

Iodolactonizations using Thallium(I) Carboxylates

By Richard C. Cambie,* Rodney C. Hayward, John L. Roberts, and Peter S. Rutledge, Department of Chemistry, University of Auckland, New Zealand

Addition of iodine to an unsaturated thallium(I) carboxylate in ether at 20° gives a convenient procedure for iodolactonization under neutral conditions. The products are predominantly those of kinetic control.

INTRAMOLECULAR cyclization of an incipient iodonium or bromonium ion intermediate with a carboxylate ion is known as halogenolactonization.¹ The reaction, which provides a useful synthetic method² for the conversion of unsaturated acids into halogenolactones, and after hydrogenolysis into saturated lactones, normally requires the use of alkaline solutions or of sodium salts. The use of readily prepared thallium(I) carboxylates and iodine for the high yield conversion of alkenes into the corresponding *vic*-iodocarboxylates reported in the preceding paper,³ suggested the extension of their use for halogenolactonization and the possibility of effecting such reactions under neutral conditions.

It was found that slow addition of iodine in ether to a stirred suspension of an unsaturated thallium(I) carboxylate in ether at 20° using a stoichiometric ratio of 1 : 1 gave high yields of iodolactones. For comparison purposes unsaturated acids which had previously been used

in halogenolactonizations were studied and the results are in Table 1.

TABLE 1
Iodolactonization products

| Thallium salt of | Iodolactone | Yield (%) | Reference |
|------------------|-------------|-----------|-----------|
| (1) | (7) | 85 | 4, 6 |
| (5) | (14) | 90 | 4 |
| (6) | (15), (19) | 88 | 4 |
| (2) | (10) | 100 | |
| (3) | (9) | 90 | 5, 7 |
| (4) | (16) | 70—80 | 5 |

With thallium(I) salts of $\gamma\delta$ -unsaturated acids, *e.g.* (1) and (5), the only product obtained was the δ -iodo- γ -lactone in accord with the work of Van Tamelen⁴ and House⁸ and the generalization that for $\gamma\delta$ -unsaturated acids the γ -lactone will be formed in preference to the δ -lactone unless γ -lactone formation is accompanied by the introduction of considerable strain.

In the case of $\beta\gamma$ -unsaturated acids, Barnett⁵ has

⁵ W. E. Barnett and J. C. McKenna, *Chem. Comm.*, 1971, 551; *Tetrahedron Letters*, 1971, 2595; W. E. Barnett and W. H. Sohn, *ibid.*, 1972, 1777; *J.C.S. Chem. Comm.*, 1972, 472.

⁶ E. N. Rengevich, V. I. Staninets, and E. A. Shilov, *Doklady Akad. Nauk S.S.S.R.*, 1962, **146**, 111.

⁷ J. Bougault, *Ann. chim. Phys.*, 1908, **14**, 145 (*J. Chem. Soc. Abs.*, 1908, i, 537).

⁸ H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, 1963, **28**, 3359.

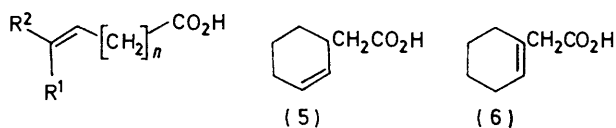
¹ H. O. House, 'Modern Synthetic Reactions,' 2nd edn., W. A. Benjamin, Menlo Park, California, 1972, p. 441.

² *E.g.* H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, 1973, **38**, 741; E. J. Corey and R. Noyori, *Tetrahedron Letters*, 1970, 311; E. J. Corey, N. M. Weinschenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675; E. Wenkert, L. H. Liu, and D. B. R. Johnston, *J. Org. Chem.*, 1965, **30**, 722.

³ R. C. Cambie, R. C. Hayward, J. L. Roberts, and P. S. Rutledge, preceding paper.

⁴ E. E. Van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315.

