1080. *Mechanism of the Conversion of α-Thujadicarboxylic Ester into Tanacetophorone.**

By L. Crombie and D. A. Mitchard.

Formation of tanacetophorone (IV) from α-thujadicarboxylic ester (I) involves alkoxide-catalysed cyclopropane cleavage to an olefinic ester followed by Dieckmann reaction (Path B), rather than Dieckmann reaction followed by retro-Michael reaction (Path A), since the intermediate keto-ester is (VI) and not (III). The retro-Michael reaction giving β-thujadicarboxylic ester (V) from the α-ester (I) is largely complete before the Dieckmann cyclisation is very far advanced. Related examples are considered.

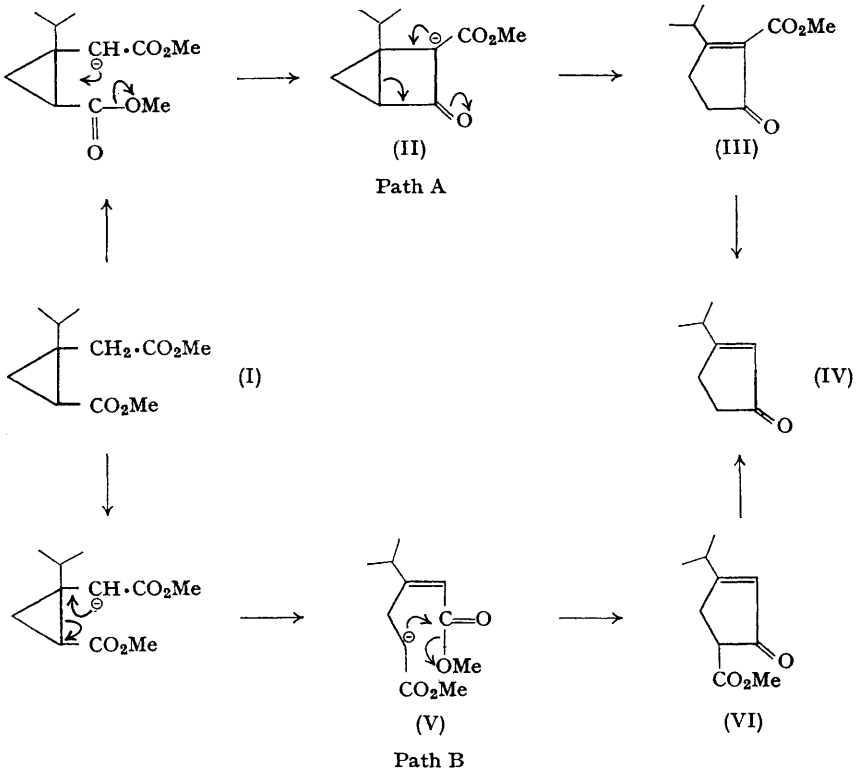
Treatment of α-thujadicarboxylic ester (I) with sodium methoxide in methanol, followed by steam-distillation from acid solution, is the classical preparation of tanacetophorone (IV).[1,2] It has been suggested[3] that Dieckmann cyclisation of α-thujadicarboxylic ester gives the keto-ester (II, shown as anion) which by retro-Michael reaction followed by hydrolysis and decarboxylation yields tanacetophorone (Path A). This mechanism has been cited,[4,5] though with reservations.† Recent work[6,7] on the base-catalysed cyclopropane

* The conclusions reached were presented at the XIXth International Congress of Pure and Applied Chemistry, London, 1963.

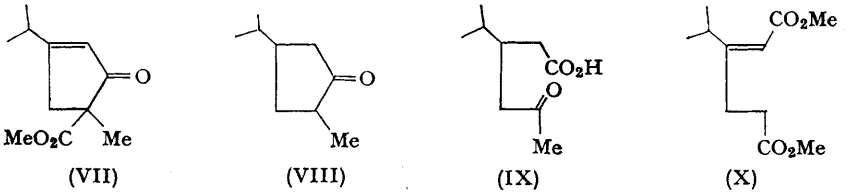
† P. de Mayo ("Molecular Rearrangements," vol. II, Interscience, New York, 1964, p. 795) prefers Path B.

