cannot be prepared by this route, since ethyl 4-bromoacetoacetate does not cyclise on heating, an α-substituent being necessary for the reaction to proceed. We have undertaken a general investigation of the utility of brominated β-keto esters as starting materials for tetronic acids and this paper deals with our results.

RESULTS AND DISCUSSION

It is generally believed that bromination of β-keto esters occurs initially at the α-C atom and under appropriate conditions rearrangement to γ-substituted products takes place.[13,14] This migration of bromine is necessary to form intermediates capable to cyclise to tetronic acids. In our case the β-keto esters were brominated in $CHCl_3$ at 0° and the rearrangement effectuated by passage of air through the solution for one hr. This process at the same time removes the developed HBr gas and introduces moisture in the reaction mixture thus creating the best conditions for the rearrangment. In Scheme 1 the β-keto esters included in this study are listed. Except for **14b** and **15b** all the brominated products were liquids.. No attempts were made to purify them as elemental analyses indicated sufficient purity. The completeness of bromine rearrangement was estimated from NMR spectroscopic investigations. The pertinent data are shown in Table 1. Only proton signals from the C atoms flanking the carbonyl groups are included in the discussion.

On bromination of **1a** the CH_3CO signal at 2·29 ppm almost completely disappeared and a new peak at 4·07 ppm arose thus indicating a successful conversion. The NMR spectra of crude **2b** and **3b** were complex. The original CH_3CO signal of **2a** at 2·25 ppm was reduced in intensity but not totally eliminated. The α-proton quartet of **2a** at 3·54 ppm was shifted at lower field and obscured by other signals in the same region. From the data obtained it was difficult to judge the amount of γ-bromoester. **3b** behaved similarly but it was possible to extract the individual data in this case. In contrast the NMR spectrum of **4b** was very informative. The $CH_3—\underset{|}{C}H—Br$ grouping was represented by a doublet (J = 7 Hz) at 1·77 ppm and a quartet at 4·66 ppm. The α-protons appeared as an AB-system. Obviously the bromine substitution introduces a center of asymmetry at the γ-C atom rendering the α-protons magnetically nonequivalent. The rearrangment was found to be virtually

Table 1. Selected ^{1}H NMR spectroscopic data of β-ketoesters (a) and brominated β-ketoesters (b) 1–10[a]

(The abbreviations are: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The chemical shift values (δ) are in ppm and the coupling constants in Hz. The solvent is $CDCl_3$).

	a		b	
	α-Protons	γ-Protons	α-Protons	γ-Protons
1	3·45 (2H, s)	2·29 (3H, s)	3·71 (2H, s)	4·07 (2H, s)
2	3·54 (1H, q, J = 7)	2·25 (3H, s)		
3	3·36 (1H, t, J = 7)	2·22 (3H, s)	3·75 (1H, t, J = 7)	4·08 (2H, s)
4	3·47 (2H, s)	2·59 (2H, q, J = 7)	AB-system[b]	4·66 (1H, q, J = 7)
5	3·55 (1H, q, J = 7)	2·59 (2H, q, J = 7)	4·10 (1H, q, J = 7)[c]	4·77 (1H, q, J = 7)
6	3·52 (2H, s)	~2·70 (1H, m)	3·90 (2H, s)	none
7	3·46 (2H, s)	2·55 (2H, t, J = 7)	AB-system[d]	*e*
8	3·41 (2H, s)	1·80–2·55 (3H, m)[f]	AB-system[g]	4·27 (1H, d, J = 8)
9	3·44 (4H, s)[h]		*i*	
10	3·51 (2H, s)	2·45–3·05 (4H, m)[j]	3·80 (2H)[k]	4·90 (1H)[l]

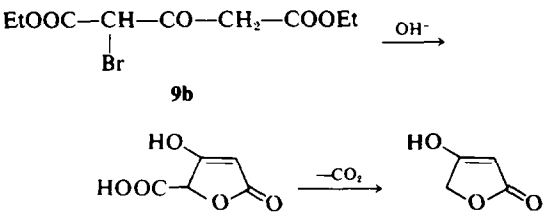
[a] Only data of unenolized forms are compiled as in most cases these were predominating.
[b] δ_A: 3·54, δ_B: 3·82 J = 16.
[c] Partly obscured by ester methylene proton signal.
[d] δ_A: 3·64, δ_B: 3·86 J = 16.
[e] Totally obscured by the ester methylene proton signal.
[f] The C-5 proton is included in this signal.
[g] δ_A: 3·60, δ_B: 3·85 J = 16.
[h] The α- and γ-protons are equivalent.
[i] The individual data could not be extracted from the complex spectrum.
[j] The γ-protons are part of an AA'BB' spectrum.
[k] The α-protons probably form an AB-system which is rendered unanalysable by the presence of other signals in the same region.
[l] X part of an ABX-system.

