264. *Eight- and Higher-membered Ring Compounds. Part VI.** cis-*Di- and Tri*-o-*thymotides.*

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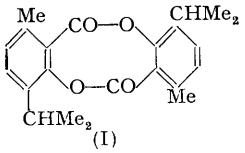
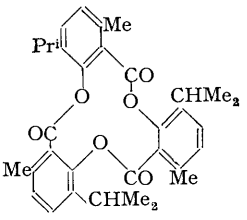
Dehydration of *o*-thymotic acid by various reagents gives *cis*-di-*o*-thymotide and tri-*o*-thymotide; higher cyclic anhydro-derivatives (cf. the salicylides and cresotides) are not formed. These compounds were described previously as isomeric di-*o*-thymotides. Their reactions with alkali and with benzylamine have been investigated. Tri-*o*-thymotide frequently crystallises with solvent of crystallisation; such solvents include light petroleum, *n*-hexane, and benzene.

Previous papers in this series (Parts II and III, *J.*, 1951, 202, 210) have described cyclic anhydro-derivatives of salicylic and of three of the cresotic acids. It was shown that, contrary to previous claims, only one dianhydro-derivative existed in each case, and that the second supposed isomer was, again in each case, a trianhydro-derivative. In view of these facts, it was clearly desirable to reinvestigate the two thymotides, derived from *o*-thymotic acid (2-hydroxy-6-methyl-3-*iso*propylbenzoic acid), which had been described by Spallino and Provenzal (*Gazzetta*, 1909, **39**, II, 325) as isomeric dithymotides (I). As already reported in a footnote to Part II (*loc. cit.*), these have also been found to be dithymotide (I) and trithymotide (II) containing an eight- and a twelve-membered ring respectively.

Spallino and Provenzal, in a reinvestigation of earlier work by Naquet (*Bull. Soc. chim.*, 1865, [ii], **4**, 93, 98), studied the action of phosphoric anhydride and of phosphorus oxychloride on *o*-thymotic acid in boiling xylene. In each case they obtained two anhydro-derivatives, which after crystallisation from light petroleum had m. p. 209° and 174°, the former being formed in larger yield. Cryoscopic molecular weight determinations in benzene


(I)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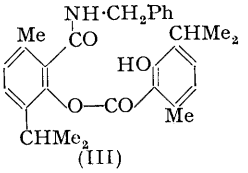
(III)

and phenol gave values in approximate agreement with the dimeric formula. Later, Lespagnol and Lupas (*ibid.*, 1937, [v], **4**, 542) reported that the action of heat on a mixture of *o*-thymotic acid, thymol, and acetic anhydride, followed by distillation, gave only the dithymotide, m. p. 212°.

In repeating the work of Spallino and Provenzal, we confirmed the production of two thymotides. They were separated by fractional crystallisation and by hand sorting, giving di-*o*-thymotide, m. p. 207° (12%), identical with the compound, m. p. 209°, described previously, and a second compound, m. p. 172° (decomp.) (from light petroleum), which was similar to Spallino and Provenzal's " dithymotide," m. p. 174°. The latter compound, however, contains light petroleum which is lost at 160°/1 mm., giving solvent-free material, m. p. 217° (decomp.), which has proved to be tri-*o*-thymotide. This previously undetected solvent of crystallisation undoubtedly led to the incorrect molecular-weight determinations by Spallino and Provenzal. The adduct must clearly be of the clathrate type (see Palin and Powell, *J.*, 1948, 815, and later papers by Powell *et al.*).

The structures of di-*o*-thymotide (I) and tri-*o*-thymotide (II) have been established by analysis, ebullioscopic molecular-weight determination, alkaline hydrolysis, and reaction with benzylamine. The *o*-thymotides are very much more stable than the corresponding

* Part V, *J.*, 1951, 1118.

salicylides and cresotides. They are unaffected by boiling 95% acetic acid, and are only very slowly hydrolysed by dilute aqueous sodium hydroxide; both these reagents cause rapid hydrolysis of *cis*-disalicylide and the *cis*-dicresotides (see Parts II and III). Alkaline hydrolysis of both thymotides was effected, however, under more vigorous conditions, giving *o*-thymotic acid, and reaction with excess of benzylamine gave *N*-benzyl-*o*-thymotamide. Reaction of *cis*-di-*o*-thymotide with half an equivalent of benzylamine gave *N*-benzyl-*O*-*o*-thymotoyl-*o*-thymotamide (III).