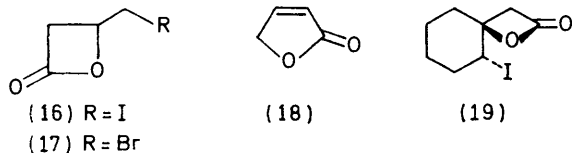
recently shown that if instead of the normal conditions^{4,9} a two phase system is used wherein the lactone is extracted into the organic phase as it is formed, γ -halogeno- β -lactones can be isolated instead of the usual γ -lactones. Barnett demonstrated that the β -lactones were the



- (1) $R^1 = R^2 = H, n = 2$
 (2) $R^1 = R^2 = Me, n = 1$
 (3) $R^1 = H, R^2 = Ph, n = 1$
 (4) $R^1 = R^2 = H, n = 1$



- (7) $R^1 = R^2 = R^3 = H, R^4 = CH_2I$
 (8) $R^1 = \beta-Me, R^2 = \alpha-I, R^3 = H, R^4 = Me$
 (9) $R^1 = I, R^2 = R^3 = H, R^4 = Ph$
 (10) $R^1 = I, R^2 = H, R^3 = R^4 = Me$
 (11) $R^1 = I, R^2 = R^3 = R^4 = H$
 (12) $R^1 = OH, R^2 = R^3 = R^4 = H$
 (13) $R^1 = OCOCH_2CH=CH_2, R^2 = R^3 = R^4 = H$
 (14) $R^1 = H, R^2 = I$
 (15) $R^1 = I, R^2 = H$



products of kinetic control since they were converted into the corresponding β -iodo- γ -lactone when subjected to normal halogenolactonization conditions. When thallium(I) salts of $\beta\gamma$ -unsaturated acids, e.g. (6), were used, both the possible products, viz. a γ -iodo- β -lactone (19) and a β -iodo- γ -lactone (15) were formed. The product of kinetic control (19) which predominated in the mixture, rearranged quantitatively into the thermodynamically more stable β -iodo- γ -lactone on standing. In the case of the thallium(I) salt of the alkylated $\beta\gamma$ -unsaturated acid (2) a quantitative yield of the hitherto unknown β -iodo- γ -lactone (10)* was obtained. 4-Phenylbut-3-enoic acid (3) also afforded a β -iodo- γ -lactone (9) in accord with published results.^{5,7}

Of particular interest was the 65% yield of the β -lactone (16) obtained when the thallium(I) salt of but-3-enoic acid (4) was the substrate. This compound had been reported as inert^{4,7} to halogenolactonization but Shilov and his co-workers¹¹ have established that iodolactonization of the pre-formed sodium salt gives a

* Reference to this compound appears in a review article¹⁰ but this seems to be in error since from the original references the names of 4-methyl-, 4-vinyl-, and 4-ethyl-pent-3-enoic acids on p. 273 of the review should read as the corresponding but-3-enoic acids.

mixture of the iodine-free lactones (18), (12), and (13). Isolation of the halogenolactones (16) and (17) was achieved in yields of 20–30 and 50% by Barnett⁵ using the two phase system. However, in our hands repeated attempts to duplicate Barnett's results with but-3-enoic acid were unsuccessful, the reactions affording a mixture of neutral products in low yields (<5%). The susceptibility of β -lactones such as (16) to nucleophilic attack has been demonstrated by a number of workers.^{5,12}

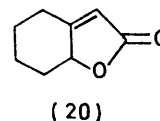
Since cyclohex-1-enylacetic acid (6) had not been studied under Barnett's conditions of iodolactonization his procedure was applied to this substrate. The results in Table 2 were obtained. The dehydrohalogenated

TABLE 2

Iodolactonization of cyclohex-1-enylacetic acid (6)

| Time (h) | Neutral material (%) | Products (%) | | |
|----------|----------------------|--------------|------|------|
| | | (15) | (19) | (20) |
| 1 | 40 | 25 | 75 | |
| 4 | 60 | 60 | 40 | |
| 20 | 85 | 50 | | 50 |

product (20) was not isolated but was identified by spectral comparison with an authentic sample.⁸ Use of the silver salt of the acid (6) gave a 45% yield of the β - and



γ -lactones in a ratio of 1 : 0.8 while the sodium salt gave a 22% yield of the same products in a ratio of 1 : 2. The use of thallium(I) salts of $\beta\gamma$ -unsaturated acids would therefore appear to be the method of choice for formation of iodolactones when they are likely to be unstable or the products of kinetic control.