quantitative. This was the case also for **7b**, **8b** and **10b**. Compounds **7b** and **8b** displayed well defined AB-systems, whereas the AB-system of **10b** was partially obscured. When **10b** was dissolved in CD_3CODC_3 and the deuterium exchange allowed to reach equilibrium a perfect ABX-system, formed by the C-4 and C-5 protons, amply confirmed the completeness of γ-substitution. The NMR spectrum of crude **5b** displayed a one proton quartet at 4·77 ppm (J = 7 Hz) and a partly obscured quartet at 4·10 ppm. No signals from **5a** were detectable so again the rearrangement was complete. The data of **6b** were extremely simple. A singlet at 1·91 ppm (6H) and a singlet at 3·90 ppm (2H) left no doubt of the identity of the product. Except for **2b** and **3b**, which could not be analysed, all compounds predominantly existed on keto form and other tautomeric forms could be neglected. This seemed not to be the case for **9b**. Although no attempt was made to analyse the spectrum in detail, since **9a** is a symmetric molecule giving rise to only one monobrominated product, signals in the vinylic region (> 5 ppm) indicated the presence of one or more enol forms. A one proton enol signal at 12·06 ppm and a broad one proton signal at 4·73 ppm revealed that crude **13b** is a rearranged product existing virtually completely on enol form. In contrast enol forms seemed unimportant for the pure compounds **14b** and **15b**. This observation has been reported earlier[16] but the conclusion from IR spectroscopic investigations was that the isolated pure bromo esters were α-substituted species. The signals from the CO group flanking protons in **14b** coalesced more or less with the ester methylene protons, but **15b** displayed distinct signals: A doublet of doublets at 3·80 ppm (1H, J = 4 and 11 Hz) and a doublet of doublets at 4·43 ppm (1H, J = 5 and 11 Hz) for the α- and γ-proton, respectively, stemming from *cis* and *trans* coupling with neighboring methylene group protons, confirmed the structure to be correct. In sum it must be concluded that all the investigated β-keto esters with the exception of **2b** and **3b**, and **14b** and **15b** which were isolated as pure compounds, on bromination and work-up as specified above and in the experimental section almost quantitatively gave proper starting materials for tetronic acids. Since **11b** and **12b** are formed directly from 2-bromopropionyl bromide and the ethoxymagnesio-derivatives of ethyl acetoacetate and diethyl 3-oxohexanedioate, respectively, a discussion of the position of the bromine substituent is not necessary.

As cyclisation of γ-bromo-β-keto esters by pyrolysis is limited to α-substituted species we searched for a more general procedure. The presence of two base labile functionalities in the molecule quite naturally led us to examine the action of aqueous KOH under various conditions. After several experiments it was found that a number of bromo esters when poured on

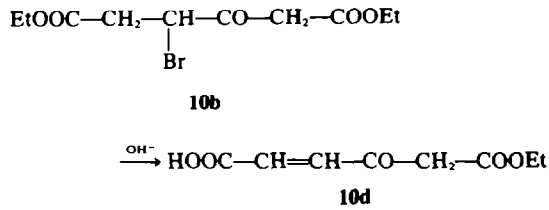
2·5 N KOH at 0° and treated at that temp for 1–4 hr were cyclised to tetronic acids. The mechanistic aspects of the cyclisation are depicted in Scheme 2. No attempts were made to find the actual mode of reaction or to rule out non-operative mechanisms.

From **1b** tetronic acid was obtained in a yield of 38%. In an effort to improve the yield the crude bromination product of **1a** was distilled prior to base treatment. The NMR spectrum and index of refraction of the distilled product were almost identical with those of the crude product and no improvement was found. All the same this procedure seems to represent the most direct route to tetronic acid. The bromination product of **2a** on isolation deposited a small amount of pure **2c**. Yet after standing at room temp for weeks no more crystalline material appeared. The remaining oil was then treated with KOH to give **2c** in 43% yield. For the sake of comparison crude **2b** was pyrolyzed *in vacuo* and **2c** was obtained in 34% yield. The cyclisation of **3b** was accomplished under alkaline conditions in a yield of 39%. The pyrolysis procedure has been reported[18] to give a 51% crude yield of **3c**. Compounds **4b** and **7b** were cyclised to the tetronic acids **4c** and **7c**, respectively, in clean reactions which were very easy to work up, thus demonstrating the effectiveness of the developed procedure. It was a surprise, therefore, that **8b** in spite of the structural resemblance to the two last mentioned bromo esters was not cyclised under the general alkaline conditions. The only well defined product isolated was isopropylsuccinic acid. As it seems this compound could only result from a Favorskii rearrangement. Compounds **5b** and **6b** did give the desired tetronic acids **5c** and **6c**, respectively, but in addition products arising from a Favorskii rearrangement were isolated. Thus, from **5b** *meso*-2,3-dimethylsuccinic acid were obtained and from **6b** 2,2-dimethylsuccinic acid resulted. Treatment of **9b** with KOH and work-up gave an oil from which gas was evolved. After one week a small amount of crystals identified as tetronic acid were isolated. Apparently cyclisation is accompanied by saponification of the remaining ester group. The free acid is labile and decarboxylates with liberation of CO_2:



9b

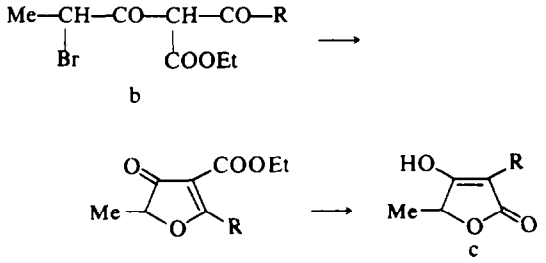
Successful conversion of **10b** to the tetronic acid **10c** was not achieved. As a number of naturally occuring tetronic acids are 3-acyl derivatives of the corresponding free acid[19] it would be valuable to prepare this synthon in quantity, but under the general reaction conditions **10b** was only converted to a viscous brown oil, from which no products were identified. In a modified procedure offering milder conditions **10b** was dissolved in ether and treated with KOH for 1·5 hr. In this case the elimination product **10d** was obtained in 69% yield:



10b **10d**

It is disappointing but not surprising that elimination was preferred to cyclisation. Pyrolysis produced no better results.