1 D. Thomson, *J.*, 1910, **97**, 1511.
2 O. Wallach, *Annalen*, 1912, **388**, 49; 1918, **414**, 220.
3 C. R. Noller and R. H. Eastman in H. Gilman, "Organic Chemistry," vol. IV, Wiley, New York, 1953, p. 632. Mechanisms attributed to R. B. Woodward.
4 E. E. Van Tamelen and G. T. Hildahl, *J. Amer. Chem. Soc.*, 1956, **78**, 4405.
5 P. de Mayo, "The Chemistry of Natural Products," vol. II, Interscience, London, 1959, p. 104.
6 G. Widmark, *Arkiv Kemi*, 1957, **11**, 195.
7 L. Crombie, J. Crossley, and D. A. Mitchard, *J.*, 1963, 4957.

ring-opening of homocaronic and related esters led us to the opinion that the first step would be formation of β-thujadicarboxylic ester (V, shown as anion) which would then undergo Dieckmann reaction followed by hydrolysis and decarboxylation (Path B).



Mechanisms A and B are experimentally distinguishable since the intermediate cyclopentenone ester (III) or (VI) is different in the two cases. This cyclopentenone ester has previously been isolated only as its sodio-derivative,[2,8] and we have now examined the nuclear magnetic resonance (n.m.r.) spectrum of this, of the parent ester, and of the ester (VII) formed by methylating the sodio-derivative. All three compounds have an olefinic proton at τ 4·18—4·22, showing that (VI) and (VII) are the correct structures as opposed to (III) which has no olefinic proton. The esters were examined in carbon tetrachloride and the



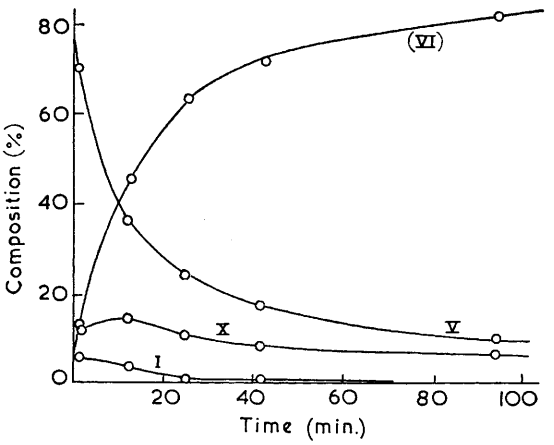
salt in dimethylformamide. The olefinic 2-hydrogen is split by long-range coupling in all three cases, and in tanacetophorone itself it appears as a quartet at τ 4·22. Long-range coupling has previously been noted in the n.m.r. spectra of cyclopentenones.[9]

Consultation of Toivonen's paper,[8] which seems to have been infrequently examined in the original, shows that he appreciated the essential structural position. He reports hydrogenation, hydrolysis, and decarboxylation of the methylated ester (VII) to give the

[8] N. J. Toivonen, *Ann. Acad. Sci. Fennicae*, 1928, *A*, 28 (*Chem. Abs.*, 1929, **23**, 1624).
[9] J. Wiemann, P. F. Casals, and S. Risse, *Bull. Soc. chim. France*, 1963, 1281.

cyclopentenone (VIII) which gave 3-isopropyl-5-oxohexanoic acid (IX) on oxidation; the latter was degraded further to 3-isopropylglutaric acid. It is also of relevance that Thomson[1] found β-thujadicarboxylic acid (and what could be its *trans*-isomer) in steam-distillation residues from the preparation of tanacetophorone; this led him to favour cyclisation of an olefinic precursor.

In the present work the composition of the mixture of products from attack of methoxide ion on α-thujadicarboxylic ester has been examined as a function of time by a gas-chromatographic procedure using a Carbowax 20M column. Difficulties were encountered as the keto-ester (VI) was demethoxycarbonylated on a wide variety of stationary phases in stainless steel or glass columns at 120—250°. The identity of the product as tanacetophorone was verified by preparative gas chromatography, but estimation of the keto-ester from the tanacetophorone produced involves a large empirical factor so the results in graphs are of restricted quantitative significance. Keto-ester (VI) and tanacetophorone can be satis-

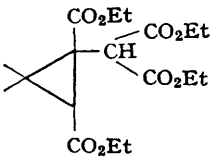


Composition of the mixture of products formed from α-thujadicarboxylic ester when attacked by methoxide ion. (The roman numbers against the curves refer to the formulæ for the compounds.)