The commonly accepted mechanism for iodolactonization¹ assumes formation of a cyclic three-membered iodonium ion by electrophilic attack of a positive iodine species on the double bond. The iodonium ion is then opened by intramolecular nucleophilic attack of the carboxylate anion to form the lactone ring. Barnett and McKenna⁵ draw a mechanistic analogy between the classical Prévost reaction and iodolactonization but since the Prévost reaction does not work with sodium carboxylates a difference must exist between the two mechanisms. With addition-cyclization reactions ring closure takes place by intramolecular participation of the nucleophile. Weak nucleophiles are incapable of effecting ring closure with iodine but will do so under the influence of powerful electrophiles such as bromine. Thus the nucleophilicity of the donor group is important

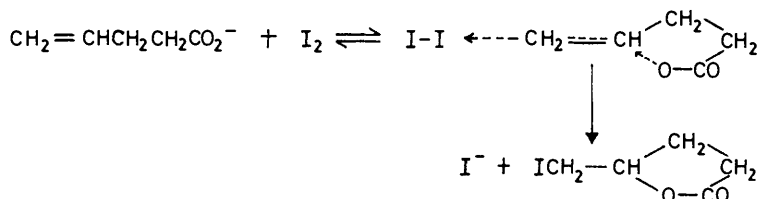
⁹ J. Klein, *J. Amer. Chem. Soc.*, 1959, **81**, 3611.

¹⁰ V. I. Staninets and E. A. Shilov, *Russ. Chem. Rev.*, 1971, **40**, 272.

¹¹ V. I. Staninets, E. A. Shilov, and E. B. Koryak, *J. Org. Chem. (U.S.S.R.)*, 1968, **4**, 259.

¹² H. Johansson, *Lunds Universitets Arvsskrift, N.F. Avd.*, **12** (8), 2; *Kungl. Fysiografiska Sällskapets Handlingar, N.F.*, **27** (8) (*Chem. Abs.*, 1917, 2576); J. Bougault, *Compt. rend.*, 1908, **146**, 140, 411 (*J. Chem. Soc. Abs.*, 1908, i, 179, 269).

and determines the overall rate of the reaction.^{6,13} The exact addition-cyclization process appears to involve a subtle interdependence of the strength and nature of the attacking electrophile and of the incoming nucleophile. Shilov¹⁴ has suggested a synchronous acceptor-donor reaction for halogenolactonization (Scheme). All available evidence indicates that iodolactonization with thallium(I) carboxylates, like normal halolactonization, is virtually stereospecific with the iodine entering *trans* to the carboxylate. This implies that an iodine-double bond complex¹⁵ is involved in thallium(I) halogeno-



SCHEME

lactonization thereby supporting conclusions reached for iodocarboxylations in the preceding paper.

Acids used in the present study were generally prepared according to standard methods. But-3-enoic acid (4) has previously been obtained in low yield (11%¹⁶ and 22%¹⁷) from a Grignard reaction with allyl bromide with the result that a route from allyl chloride *via* the corresponding cyanide (50% overall yield) has been preferred.¹⁸ However, Kharasch¹⁹ has pointed out that in contrast to the bromide, allylmagnesium chloride is insoluble in dry ether and thus leads to better yields in Grignard reactions. Use of allylmagnesium chloride in the present work gave the desired butenoic acid (4) in 72% yield. Pent-4-enoic acid is usually synthesized by condensation of allyl iodide with diethyl sodiomalonate.²⁰ A more convenient method was by Jones oxidation of pent-4-en-1-ol which is readily prepared from ethylene oxide and allylmagnesium chloride.²¹

EXPERIMENTAL

General experimental details are given in the preceding paper.