The intermediates **11b** and **12b**, prepared as mentioned above, have been reported to undergo spontaneous cyclisation to 4-oxo-4,5-dihydrofurans which in turn when treated with base rearranged to tetronic acids:



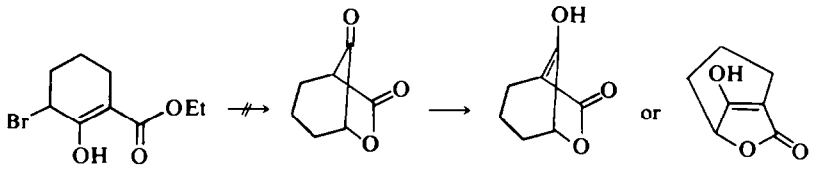
b c

11: R = Me
12: R = CH_2CH_2COOEt

Following the indicated procedure with care we isolated no 4-oxo-4,5-dihydrofurans. The crude condensation products were then treated with KOH as usual. From **11b** no tetronic acid was obtained although TLC indicated the presence of it in the reaction mixture. In contrast **12b** gave carolinic acid in 42% yield.

The conversion of cyclic β-keto esters must depend strongly on ring size. Thus **13b** was not considered to be a promising starting material for a tetronic acid since **13c** represents a bicyclic system with a double bond in a position so that Bredt's rule is strongly violated.

Model studies indicated that a planar lactone ring was difficult if not impossible to obtain, so that **13c** would be a molecule without the characteristics of a tetronic acid as these are closely connected with planarity of the ring. For larger ring sizes the bicyclic system with a planar lactone ring is a realistic possibility. However, all the cyclic compounds **31b**, **14b** and **15b** behaved identically and gave no tetronic acids. In all cases ringcontracted cycloalkane-



13b 13c

1,2-dicarboxylic acids and acid esters were the sole products isolated.

It is not unexpected that a Favorskii rearrangement was encountered in some cases. Especially the cyclic bromo β-keto esters have been shown earlier to be prone to rearrange.[16] Previous experiments with bromo ketones have been carried out, generally, under more vigorous conditions, but it is obvious that the presence of the ethoxycarbonyl-group facilitates α-proton abstraction, the reaction thus demanding less drastic conditions. Several mechanistic suggestions about the Favorskii rearrangement have been put forward.[20-23] Accepting a cyclopropane intermediate the scheme may be set up.

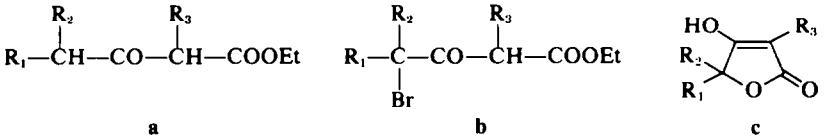
Many attempts have been made to draw conclusions about the stereochemistry in the rearrangement[24,25] but no general features seem to have been extracted as the stereochemical outcome appears to be dependent on the polarity of the reaction medium.[26] The only conclusion from our data is that a possible cyclopropane intermediate ringopens in such a fashion as to create products derived from the most stable carbanion (path B *vs* path A). Exclusively succinic acid derivatives and not malonic acid derivatives were isolated.

EXPERIMENTAL

All m.p.s are uncorrected. Microanalyses were performed at the microanalytical department of the University of Copenhagen. UV spectra were recorded on a Beckman ACTA III spectrophotometer. The solvent was abs EtOH. NMR spectra were recorded on a JEOL C-60 HL spectrometer with TMS as internal standard. The chemical shifts are expressed in δ-values (ppm) downfield from TMS. Coupling constants are expressed in Hz. The progression of the reactions was monitored conveniently on TLC with ether as eluant. All starting materials were prepared by known methods.

Ethyl 4-bromoacetoacetate (**1b**). To a Br_2 of ethyl acetoacetate (13·0 g, 0·1 mole) in $CHCl_3$ (90 ml) br_2 (5·2 ml; 0·1 mole) was added in $CHCl_3$ (10 ml) at 0° and the mixture was left for 15 hr at room temp. Then a stream of air was passed through the soln for 1 hr. After drying (Na_2SO_4) the solvent was removed in vacuo to give 20·9 g of a yellow oil, n_D^{25}: 1·4767; NMR see Table 1. (Found: Br: 38·80. $C_6H_9BrO_3$ requires: Br, 38·22%.) Distillation, b.p.$_{12}$ 110–120°, n_D^{27}: 1·4750 (lit.[27] b.p.$_{16}$ 115–119°, n_D^{20}: 1·4823); NMR practically identical with that of crude **1b**.