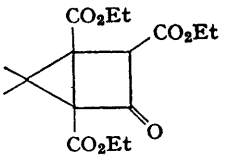
factorily separated by thin-layer chromatography, and contamination by even 2% of the latter would have been detectable had it been produced in the reaction by demethoxycarbonylation by methoxide ion. The Figure shows clearly that α-thujadicarboxylic ester (I) is rapidly converted by methoxide ion into β-thujadicarboxylic ester and that this is then more slowly converted into the ester (VI), precursor of tanacetophorone. Two other minor products appear in the reaction; the first of these, compound B, rapidly reaches maximum concentration and this then slowly declines. It is tentatively identified as the *trans*-form of β-thujadicarboxylic ester (X) which cannot be removed by cyclisation to give (VI) until it has been stereomutated to the usual *cis*-β-thujadicarboxylic ester. Ranta[10] claimed that there is some conversion (~ 7%) of the usual isomer of β-thujadicarboxylic acid into a second form (which might be the *trans*) on heating with water. We have repeated Ranta's experiment but have not succeeded in finding a second acid by gas or thin-layer chromatography. The other minor product, compound A, is barely detectable at the earliest stages and reaches a concentration of only 1·3% after 94 minutes, so it is not shown in the Figure. However, on prolonged heating, compound A continues to increase in quantity; it has not been further investigated.

Two related transformations are worthy of mention. Treatment of the cyclopropane tetraester (XI) with sodium ethoxide gives not the cyclobutanone (XII)[11,12] but the cyclopentenone (XIII).[13] It is probable that the latter arises by Dieckmann reaction prefaced by a cyclopropane cleavage to give the ester (XIV) and is analogous to the conversion examined

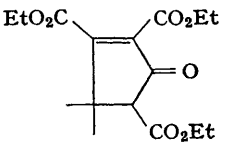
[10] S. Ranta, *Suomen Kem.*, 1938, **11**, *B*, 8 (*Chem. Abs.*, 1938, **32**, 3365).
[11] W. H. Perkin, jun., and J. F. Thorpe, *J.*, 1901, **79**, 729.
[12] R. C. Grimwood, C. K. Ingold, and J. F. Thorpe, *J.*, 1923, **123**, 3303 *et seq.*
[13] R. N. Adhya, A. C. Ghosh, and J. C. Bardhan, *J.*, 1956, 358.



(XI)



(XII)



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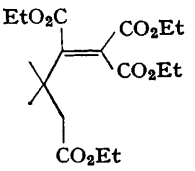
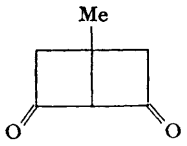
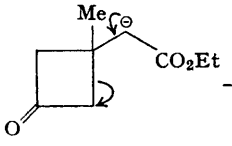


(XIV)

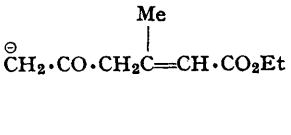
above. In the conversion of the cyclobutanone (XVI) into orcinol (XVIII) under Dieckmann conditions,[14] formation of the bicyclo-compound (XV) has been proposed, but from the information on cyclopropanes a retro-Michael reaction leading to keto-ester (XVII) with ensuing Claisen cyclisation seems more likely.



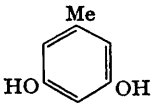
(XV)



(XVI)



(XVII)



(XVIII)

Experimental

Melting points are corrected. Optical rotations and ultraviolet spectra were measured in ethanol unless otherwise mentioned, and n.m.r. spectra with a Perkin-Elmer Model R10 spectrometer (permanent magnet) at 60 Mc. Gas chromatography was done on a Wilkins Aerograph Hy-Fi flame ionisation instrument. Evaporation was carried out under reduced pressure, and drying with anhydrous sodium sulphate.

α-Thujadicarboxylic Acid.—α-Thujone (123 g.), obtained by fractionation of commercial Dalmatian sage oil (1 kg.) through a 60 × 2 cm. electrically heated Stedman gauze-packed column, had b. p. 98—100°/40 mm., n_D^{20} 1·4557, $[\alpha]_D^{18}$ −10·3° ± 0·1° (homogeneous) (Found: C, 78·8; H, 10·65. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%); semicarbazone, m. p. 184—186°, $[\alpha]_D^{20}$ +61·6° ± 3° (*c* 1·9) (lit.,[15] b. p. 80—82°/20 mm., n_D^{16} 1·4584, $[\alpha]_D^{16}$ −15·43°; semicarbazone, m. p. 186—188°, $[\alpha]_D$ +64·4°). α-Thujone (50 g.) was oxidised with permanganate,[16] to give, after recovery of unreacted thujone (5·54 g.), α-thujaketonic acid (21·3 g.), m. p. 74—74·5°, $[\alpha]_D^{25}$ +219·9° ± 1·0° (*c* 4·31 in methanol), $\nu_{max.}$ ($CHCl_3$) 1709 and 1695 cm.$^{-1}$ {lit.,[1] m. p. 75—76°, $[\alpha]_D^{25}$ +214·8° (*c* 5·56 in methanol)}.