But-3-enoic Acid (4).—Allylmagnesium chloride,¹⁹ prepared from allyl chloride (46.0 g) and magnesium (16.0 g) in dry ether (180 ml), was added to a vigorously stirred suspension of solid carbon dioxide (400 g) in ether (200 ml). The mixture was stirred for 1.5 h and worked up in the normal manner to give but-3-enoic acid (39.1 g, 72%), b.p. 162–163° (lit.,¹⁸ 163°), n_D^{25} 1.4252 (lit.,¹⁸ 1.42527), ν_{max} 3610–2250 and 1705 cm^{-1} (CO_2H), δ 3.15 (m, $J_{2,3}$ 6.8, $J_{2,4}$ 1.2 Hz,

¹³ V. I. Staninets, E. A. Shilov, and E. B. Koryak, *Doklady Akad. Nauk, S.S.S.R.*, 1970, **192**, 817.

¹⁴ E. A. Shilov, F. M. Vainshtein, and A. A. Yasnikov, *Kinetika Kataliz*, 1961, **2**, 214 (*Chem. Abs.*, 1961, **55**, 22,081); F. M. Vainshtein and E. A. Shilov, *Doklady Akad. Nauk, S.S.S.R.*, 1958, **123**, 93.

¹⁵ L. do. Amaral and S. C. Melo, *J. Org. Chem.*, 1973, **38**, 800.

¹⁶ J. Houben, *Ber.*, 1903, **36**, 3897.

¹⁷ H. Gilman and J. H. McGlumpy, *Bull. Soc. chim. France*, 1928, **43**, 1322.

¹⁸ E. Rietz, *Org. Synth.*, Coll. Vol. III, 1955, p. 851; R. P. Linstead, E. G. Noble, and E. J. Boorman, *J. Chem. Soc.*, 1933, 557.

2-H₂), 5.10, 5.33 (2m, 4-H₂), and 6.0 (m, $J_{3,4\text{-trans}}$ 18.0, $J_{3,4\text{-cis}}$ 9.2, $J_{2,3}$ 6.8 Hz, 3-H).

Pent-4-enoic Acid (1).—Jones reagent²² (15.2 ml) was added slowly to a stirred solution of pent-4-en-1-ol (2.58 g) in acetone (20 ml) at 0° and the mixture was warmed to 20° over 2 h. Work-up in the normal manner gave pent-4-enoic acid (2.45 g, 81%), b.p. 179–181° (lit.,²³ 180–181, 186–188°), ν_{max} 3580–2250 and 1710 cm^{-1} (CO_2H), δ 2.50 (m, 2- and 3-H), 5.00, 5.17, and 5.26 (3m, 5-H₂), 5.93 (m, $J_{4,5\text{-trans}}$ 17.2, $J_{4,5\text{-cis}}$ 9.5 Hz, 4-H), and 9.67 (s, CO_2H).

4-Methylpent-2-enoic Acid.²⁴—This had n_D^{25} 1.4472 (lit.,²⁴ 1.4475), ν_{max} 3530–2400 and 1690 cm^{-1} (CO_2H), δ 1.08 (d,

$J_{4,5}$ 6.8 Hz, 5-H and 4-Me), 2.40 (m, $J_{4,5}$ 6.8, $J_{3,4}$ 6.8, $J_{2,4}$ 1.4 Hz, 4-H), 5.79 (dd, $J_{2,3}$ 16.2, $J_{2,4}$ 1.4 Hz, 2-H), 7.07 (dd, $J_{2,3}$ 16.2, $J_{3,4}$ 6.8 Hz, 3-H), and 10.13 (s, CO_2H).

4-Methylpent-3-enoic Acid (2).²⁴—This had b.p. 90° at 1.0 mmHg, and contained 4-methylpent-2-enoic acid as an impurity, ν_{max} 3580–2250 and 1710 cm^{-1} (CO_2H), δ 1.67, 1.77 (2s, 4-Me₂), 3.09 (d, $J_{2,3}$ 7.2 Hz, 2-H), 5.33 (m, $J_{2,3}$ 7.2, $J_{3,5}$ 1.5 Hz, 3-H), and 10.13 (s, CO_2H).