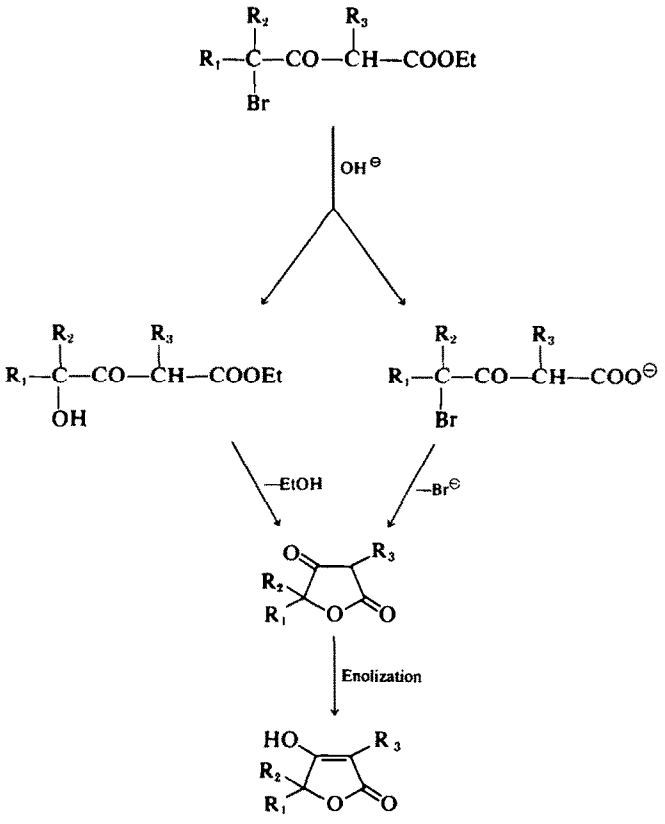
Tetronic acid (**1c**). Crude **1b** (20·9 g) was poured into 100 ml 2·5 N KOH at 0° and vigorously stirred for 4 hr at that temp. After extraction with ether to remove unreacted starting material the mixture was acidified with 4 N HCl to pH < 1 and exhaustively extracted with ether. The ether extract gave 11·9 g of an oil which partially solidified in the refrigerator. The crystals were washed with



a b c

	R_1	R_2	R_3
1	H	H	H
2	H	H	CH_3
3	H	H	Et
4	CH_3	H	H
5	CH_3	H	CH_3
6	CH_3	CH_3	H
7	Et	H	H
8	iso-Pr	H	H
9	COOEt	H	H
10	CH_2COOEt	H	H
11	CH_3	H	$COCH_3$
12	CH_3	H	$COCH_2CH_2COOEt$
13	H	$(CH_2)_3$	
14	H	$(CH_2)_5$	
15	H	$(CH_2)_9$	

SCHEME 1



SCHEME 2

ice-cold ether and filtered (4·0 g). Recrystallisation from EtOAc yielded 3·8 g (38%), m.p. 140–141° (lit.[9] m.p. 141°); λ_{max} (log ϵ_{max}): 222 nm (4·10); NMR (DMSO-d_6): 4·67 (2H, d, $J \sim 0{\cdot}5$), 4·97 (1H, t, $J \sim 0{\cdot}5$). (Found: C, 48·05; H, 4·01; $C_4H_4O_3$ requires: C, 48·01; H, 4·03%).

Ethyl 4-bromo-2-methylacetoacetate (**2b**). Ethyl 2-methyl-acetoacetate (15·8 g) was brominated and airated as above to give 23·8 g of an oil which upon standing deposited white crystals of 3-methyltetronic acid. When filtered off and washed with cyclohexane the m.p. was 187–189°. The residual oil had n_D^{23}: 1·4677 and its NMR spectrum was very complex.

3-Methyltetronic acid (**2c**). (a) Crude **2b** (22·1 g) was cyclised using the above method to give after recryst. from EtOAc 4·9 g (43%) of **2c**, m.p. 186–189° (lit.[17] m.p. 189°); λ_{max} (log ϵ_{max}): 228 nm (4·08); NMR (DMSO-d_6): 1·60 (3H, t, $J \sim 0{\cdot}5$), 4·59 (2H, q, $J \sim 0{\cdot}5$), 11·70 (1H, br). (Found: 52·70; H, 5·33. $C_5H_6O_3$ requires: C, 52·63; H, 5·30%).

(b) Crude **2b** (26·2 g) was heated at 130°/11 mm Hg for 3 hr to give after washing with ether and filtration 4·3 g (34%) of **2c**, data as above.

Ethyl 4-bromo-2-ethylacetoacetate (**3b**). Bromination of ethyl 2-ethylacetoacetate (17·4 g; 0·11 mole) gave 26·6 g of a liquid, n_D^{26}: 1·4635; NMR ($CDCl_3$): 0·94 (3H, t, $J = 7$), 2·22 (3H, t, $J = 7$), 1·65–2·30 (2H, m), 3·75 (1H, t, $J = 7$), 4·08 (2H, s), 4·20 (2H, q, $J = 7$). (Found: Br, 33·86. $C_8H_{13}BrO_3$ requires: Br, 33·70%).