[14] C. K. Ingold, *J.*, 1922, **121**, 1143.
[15] A. G. Short and J. Read, *J.*, 1938, 2016.
[16] J. Werner and T. Bogert, *J. Org. Chem.*, 1938, **3**, 578.

Hypobromite degradation[17] of α-thujaketonic acid (19·3 g.) gave, after crystallisation once from water and twice from nitromethane, α-thujadicarboxylic acid (12·1 g.), m. p. 138—142°, $[\alpha]_D^{27}$ +110·0° ± 2·0° (*c* 1·47), $\nu_{max.}$ ($CHCl_3$) 1704, (mull) 1692 and 1701 cm.$^{-1}$ {lit.,[1,17] m. p. 141·5°, $[\alpha]_D^{16}$ +104·0° (*c* 4·7 in methanol)}. The dimethyl ester of α-thujadicarboxylic acid, made in 88% yield by esterification with diazomethane, had b. p. 106—108°/8 mm., n_D^{22} 1·4502—1·4510, $[\alpha]_D^{27}$ +138·0° ± 3·0° (homogeneous), $\nu_{max.}$ (film) 1733 and 1724 cm.$^{-1}$ {lit.,[1] b. p. 126—127°/13 mm., n_D^{20} 1·4506, $[\alpha]_D^{18}$ +142·5° (homogeneous)}. The n.m.r. spectrum in carbon tetrachloride showed resonances at τ 6·38, 6·40 (6 protons, dimethyl ester), 7·46 (2 protons, AB quartet, *J* 7·8 c./sec., exocyclic CH_2), 8·40 (1 proton, two doublets, *J* 2·4, 13·2 c./sec., cyclopropane ring proton), 8·8—9·2 p.p.m. (8 protons, complex, cyclopropyl ring CH_2 and isopropyl methyls).

β-Thujadicarboxylic Acid.—α-Thujaketonic acid (7·3 g.) was isomerised[17] by distillation, b. p. 167—173°/7 mm. The solid distillate crystallised from ether–light petroleum (1:1) as needles (6·1 g.) of β-thujaketonic acid, m. p. 76·5—78·5° (lit.,[17] 78°) (depressed on admixture with α-acid), $[\alpha]_D$ 0°, $\lambda_{max.}$ 217 mμ (ε 10,800), $\nu_{max.}$ ($CHCl_3$) 1704 (ketone), 1689 (acid), and 1631 (conj. C=C) cm.$^{-1}$.

(*a*) β-Thujaketonic acid (10·5 g.) in aqueous sodium hydroxide (20 ml.; 10%) was added during 30 min. to bromine (28·8 g.) in sodium hydroxide solution (20 ml.; 10%). After stirring (30 min.) at 20° and extracting with ether (2 × 60 ml.) the solution was acidified and again extracted with ether (5 × 100 ml.). The latter extracts were washed, dried, and evaporated to a waxy solid (8·2 g.) which crystallised from nitromethane to give β-thujadicarboxylic acid (1·2 g.), m. p. 117—119° (lit.,[18] 116—118°), $\lambda_{max.}$ 218 mμ (ε 11,000), $\nu_{max.}$ ($CHCl_3$) 1706 (sat. CO_2H), 1692 (unsat. CO_2H), and 1642 (conj. C=C) cm.$^{-1}$.

(*b*) Thermal isomerisation[8] of the dimethyl ester of α-thujadicarboxylic acid (1·9 g.) at 230° for 40 hr. resulted in a fall in rotation to $[\alpha]_D^{22}$ +1·21° (homogeneous). The crude β-ester (915 mg.) thus obtained was distilled and hydrolysed with methanolic potassium hydroxide (15 ml.; 10%) at 20° for 16 hr. Working up in the usual way gave β-thujadicarboxylic acid (122 mg.), m. p. 119—121° (from water), identical with the specimen above.