4-Phenylbut-3-enoic Acid (3).²⁵—This had m.p. 83–85° (lit.,²⁵ 87°), ν_{max} 3600–2400 and 1705 cm^{-1} (CO_2H), δ 3.24 (d, J 6 Hz, 2-H₂), 6.10 (dd, $J_{3,4}$ 15, $J_{2,3}$ 6 Hz, 3-H), 6.51 (d, $J_{3,4}$ 15 Hz, 4-H), 7.23 (m, ArH), and 6.10 (s, $W_{\frac{1}{2}}$ 8 Hz, CO_2H).

Cyclohex-1-enylacetic Acid (6).⁸—This had m.p. 34° (lit.,⁸ 33–34°), ν_{max} 3530–2400 and 1702 cm^{-1} (CO_2H), δ 1.38–1.90 (m, 4' and 5'-H), 1.90–2.38 (m, 3' and 6'-H), 3.00 (s, 2-H₂), 5.68br (s, 2'-H), and 11.70 (s, CO_2H).

Cyclohex-2-enylacetic Acid (5).⁹—This had b.p. 101–102° at 1 mmHg (lit.,⁹ 101.5–104° at 1 mmHg), n_D^{25} 1.4783 (lit.,⁹ 1.4800), ν_{max} 3600–2400 and 1705 cm^{-1} (CO_2H), δ 1.20–2.17 (m, 1', 4', 5', and 6'-H), 2.40 (s, 2-H), 5.57 (d, $J_{2',3'}$ 12.0 Hz, 2'-H), 5.77 (m, $J_{2',3'}$ 12.0 Hz, 3'-H), and 11.63 (s, CO_2H).

Formation of Thallium(I) Salts; General Procedure.—To a stirred solution of the acid in dry benzene or ether was added thallium(I) ethoxide and the resulting precipitate was washed with pentane and dried to give the salts described below: *thallium cyclohex-2-enylacetate* (95%), m.p. 140–141° (Found: C, 28.5; H, 3.4. $\text{C}_8\text{H}_{11}\text{O}_2\text{Tl}$ requires C, 28.0; H, 3.2%); *thallium cyclohex-1-enylacetate* (96%), m.p. 119.5–120° (Found: C, 28.3; H, 3.25. $\text{C}_8\text{H}_{11}\text{O}_2\text{Tl}$ requires C, 28.0; H, 3.2%); *thallium 4-phenylbut-3-enoate* (90%), m.p. 147–148.5° (Found: C, 33.1; H, 2.5. $\text{C}_{10}\text{H}_9\text{O}_2\text{Tl}$ requires

¹⁹ M. S. Kharasch and O. Reinmuth, 'Grignard Reactions of Nonmetallic Substances,' Constable, London, 1954, p. 27.

²⁰ R. Fittig and A. Messerschmidt, *Annalen*, 1881, **208**, 92.

²¹ M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, 1944, **9**, 359.

²² L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' John Wiley and Sons, New York, 1967, p. 142.

²³ H. J. Bestmann and H. Schulz, *Chem. Ber.*, 1962, **95**, 2921.

²⁴ B. J. Clarke and R. P. Hildebrand, *J. Inst. Brewing*, 1967, **73**, 60 (*Chem. Abs.*, 1967, **67**, 32,303); A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 1928, 2343.

²⁵ R. P. Linstead and L. T. D. Williams, *J. Chem. Soc.*, 1926, 2735.

C, 32.9; H, 2.5%); *thallium but-3-enoate* (90%), m.p. 113—115° (Found: C, 17.0; H, 2.0. $C_4H_5O_2Tl$ requires C, 16.6; H, 1.7%); *thallium pent-4-enoate* (85%), m.p. 148—150° (Found: C, 20.4; H, 2.5. $C_5H_7O_2Tl$ requires C, 19.8; H, 2.3%).