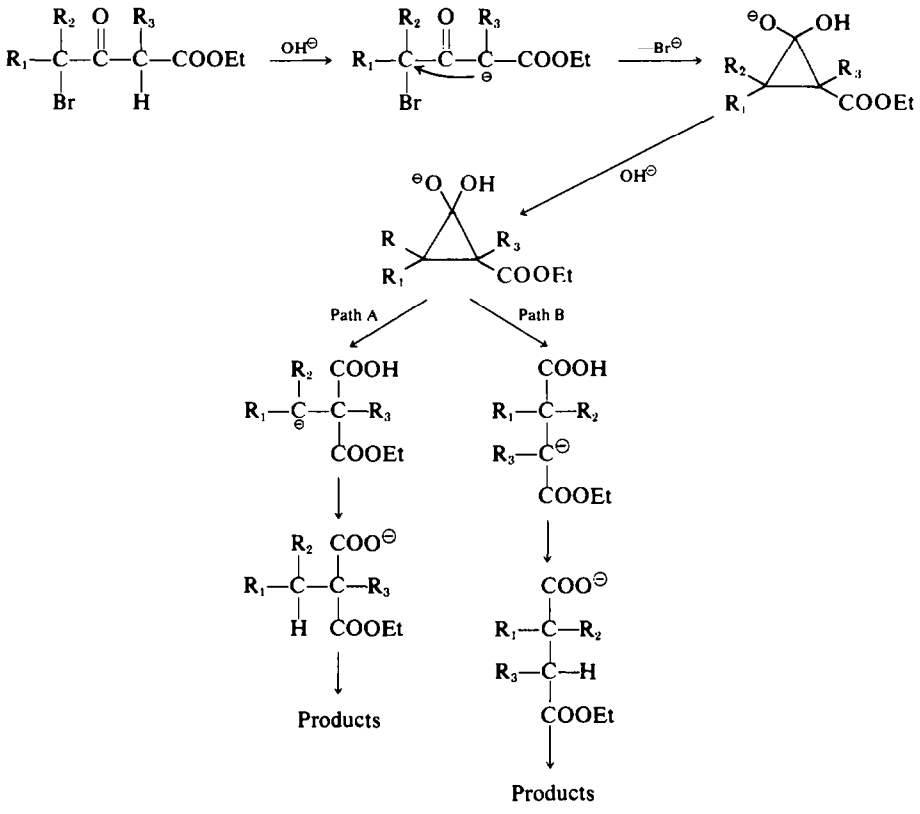
3-Ethyltetronic acid (**3c**). Crude **3b** (22·2 g) treated with KOH gave 12·6 g of a dark oil from which **3c** crystallised on cooling. Recrystallisation from EtOAc gave 4·7 g (39%), m.p. 128–130° (lit.[18] m.p. 127–128°); NMR ($CDCl_3$): 0·99 (3H, t, $J = 7$), 2·10 (2H, q, $J = 7$), 4·58 (2H, s), 11·05 (1H, br). (Found: C, 52·70; H, 6·27. $C_6H_8O_3$ requires: C, 56·24; H, 6·29%).

Ethyl 4-bromo-3-oxopentanoate (**4b**). From ethyl 3-oxopentanoate (28·8 g) 45·4 g of **4b** was obtained as an oil, n_D^{25}: 1·4710; NMR ($CDCl_3$): 1·30 (3H, t, $J = 7$), 1·76 (3H, d, $J = 7$), 3·67 (2H, AB-system), 4·19 (2H, q, $J = 7$), 4·66 (1H, q, $J = 7$). (Found: Br, 35·65. $C_7H_{11}BrO_3$ requires: Br, 35·82%.)

5-Methyl tetronic acid (**4c**). Cyclisation of crude **4b** (22·7 g) gave upon recrystallisation from EtOAc 7·8 g (68%) of **4b**, m.p. 121–122° (lit.[8] m.p. 118–120°); λ_{max} (log ϵ_{max}): 221 nm (4·12); NMR (DMSO-d_6): 1·35 (3H, d, $J = 7$), 4·86 (1H, q, $J = 7$), 4·91 (1H, s), 12·15 (1H, br).

Ethyl 4-bromo-2-methyl-3-oxopentanoate (**5b**). Ethyl 2-methyl-3-oxopentanoate (31·6 g) on bromination and airation gave 49·8 g of an oil, n_D^{27}: 1·4630; NMR ($CDCl_3$): 1·26 (3H, t, $J = 7$), 1·41 (3H, d, $J = 7$), 1·76 (3H, d, $J = 7$), 4·10 (1H, q, $J = 7$), 4·20 (2H, q, $J = 7$), 4·77 (1H, q, $J = 7$). (Found: Br, 35·23. $C_8H_{13}BrO_3$ requires: Br, 33·70%.)

3,5-Dimethyltetronic acid (**5c**). The bromoester **5b** was cyclised as above. Work-up gave 15·8 g of a crystalline mass which then triturated with ether left 10·4 g of crystals softening and melting in the range 117–170°. The crystals, found to consist of **5c** and 2,3-dimethylsuccinic acid, could be separated utilizing their different solubility in



SCHEME 3

$CHCl_3$. After washing the crystal mixture repeatedly with $CHCl_3$ the pooled extracts were evaporated and the residue recrystallised from $CHCl_3$/hexane to give pure **5c**, yield 6·7 g (59%), m.p. 124–125° (lit.[18] m.p. 121–122·5°); λ_{max} (log ϵ_{max}): 227 nm (4·07); NMR ($CDCl_3$): 1·51 (3H, d, J = 7), 1·75 (3H, d, $J \sim 1$), 4·87 (1H, dq, J = 7 and 1), 10·45 (1H, br).

meso-2,3-*Dimethylsuccinic acid.* The $CHCl_3$ insoluble part of the crystal mixture mentioned under **5c** was recrystallised from EtOAc, yield 3·2 g (22%), m.p. 203–204° (lit.[28] m.p. 206° for the *meso*-form); eq. weight: found 71, calc. 73; NMR (DMSO-d_6): 1·09 (6H, d, J = 7), 2·55 (2H, q, J = 7), 10·21 (2H, br).