The dimethyl ester of β-thujadicarboxylic acid (450 mg.), obtained from the acid (600 mg.) by diazomethane esterification, had b. p. 81·0–81·5°/0·2 mm. (lit.,[8] 140°/14 mm.), n_D^{19} 1·4601, $\lambda_{max.}$ 219 mμ (ε 12,700), $\nu_{max.}$ (liq.) 1735 (sat. ester), 1720 (α-unsat. ester), and 1639 (conj. C=C) cm.$^{-1}$. In the n.m.r. spectrum (carbon tetrachloride) there were resonances at τ 4·38 (1 proton, olefinic), 6·38 (6 protons, dimethyl ester), 7·1—7·8 (complex, 4 protons, adjacent interacting methylenes), and 8·91 (6 protons, doublet, *J* 6·6 c./sec., isopropyl methyls).

Attempted Stereomutation of β-Thujadicarboxylic Acid.[10]—The acid, in 4% aqueous solution, was refluxed for 30 min. and cooled, to give fine rhombic crystals, m. p. 115—116° undepressed by the starting acid. Thin-layer chromatography on Kieselgel G., eluting with methanol–water (4:1), gave only a single spot, R_F 0·65. The crystals (21 mg.) were methylated with diazomethane in ether; the ethereal solution of the ester showed a single peak on gas chromatography (Carbowax 20M at 180°).

Methyl 4-Isopropyl-2-oxocyclopent-3-enecarboxylate.—α-Thujadicarboxylic dimethyl ester (526 mg.) was refluxed in methanol (1·04 ml.) containing sodium (71 mg.) for 2 hr. After cooling to −5°, the yellow crystals were filtered off, washed with cold methanol, and dried in a vacuum, to give the sodio-derivative of methyl 4-isopropyl-2-oxocyclopent-3-enecarboxylate, $\lambda_{max.}$ (ethanol) 230 and 280 mμ (ε 9080 and 1700). In the n.m.r. spectrum (dimethylformamide) there were resonances at τ 4·21 (olefin), 6·50 (methyl ester), and 8·91 (doublet, *J* 6·6 c./sec., isopropyl methyls).

Crude sodio-derivative was made from α-thujadicarboxylic dimethyl ester (4·01 g.), treated with water (10 ml.), and acidified with 10% aqueous oxalic acid. Extraction with light petroleum, evaporation, and distillation gave methyl 4-isopropyl-2-oxocyclopent-3-enecarboxylate (1·5 g.), b. p. 92—93°/0·5 mm., n_D^{19} 1·4841. The keto-ester was analysed as its *2,4-dinitrophenylhydrazone*, orange micro-crystals (from methanol), m. p. 112—113·5°, after chromatography on bentonite–kieselguhr (4:1), eluting with benzene (Found: C, 52·6; H, 5·15; N, 15·7. $C_{16}H_{18}N_4O_6$ requires C, 53·0; H, 5·0; N, 15·4%), $\nu_{max.}$ (mull) 1760 (ester), 1624 (C=C), and 1611 cm.$^{-1}$ (conj. C=C). The keto-ester, $\lambda_{max.}$ (ethanol) 233 and 313 mμ (ε 14,000 and 580), gave a violet colour with ethanolic ferric chloride and had $\nu_{max.}$ 1743 (ester), 1712 (ketone), and 1615 (conj. C=C) cm.$^{-1}$.

[17] F. W. Semmler, *Ber.* 1892, **25**, 3343.
[18] F. Tiemann and F. W. Semmler, *Ber.*, 1897, **30**, 431.

In the n.m.r. spectrum (carbon tetrachloride) there were resonances at 4·26 (1 proton, olefinic), 6·32 (3 protons, methyl ester), 8·78 (6 protons, doublet, J 7·2 c./sec., isopropyl methyls).

Methyl 4-Isopropyl-1-methyl-2-oxocyclopent-3-enecarboxylate.—The sodio-derivative above (737 mg.) was refluxed for 90 min. with methyl iodide (1·65 g.) in methanol (5 ml.). Working up and distillation gave the 1-methylated ester (350 mg.), b. p. 65—66°/0·05 mm. (lit.,[8] 142—143°/14 mm.), n_D^{21} 1·4741 (Found: C, 66·8; H, 8·2. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2%), $\lambda_{max.}$ (ethanol) 232 and 310 mμ (ε 13,090 and 220), $\nu_{max.}$ (liq. film) 1747 (ester), 1709 (ketone), and 1617 cm.$^{-1}$ (conj. C=C). In the n.m.r. spectrum (carbon tetrachloride) there were resonances at τ 4·18 (1 proton, olefin), 6·34 (3 protons, methyl ester), 8·69 (3 protons, tert. methyl), and 8·78 (6 protons, doublet, J 7·8 c./sec., isopropyl methyls).