The dipole moments of di- (6·63 D) and tri-*o*-thymotide (4·13 D), determined by Dr. L. E. Sutton and Mr. M. F. Saxby of the Physical Chemistry Laboratory, Oxford (forthcoming publication; see also Edgerley and Sutton, *J.*, 1951, 1069), show that di-*o*-thymotide, like disalicylide and the dicresotides, has the *cis*-configuration and that tri-*o*-thymotide has a constellation similar to that proposed for trisalicylide (2·95 D) and tri-*o*-cresotide (4·28 D). The three *o*-thymotide residues are arranged approximately on the faces of a triangular-based pyramid (see photograph facing p. 1070, *J.*, 1951). Steric factors probably account for the marked stability towards hydrolysis of *cis*-di-*o*-thymotide and of tri-*o*-thymotide, compared with the corresponding salicylides and cresotides. In this connection it may be noticed that tri-*o*-cresotide is much more stable to alkali than is trisalicylide.

We have also investigated other methods for the dehydration of *o*-thymotic acid that had been used previously for the preparation of salicylides and cresotides. The action of phosphorus oxychloride on *o*-thymotic acid gave *cis*-di- and tri-*o*-thymotides in 8% and 36% yields respectively. A careful search failed to reveal any higher cyclic anhydro-derivatives, whereas salicylic and cresotic acids yield tetramers and, in two cases, hexamers with this reagent. Low-pressure distillation of *O*-acetyl-*o*-thymotic acid, a method which has been used for the preparation of the lower salicylides and cresotides, gave *cis*-di-*o*-thymotide (39%) and tri-*o*-thymotide (2·5%).*

Tri-*o*-thymotide forms crystal complexes with a wide variety of solvents (see experimental section). The adducts with light petroleum, *n*-hexane, and ethanol are remarkably stable; they dissociate only very slowly below 160°. The other adducts investigated decompose more readily, but incompletely, below this temperature.

The crystalline unsolvated form of tri-*o*-thymotide is obtained by crystallisation from methanol, but careful exclusion of seeds of solvated material is necessary, and even then some methanol complex may separate. The unsolvated compound may also crystallise partly unchanged from light petroleum or from dioxan.

Experimental

M. p.s are uncorrected. Molecular weights were determined in the Menzies–Wright apparatus as described in Part II, p. 208. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

o-*Thymotic Acid*.—The method described by Spallino and Provenzal (*loc. cit.*) gives a 35% yield. By increasing the reaction time from 5 to 20 hours, the yield of once recrystallised *o*-thymotic acid was raised to 79%.

Action of Phosphoric Anhydride on o-*Thymotic Acid* (cis-*Di*-o-*thymotide and Tri*-o-*thymotide*).—A mixture of *o*-thymotic acid (15 g.), phosphoric anhydride (15 g.), and xylene (78 c.c.) was boiled under reflux for 5 hours. The cooled mixture was shaken with water, then with 5% aqueous sodium hydrogen carbonate (50 c.c.), and again with water, dried ($MgSO_4$), and evaporated, leaving a crystalline residue, m. p. 130—170° (10·9 g.). This was heated with ethanol (100 c.c.) for ½ hour and the mixture filtered whilst hot, leaving the crude, sparingly soluble *tri*-o-*thymotide* (2·2 g.) as colourless crystals, m. p. 177—184°. The filtrate on cooling deposited a mixture of di-*o*-thymotide and a smaller quantity of the tri-*o*-thymotide–ethanol complex.

* [*Note added in proof*, 3.3.52.] *X*-Ray crystallographical examination of the *n*-hexane and benzene complexes of trithymotide is being carried out by H. M. Powell and A. C. D. Newman of the Chemical Crystallography Laboratory, Oxford. Enantiomorphous forms of trithymotide resembling right- and left-handed three-bladed propellors are possible, and resolution occurs during crystallisation. Single crystals of the benzene complex give optically active solutions which racemise fairly rapidly. This is the first case of the detection of optical activity due to enantiomorphous constellations of molecules of this type. Details of this work will be published later.

This mixture was partially separated by hand, and the remainder of the material was subjected to a repetition of the above process, eventually giving *cis*-di-*o*-thymotide (1·6 g.) and the tri-*o*-thymotide–ethanol complex (0·5 g.). The di-*o*-thymotide, after recrystallisation from light petroleum (b. p. 80—100°; 100 c.c.) and twice from ethanol (50 c.c.), was obtained as colourless needles (0·9 g.), m. p. 207° (Found: C, 74·7; H, 7·0%; *M*, ebullioscopic in benzene, 353; ebullioscopic in chloroform, 353. Calc. for $C_{22}H_{24}O_4$: C, 75·0; H, 6·9%; *M*, 352).