Ethyl 4-bromo-4-methyl-3-oxopentanoate (**6b**). On bromination and airation **6a** (17·4 g) gave **6b** (26·7 g) as an oil, n_D^{26}: 1·4660; NMR ($CDCl_3$): 1·28 (3H, t, $J \approx 7$), 1·91 (6H, s), 4·22 (2H, q, J = 7). (Found: Br, 33·67. $C_8H_{13}BrO_3$ requires: Br, 33·70%.)

5,5-*Dimethyltetronic acid* (**6c**). The other extract obtained from the cyclisation of **6b** (24·3 g) upon evaporation gave 10·5 g of crystals consisting of a 60:40 mixture of **6c** and 2,2-dimethylsuccinic acid. The crystal mixture was washed several times with ether leaving undissolved 4·0 g (31%) of **6c**, m.p. 144–146°. Recrystallisation from EtOAc gave unchanged m.p. (lit.[6] m.p. 142–144°); NMR (DMSO-d_6): 1·41 (6H, s), 4·81 (1H, s), 11·60 (1H, br).

2,2-*Dimethylsuccinic acid.* The combined ether washings obtained under **6c** contained 6·0 g (41%) of 2,2-dimethylsuccinic acid of m.p. 119–135°. Recrystallisation from cyclohexane raised the m.p. to 141–143° (lit.[29] m.p. 144°); NMR (DMSO-d_6): 1·20 (6H, s), 2·48 (2H, s), 10·11 (2H, br).

Ethyl 4-bromo-3-oxohexanoate (**7b**). According to the general procedure **7a** (18·4 g) was brominated and rearranged to give 27·9 g of **7b** as an oil, n_D^{26}: 1·4700; NMR ($CDCl_3$): 1·05 (3H, t, J = 7), 1·30 (3H, t, J = 7), 1·75–2·40 (2H, m), 3·75 (2H, AB-system), 4·24 (2H, q, $J \approx 7$), 4·45 (1H, t, J = 7). (Found: Br, 32·82. $C_8H_{13}BrO_3$ requires: Br, 33·70%).

5-Ethyltetronic acid (**7c**). Crude **7b** (23·7 g) when cyclised with KOH and extracted with ether prior to acidification gave 2·3 g of nonacidic material. Acidification and exhaustive ether extraction gave 12·8 g of an oil from which 10·7 g of colourless crystals were isolated. Recrystallisation from EtOAc resulted in 7·3 g (57%) of pure **7c**, m.p. 129–130° (lit.[6] m.p. 127–129°); λ_{max} (log ϵ_{max}): 221 nm (4·13); NMR (DMSO-d_6): 0·87 (3H, t, J = 7), 1·16–2·16 (2H, m), 4·79 (1H, dd, J = 4·5 and 6), 4·93 (1H, br s), 12·30 (1H, br). (Found: C, 56·30; H, 6·32. $C_6H_8O_3$ requires: C, 56·24; H, 6·29%.)

Ethyl 4-bromo-5-methyl-3-oxohexanoate (**8b**). Bromination of **8a** (18·9 g) and work-up as usual gave 26·8 g of **8b** as a dark coloured oil, n_D^{25}: 1·4670; NMR ($CDCl_3$): 1·05 (3H, d, J = 6), 1·14 (3H, d, J = 6), 1·29 (3H, t, J = 7), 1·95–2·65 (1H, m), 3·74 (2H, AB-system), 4·22 (2H, q, J = 7), 4·27 (1H, d, J = 8). (Found: Br, 31·73. $C_9H_{15}BrO_3$ requires: Br, 31·82%).

Isopropylsuccinic acid. Crude **8b** (13·4 g) was poured

into 50 ml 2·5 N KOH and treated 3 hr to give 9·6 g of a reddish brown oil, which after standing for 3 days in the refrigerator deposited 2·6 g of crystals. Recrystallisation from benzene gave 2·4 g (27%) of pure title comp, m.p. 117–118° (lit.[30] m.p. 115·5–116·5); NMR (DMSO-d_6): 0·90 (3H, d, J = 7), 0·93 (3H, d, J = 7), 1·60–2·20 (1H, m), 2·25–2·68 (3H, m), 10·57 (1H, br). (Found: C, 52·77; H, 7·61. $C_7H_{12}O_4$ requires: C, 52·49; H, 7·55%).

Diethyl 2-bromo-3-oxopentanedioate (**9b**). Monobromination of **9a** (40·4 g) gave 56·4 g of **9b**, n_D^{27}: 1·4701. (Found: Br, 29·43. $C_9H_{13}BrO_5$ requires: Br, 28·43%).

Attempted synthesis of 5-ethoxycarbonyltetronic acid (**9c**). Treatment of **9b** (28·2 g) with 100 ml 2·5 N KOH for 4 hr gave 21·4 g of a reddish brown oil. After standing at room temp for some days gas was evolved from the oil and after weeks a small amount (90 mg) of crystals was deposited. These were identified as tetronic acid. Reducing the reaction time to 1 hr produced no better result.