Iodolactonizations; General Procedure.—A solution of iodine (1 equiv.) in ether was added slowly to a stirred suspension of the thallium(I) salt of the acid (1 equiv.) in dry ether. The mixture was stirred for 3—4 h and the precipitate of thallium(I) iodide was filtered off. The filtrate was washed with saturated aqueous sodium thiosulphate and saturated aqueous sodium hydrogen carbonate and then dried. Removal of solvent afforded the iodolactone as described below: *5-iodomethyloxolan-2-one* (7), prisms (from aqueous ethanol), m.p. 74° (lit.,⁶ 75—76°), ν_{max} 1775 cm^{-1} (lactone), δ 1.93—2.93 (m, 3- and 4-H), 3.15—3.50 (m, CH_2I), and 4.33—4.77 (m, 5-H); *5 α -iodo-1 α ,6 α -7-oxabicyclo[4.3.0]nonan-8-one* (14), prisms (from ethanol—hexane), m.p. 64—65°, mixed m.p. undepressed by a sample prepared (95%) as previously described,^{8,25} ν_{max} 1775 cm^{-1} (lactone), δ 1.30—3.07 (m, 1-, 2-, 3-, 4-, and 9-H), and 4.67 (m, 5- and 6-H); (*4RS,5SR*)-*5-iodo-1-oxaspiro[3,5]nonan-2-one* (19) and *cis-1-iodo-7-oxabicyclo[4.3.0]nonan-8-one* (15), ob-

tained in a ratio of 7 : 3, ν_{max} 1825 (β -lactone) and 1780 cm^{-1} (γ -lactone), δ 1.27—1.87, 1.87—2.47 [2m, 6-, 7-, 8-, and 9-H of (19), 2-, 3-, 4-, and 5-H of (15)], 2.90 [d, J_{gem} 17.2 Hz, 9-H of (15)], 3.07 [d, J_{gem} 16.1 Hz, 3-H of (19)], 4.57 [m, J 4.2 Hz, 5-H of (19)] and 4.81 [t, J 3.7 Hz, 6-H of (15)]. A pure sample of (15) was prepared as previously described;²⁶ *4-iodo-5-phenyloxolan-2-one* (9), needles (from aqueous ethanol), m.p. 115° (lit.,^{7,11} 115—116°), ν_{max} 1780 cm^{-1} (lactone), δ 2.92 (dd, $J_{3,3'}$ 18.0, $J_{3,4}$ 9.6 Hz, 3-H), 3.32 (dd, $J_{3,3'}$ 18.0, $J_{3',4}$ 7.8 Hz, 3'-H), 4.27 (m, $J_{3,4}$ 9.6, $J_{3',4} = J_{4,5}$ 7.8 Hz, 4-H), and 5.67 (d, $J_{4,5}$ 7.8 Hz, 5-H); *4-iodo-5,5-dimethyloxolan-2-one* (10), m.p. 77—78° (Found: C, 29.9; H, 3.75. $C_6H_9IO_2$ requires C, 30.0; H, 3.8%), ν_{max} 1780 cm^{-1} (lactone), δ 1.50, 1.60 (2s, 5-Me₂), 2.84 (dd, $J_{3,3'}$ 18.4, $J_{3,4}$ 9.0 Hz, 3-H), 3.22 (dd, $J_{3,3'}$ 18.4, $J_{3',4}$ 8.0 Hz, 3'-H), and 4.27 (dd, $J_{3,4}$ 9.0, $J_{3',4}$ 8.0 Hz, 4-H); *4-iodomethyloxetan-2-one* (16) was prepared in dry benzene and obtained as an oil,⁵ ν_{max} 1833 cm^{-1} (lactone); δ 3.00—3.80 (overlapping m, 3-H and CH_2I) and 4.40—4.80 (m, 4-H).

[4/092 Received, 18th January, 1974]

²⁶ Yu. A. Arbutov, V. T. Ivanov, M. N. Kolosov, Yu. A. Ovchinnikov, and M. M. Shemyakin, *J. Gen. Chem. (U.S.S.R.)*, 1964, **34**, 1081.