The crude tri-*o*-thymotide and tri-*o*-thymotide–ethanol complex were recrystallised separately from dioxan (20 c.c./g.) and then from light petroleum (b. p. 80—100°), giving in each case the *tri-o-thymotide–light petroleum* complex as a mixture of long and slender, or short and thick, hexagonal prisms, both having m. p. (and mixed m. p.) 172° (decomp.). Both forms of the light petroleum complex lost the solvent when heated for 5 hours at 160°/1 mm., giving *tri-o-thymotide* as a microcrystalline powder, m. p. 217° (decomp.) [Found: C, 74·9; H, 7·2%; *M* (ebullioscopic) in benzene 522, in chloroform 538, in carbon tetrachloride 515. $C_{33}H_{36}O_6$ requires C, 75·0; H, 6·9%; *M*, 528].

Action of Phosphorus Oxychloride on o-*Thymotic Acid* (cis-*Di-o-thymotide and Tri-o-thymotide*).—A mixture of *o*-thymotic acid (20 g.), redistilled phosphorus oxychloride (9·4 c.c.), and dry xylene (114 c.c.) was heated on a steam-bath for 12 hours. The cooled mixture was shaken with water and the solid, crude tri-*o*-thymotide–xylene complex (1·9 g.; m. p. 169—180°) collected. The xylene layer of the filtrate was separated and deposited more of the tri-*o*-thymotide–xylene complex (2·5 g.) on being kept. The final xylene filtrate was then washed with 5% aqueous sodium hydrogen carbonate (2 × 50 c.c.), then with water, and evaporated, leaving a partly crystalline residue (9·6 g.). This was separated as described above into *cis*-di-*o*-thymotide (1·4 g.) and the tri-*o*-thymotide–ethanol complex (3·4 g.). The *cis*-di-*o*-thymotide, after 3 further recrystallisations from ethanol and then from light petroleum (b. p. 80—100°), was obtained as colourless needles, m. p. 207°. The tri-*o*-thymotide–ethanol complex was recrystallised from dioxan and then from methanol (50 c.c./g.), eventually giving tri-*o*-thymotide (3·5 g.) as fine, colourless needles, m. p. 217° (decomp.) (Found: C, 74·8; H, 6·7%), and the *tri-o-thymotide–methanol* complex (0·9 g.), m. p. 175—185° (decomp.).

O-*Acetyl-o-thymotic Acid.*—Lespagnol and Bar (*Bull. Soc. chim.*, 1938, [v], **5**, 1360) obtained *O*-acetyl-*o*-thymotic acid as a colourless oil by the action of acetic anhydride on *o*-thymotic acid in the presence of sodium acetate. *o*-Thymotic acid (20 g., 0·13 mole), acetic anhydride (33 g., 0·33 mole), and concentrated sulphuric acid (0·5 g.) were heated at 55—60° for ½ hour and then at 90° for 3 hours. The cooled solution was poured into water (500 c.c.) and stirred for 5 hours, and the resulting oil was dissolved in chloroform (200 c.c.) and extracted with 5% aqueous sodium hydrogen carbonate (150 c.c.). The aqueous layer was washed with chloroform and acidified, yielding an oil which was extracted with chloroform (150 c.c.), dried ($MgSO_4$), and evaporated, giving *O*-acetyl-*o*-thymotic acid as a colourless oil (13·5 g.) (Found: equiv., 243. Calc. for $C_{12}H_{15}O_2{\cdot}CO_2H$: equiv., 236). The use of pyridine in place of sulphuric acid gave a similar result.

Action of Heat on O-*Acetyl-o-thymotic Acid* (cis-*Di-o-thymotide and Tri-o-thymotide*. Cf. Lespagnol and Lupas, *loc. cit.*).—*O*-Acetyl-*o*-thymotic acid (17 g.) was slowly distilled at 18·5 mm. pressure, using an air-bath, the temperature of which was gradually raised to 300° (cf. preparation of disalicylide, Part II). Brisk evolution of acetic acid occurred at about 150°, and a solid distillate (8·9 g.) was collected mainly between 230° and 250° (internal temp.). This was dissolved in chloroform (50 c.c.), washed with 2N-sodium hydroxide (2 × 50 c.c.), then with water, dried ($MgSO_4$), and evaporated, leaving a crystalline residue (8·2 g.). This was dissolved in hot ethanol and worked up as before, giving crude *cis*-di-*o*-thymotide (5·0 g.) and the tri-*o*-thymotide–ethanol complex (0·32 g.). After two recrystallisations from ethanol (200 c.c.), the *cis*-di-*o*-thymotide was obtained as needles (4·2 g.), m. p. 207°. The tri-*o*-thymotide–ethanol complex was recrystallised 3 times from light petroleum (b. p. 80—100°; 5 c.c.), giving the light petroleum complex (0·28 g.), m. p. 172° (decomp.).