Diethyl 4-bromo-3-oxohexanedioate (**10b**). **10a** (43·2 g) on bromination afforded **10b** (60·0 g) as an oil, n_D^{27}: 1·4700; NMR ($CDCl_3$): 1·27 (3H, t, J = 7), 1·30 (3H, t, J = 7), 2·60–3·05 (2H, m), 3·79 (2H, AB-system), 4·18 (2H, q, J = 7), 4·23 (2H, q, J = 7), 4·90 (1H, t, J = 7).

Attempted synthesis of 5-ethoxycarbonylmethyltetronic acid (**10c**). Treatment of **10b** with KOH gave 22·2 g of a brown oil. TLC revealed "tailing" thus indicating progressive deterioration of starting material. No well defined products could be isolated.

1-Ethyl hydrogen (E)-3-oxo-4-hexenedioate (**10d**). **10b** (27·3 g) was dissolved in ether (100 ml) and cooled to 0°. Precooled 2·5 N KOH (100 ml) was poured into the soln and the mixture was vigorously stirred for 1·5 hr. After acidification with 4 N HCl the ether layer was separated, the water phase extracted with another 100 ml portion of ether and the combined ether extracts dried (Na_2SO_4). Evaporation of the solvent left 13·3 g of solid material, which after recrystallisation from $CHCl_3$/cyclohexane gave 10·1 g (59%) of the title comp as shining microneedles, m.p. 138–141° (lit.[31] m.p. 137–139°); λ_{max} (log ϵ_{max}): 283 nm (4·15) and 223 nm (3·83); NMR* ($CDCl_3$): 1·30 (3H, t, J = 7), 4·25 (2H, q, J = 7), 5·25 (1H, s), 6·50 (1H, d, J = 15), 6·95 (1H, d, J = 15). (Found: C, 51·35; H, 5·42. $C_6H_{10}O_5$ requires: C, 51·61; H, 5·41%), m.p. of 2,4-dinitrophenylhydrazone 190–194°.

Diethyl 2-(2-bromopropionyl)-2-oxohexanedioate (**12b**). With the directives of Ref 13 in mind **12b** was prepared in the following way. Mg flakes (2·5 g; 0·1 mole) and abs EtOH (15 ml) were gently heated in benzene (30 ml) with CCl_4 (0·5 ml) as initiator. After 1 hr **10a** (21·6 g; 0·1 mole) in benzene (15 ml) was added dropwise. The mixture was refluxed for 30 min giving a light green, clear soln. The solvent and excess EtOH was removed under reduced pressure and the resultant grey salt redissolved in benzene (75 ml). This soln was added to a soln of 2-bromopropionyl bromide (25·0 g) in benzene (50 ml) with cooling at a rate so that the temp did not exceed 30°. After 3 hr at room temp the Mg complex was hydrolysed with 4 N HCl. The benzene layer was separated and washed with sat $NaHCO_3$ aq and then water. Drying (Na_2SO_4) and evaporation of the solvent *in vacuo* below 40° afforded 33·2 g of an oil, n_D^{26}: 1·4693.

RS-*Carolinic acid* (**12c**, R = $COCH_2CH_2COOH$). Crude **12b** (17·8 g) was treated with KOH for 50 min. The reaction was quenched with 4 N HCl and the mixture exhaustively extracted with ether to give 13·2 g of an oil. The oil was dissolved in a 1:1 mixture (20 ml) of ether and cyclohexane and chilled at − 15° for 24 hr. Filtration of the developed crystals gave 5·0 g of crude product. Recrystallisation from EtOAc yielded 4·5 g (42%) of analytically pure **12b**, m.p. 141–142° (lit.[4] m.p. 137·5°; λ_{max} (log ϵ_{max}): 235 nm (shoulder) and 258 nm (3·94); NMR (DMSO-d_6): 1·40 (3H, d, J = 7), 2·28–3·20 (4H, m), 4·89 (1H, q, J = 7), 10·63 (2H, br). (Found: C, 50·45; H, 4·68. $C_9H_{10}O_6$ requires: C, 50·47; H, 4·71%).

Ethyl 2-(2-bromopropionyl)-acetoacetate (**11b**). This comp was prepared by the procedure for **12b**. From Mg flakes (5·0 g), abs EtOH (30 ml), ethyl acetoacetate (26·0 g) and 2-bromopropionyl bromide (49·0 g) **11b** (38·0 g) was obtained as a slightly green oil, n_D^{27}: 1·4800. Distillation of a 10 g sample apart from unreacted starting material gave a small amount (< 1 g) of a liquid, n_D^{26}: 1·4859; b.p.$_{0.2}$: 110–130°, which did not crystallise. The destillation residue was considerable.

Attempted synthesis of 2-acetyl-5-methyltetronic acid (**11c**). Crude **11b** (28·6 g) after treatment with KOH for 1 hr was worked up to give 19·3 g of an oil, n_D^{26}: 1·4885, which remained liquid even after prolonged standing at − 15°. All attempts to isolate identifiable material failed.