Tanacetophorone.—α-Thujadicarboxylic acid dimethyl ester (3·2 g.), treated with sodium methoxide as above, gave the sodio-derivative of the cyclopentenone ester which, after removal of methanol, was steam-distilled from dilute sulphuric acid into semicarbazide hydrochloride–sodium acetate reagent. After 12 hr., tanacetophorone semicarbazone (1·25 g.) separated, m. p. 182—183° (lit.,[2] 185°). It was decomposed with refluxing aqueous oxalic acid (20%), and the ketone isolated with n-pentane and distilled, b. p. 75—76°/3 mm., n_D^{15} 1·4850 (lit.,[1] b. p. 99°/17—18 mm., n_D^{20} 1·4788), $\lambda_{max.}$ (ethanol) 226·5 and 301 mμ (ε 13,750 and 66), $\nu_{max.}$ (liquid) 1708 (C=O) and 1613 cm.$^{-1}$ (conj. C=C); in the n.m.r. spectrum (carbon tetrachloride) there were resonances at τ 4·22 (1 proton, quartet, olefin), 7·2—7·8 (4 protons, complex, adjacent methylenes), and 8·83 (6 protons, doublet, J 6·6 c./sec., isopropyl methyls).

Analytical Investigation of the Action of Sodium Methoxide on α-Thujadicarboxylic Acid.—In searching for suitable gas chromatography conditions it was found that the β-keto-ester (VI) and tanacetophorone apparently had the same retention times on Carbowax 20M (180°), Apiezon L (190°), diethylene glycol succinate (150°), XF-1150 cyanosilicone (160°), phenyl diethanolamine succinate (160°), SE-30 Silicone gum rubber (150°), and didecyl phthalate (140°). Mixtures of the keto-ester and tanacetophorone were not separated although they could be resolved by thin-layer chromatography. Injection of the β-keto-ester (VI) on to a preparative column of Carbowax 20M at 250° (Wilkins Autoprep) gave only tanacetophorone (approx. 10% recovery), identified by infrared comparison and thin-layer chromatography. On thin-layer chromatography on Kieselgel G, eluting with ethyl acetate, tanacetophorone and the keto-ester (VI) each gave single spots, R_F 0·55 and 0·67, respectively. On developing the plates with an iodine spray the keto-ester spot appeared after 1 min., and the tanacetophorone after 5 min. 2% of tanacetophorone added to the keto-ester could be detected.

Solutions of tanacetophorone and the β-keto-ester (VI) in carbon disulphide were injected in turn on to a Wilkins Aerograph analytical column (stainless steel) containing Carbowax 20M on Chromosorb P. In the temperature range 120—230°, correlation of peak areas showed that tanacetophorone was being derived from the keto-ester in 17·5% yield with little variation. Use of glass columns and of an argon ionisation system gave similar results. These findings were used empirically for analytical purposes, the tanacetophorone emerging from the column being expressed as β-keto-ester (VI).

For study of the reaction a stock solution containing α-thujadicarboxylic dimethyl ester (1 mol.) in sodium methoxide (0·7 mol.) in methanol (7 mol.) was made up at low temperature and aliquot portions containing 20 mg. of ester were sealed up rapidly. The tubes were heated in a boiling-water bath, and at appropriate intervals the tubes were rapidly cooled and opened. The contents were acidified with aqueous oxalic acid, and extracted with n-pentane. Samples of the n-pentane extract were injected directly on to an analytical column of Carbowax 20M at 179°. Peak areas were measured with a disc-integrator. Approximate retention times were: tanacetophorone, 4·6 min.; α-thujadicarboxylic dimethyl ester, 8·3 min.; compound A, 10·5 min.; β-thujadicarboxylic dimethyl ester, 11·9 min.; compound B, 13·3 min. The accuracy of the analytical procedure was tested by analysis of four synthetic mixtures of tanacetophorone and β-thujadicarboxylic ester. Results were within ± 2% of the known composition.

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