Alkaline Hydrolysis of the o-*Thymotides.*—The *o*-thymotides could only be hydrolysed by concentrated aqueous sodium hydroxide. *cis*-Di-*o*-thymotide (0·10 g.) was heated at 95—100° with (initially 50%) aqueous sodium hydroxide (1 c.c.) in a nickel vessel for 3 days. Water (75 c.c.) was added, and the solution filtered from unchanged *cis*-di-*o*-thymotide (0·2 mg.) and acidified, precipitating *o*-thymotic acid (0·102 g., 93%), m. p. and mixed m. p. 122—123°.

Tri-*o*-thymotide (50 mg.) and 10% ethanolic potassium hydroxide (5 c.c.) were heated under reflux for 9 hours, freed from ethanol under diminished pressure, treated with water (5 c.c.), and acidified, giving *o*-thymotic acid (50 mg., 91%), m. p. and mixed m. p. 122—123°.

Reaction of the o-*Thymotides with Excess of Benzylamine* (N-*Benzyl-o-thymotamide*).—*cis*-

Di- and tri-*o*-thymotide were each boiled under reflux for 3 hours with excess of benzylamine and a trace of ammonium chloride, cooled, and poured into 2N-hydrochloric acid. The solid was collected and recrystallised from aqueous methanol (1 : 1), giving in each case N-*benzyl*-o-*thymotamide* as colourless needles, m. p. 92·5° (Found : C, 76·3; H, 6·9; N, 5·0. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 5·0%). The yields were 96% from *cis*-di-*o*-thymotide and 92% from tri-*o*-thymotide. The *N*-benzyl-*o*-thymotamide obtained by this method was identical (mixed m. p.) with a specimen prepared from methyl thymotate and excess of benzylamine under the same conditions.

N-*Benzyl*-O-o-*thymotoyl*-o-*thymotamide* (III).—*cis*-Di-*o*-thymotide (0·5 g.) and benzylamine (0·15 g.), dissolved in dry xylene (25 c.c.), were boiled under reflux for 40 hours. The xylene was then removed, leaving an oil which crystallised when kept. One recrystallisation from alcohol gave a product (0·068 g.; m. p. 202—204°) which, after purification, was identified as unchanged *cis*-di-*o*-thymotide. The residue obtained by evaporation of the mother-liquor was recrystallised 6 times from methanol (5 c.c.)–water (1 c.c.), giving N-*benzyl*-O-o-*thymotoyl*-o-*thymotamide* as needles (0·045 g.), m. p. 163° (Found : C, 75·9; H, 7·7; N, 3·2. $C_{29}H_{33}O_4N$ requires C, 75·8; H, 7·2; N, 3·1%).

Crystal Complexes of Tri-o-thymotide.—Crystallisation of tri-*o*-thymotide from a variety of solvents gives *complexes* containing solvent of crystallisation (see Table). Except in the case of the light petroleum and *n*-hexane complexes, slow cooling (*ca.* 5°/hr.) of the hot solution of tri-*o*-thymotide is necessary to obtain a homogeneous product free from unsolvated tri-*o*-thymotide. The methanol complex has not been obtained free from unsolvated material. Loss in weight was determined, in general, at 160°/1 mm. The approximate times, in hours, necessary for complete dissociation were : light petroleum, 3; *n*-hexane, 4½; ethanol, 13, followed by 6 at 178°; methanol, 4; *m*- and *p*-xylene, some loss occurs at 18°, and at 100° approximately half a molecule of solvent is lost in 4 hours; complete loss occurs after a further 2 hours at 160°.

*Crystalline complexes formed by tri-*o*-thymotide.*

Component	M. p.* (dissociation)	Mol. ratio, component/ tri-*o*-thymotide.	Found (required in parentheses): Carbon, %	Hydrogen, %	Loss in wt., %
Light petroleum (b. p. 80—100°) †	172°	½	76·0 (75·8)	7·6 (7·6)	8·7 (8·7)
n-Hexane	173	½	75·3 (75·6)	7·4 (7·6)	7·6 (7·5)
Ethanol	178	½	73·6 (74·0)	7·2 (7·1)	4·7 (4·2)
Methanol	175	<½	—	—	2·3 (2·9) ‡
m-Xylene	172	¾	—	—	13·5 (13·1)
p-Xylene	159	1	—	—	16·3 (16·7)

* M. p.s are those at which melting begins. It usually occurs over a range of 10—20°.

† Largely heptanes. The calculated analytical figures are those for a heptane complex. The determinations were made on the slender, prismatic form.

‡ The required loss in weight (2·9%) is for a methanol complex containing half a molecule of methanol per molecule of trimer. The complex used for this determination was non-homogeneous and satisfactory analytical figures could not be obtained. Analysis of the *m*- and *p*-xylene complexes was not possible owing to their instability.

Complexes are also formed with benzene, carbon tetrachloride, chloroform, and dioxan.

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