Ethyl 3-bromo-2-oxocyclohexanecarboxylate (**13b**). From **13a** (34·0 g; 0·2 mole) and Br_2 (32·0 g; 0·2 mole) **13b** (52·9 g) was obtained as a brown oil, n_D^{26}: 1·5269; NMR ($CDCl_3$): 1·31 (3H, t, J = 7), 1·55–2·60 (6H, m), 4·27 (2H, q, J = 7), 4·72 (1H, br), 12·06 (1H, br). (Found: Br, 31·94. $C_9H_{13}BrO_3$ requires: Br, 32·08%).

Ethyl hydrogen 1,2-cyclopentanedicarboxylate. **13b** (26·4 g) was treated with KOH for 1·5 hr and worked up to yield 16·8 g of a viscous oil, n_D^{27}: 1·4695. After 2 days at room temp crystals appeared. The residual oil was dissolved in light petroleum and the crystals filtered. Evaporation of the solvent left 14·8 g of crude title comp, n_D^{25}: 1·4691; NMR ($CDCl_3$): 1·23 (3H, t, J = 7), 1·50–2·35 (6H, m), 2·90–3·30 (2H, m), 4·15 (2H, q, J = 7), 10·50 (1H, br).

trans-1,2-Cyclopentanedicarboxylic acid. The crystals mentioned above had m.p. 156–161°. Recrystallisation from EtOAc gave m.p. 161–163° (lit.[32] m.p. 161°). (Found: C, 53·00; H, 6·34. $C_7H_{10}O_4$ requires: C, 53·16; H, 6·37%).

Ethyl 3-bromo-2-oxocyclooctanecarboxylate (**14b**). From **14a** (19·8 g) and Br_2 (16·0 g) a viscous oil was obtained which solidified on standing. The crystalline mass was triturated with ether/light petroleum and filtered. Recrystallisation from cyclohexane/$CHCl_3$ gave 15·2 g (56%) of analytically pure **14b**, m.p. 77–78° (lit.[16] m.p. 78°); NMR ($CDCl_3$): 2·24 (3H, t, J = 7), 1·30–2·50 (10H, m), 4·20 (2H, q, J = 7), 3·80–4·55 (2H, obscured signals). (Found: C, 47·55; H, 6·13; Br, 29·00. $C_{11}H_{17}BrO_3$ requires: C, 47·67; H, 6·18; Br, 28·83%).

Ethyl hydrogen 1,2-cycloheptanedicarboxylate. **14b** was treated with KOH (from 25 ml H_2O and 4·2 g 86% KOH) for 4 hr after which time extra H_2O (75 ml) was added. Extraction with ether (80 ml) gave 0·9 g of unreacted starting material. After acidification repeated ether extractions afforded 4·6 g of the title comp as a colourless, viscous oil. NMR ($CDCl_3$): 1·21 (3H, t, J = 7), 1·10–2·25 (10H, m), 2·77–3·15 (2H, m), 4·12 (2H, q, J = 7), 10·67 (1H, br).

1,2-Cycloheptanedicarboxylic acid. The above monoethyl ester was dissolved in excess 2 N KOH and saponified for 2 days at room temp. Acidification and ether extraction afforded a white solid. Recrystallisation from cyclohexane/$CHCl_3$ gave the pure diacid, m.p. 140–143° (lit.[33] m.p. 130–131° for the *cis*-diacid and m.p. 156–157° for the *trans*-diacid). Probably a mixture of *cis*

*10d is enolized to 85% in $CDCl_3$ and only data of the enolized form are given.

and *trans* form. (Found: C, 58·10; H, 7·69. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%).

Ethyl 3 - bromo - 2 - oxocyclododecanonecarboxylate From **15a** (25·4 g; 0·1 mole) and Br_2 (16·0 g) a viscous brown oil (34·2 g) was isolated. The oil was dissolved in light petroleum (50 ml), seeded with crystals from an earlier preparation and chilled at − 15°. After 24 hr the resultant crystalline mass was broken up, filtered and recrystallised from light petroleum, m.p. 94–96° (lit.[16] m.p. 94°), yield: 22·4 g (67%); NMR ($CDCl_3$): 1·25 (3H, t, J = 7), 1·10–2·55 (18H, m), 4·19 (2H, q, J = 7). (Found: C, 54·25; H, 7·59; Br, 23·93. $C_{15}H_{25}BrO_3$ requires: C, 54·06; H, 7·56; Br, 23·98%).

Ethyl hydrogen 1,2-cycloundecanedicarboxylate. **15b** (8·4 g; 0·025 mole) was treated with KOH in analogy with the procedure for **14b**. Ether extraction gave 2·1 g of nonacidic material. From the acidified reaction mixture 5·3 g of crude title comp was obtained as a viscous liquid; NMR ($CDCl_3$): 2·23 (3H, t, J = 7), 1·10–2·10 (18H, m), 2·70–3·00 (2H, m), 4·14 (2H, q, J = 7), 10·04 (1H, br).

1,2-Cycloundecanedicarboxylic acid. The above monoethylester was saponified with excess KOH as above. Recrystallisation from cyclohexane/$CHCl_3$ yielded a mixture of pure *cis* and *trans* diacid, m.p. 176–182° (lit.[16] m.p. 171–172° and 196–197° unspecified); NMR (DMSO-d_6): 1·00–2·00 (18H, m), 2·55–2·85 (2H, m), 10·31 (2H, br). (Found: C, 64·31; H, 9·21. $C_{13}H_{22}C_4$ requires: C, 64·44; H, 9·15%).

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