Evidence for the Formation of the Oxacyclopentenyl Cation from a Cyclopropyl Ketone

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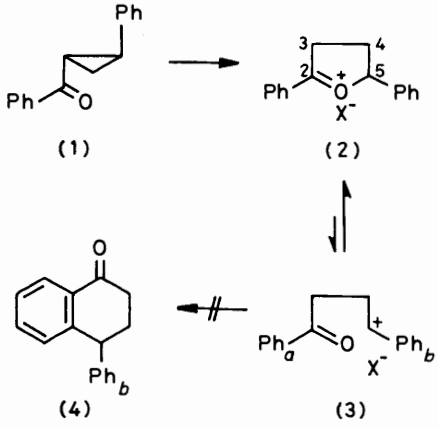
On treatment with stannic chloride in nitromethane or concentrated sulphuric acid *trans*-2-phenylcyclopropyl phenyl ketone (1) gives the same intermediate as shown by an *in situ* ^1H and ^{13}C n.m.r. investigation. In concentrated sulphuric acid this intermediate had been assigned an oxacyclopentenyl cation structure (2); this is confirmed here. The assignment is supported chemically by synthesising (2) in an inert solvent and treating it with methylmagnesium iodide. The expected trisubstituted tetrahydrofuran (7) is isolated in 53% yield.

Cyclopropyl ketones continue to find extensive application in organic synthesis.[1] Following our application of them in the synthesis of 1-aryltetralones,[2] γ-hydroxyketones,[3] 1-arylnaphthalenes,[4] and the total synthesis of picropodophyllone,[5] a detailed study of reaction pathways led us [6] to conclude that a five-membered cyclic oxonium ion was a probable intermediate. We now report an investigation which set out to prove this hypothesis.

There is now a considerable literature on cyclic and most particularly oxacyclopentyl oxonium ions. From rate studies and product analysis Oae,[7] Pasto,[8] and Baddeley [9] each concluded that cyclic oxonium ions were involved in the course of hydrolysis of γ-halogenoketones. Meerwein and coworkers [10] also proved their formal existence. Pines and Douglas [11] underlined the value of ^{13}C n.m.r. spectroscopy when they unexpectedly detected a 1-aryloxacyclopentenyl ion in solution. Bégué and Charpentier-Morize have investigated bicyclic oxonium ions extensively,[12] applied them to synthesis by remote functionalisation,[13] and correlated their ^{13}C n.m.r. spectra.[14] Of greater relevance to this study was the study by Pittman and McManus.[15] Using ^1H n.m.r. spectroscopy they proved the formation of oxacyclopentenyl oxonium ions when cyclopropyl ketones were heated in concentrated sulphuric acid. The stability of cyclic oxonium ions in this medium has been confirmed recently by Bates.[16]

To initiate our study, we chose *trans*-2-phenylcyclopropyl phenyl ketone (1) for investigation since comparison could be made with spectral data determined by others [11,14,15] and complicating reactions of (3) could be avoided. We had found [2,6] that unless the phenyl group *a* (Scheme 1) is appropriately activated, products such as (4) are not formed.

We had used stannic chloride in nitromethane as the catalyst and medium for all our reactions with cyclopropyl ketones.[2-6] Our first objective then was to compare the immediate product of the ketone (1) in concentrated sulphuric acid with that in perdeuterionitromethane with stannic chloride, using ^1H and ^{13}C n.m.r. *in situ*. Addition of (1) to sulphuric acid at *room* temperature resulted in the immediate appearance of a product which had a ^1H n.m.r. spectrum identical with that observed by Pittman and McManus.[15] Of particular note was the one-proton triplet at δ 6.96 which is assigned to the C-5 proton. The ^{13}C n.m.r. spectrum (Figure) which has not been reported previously, is fully consistent with structure (2; X = HSO_4). The assignments were confirmed by off-centre decoupling. Both the chemical shift of C-5 and J_{5-H} are of the expected [11,14] magnitude and are consistent with a carbon bearing a strongly polar substituent.[11] 4-Hydroxy-4-phenylbutyrophenone (5) was isolated in high yield by quenching the reaction with ice. Identical ^1H and ^{13}C n.m.r. spectra were obtained when this hydroxyketone (5) was dissolved in sulphuric acid. Identical results, albeit more slowly, were observed when trifluoroacetic acid was used in place of sulphuric acid. When the ketone (1) was treated with stannic chloride in trideuterionitromethane both the ^1H and ^{13}C n.m.r. spectra were the same as those observed in sulphuric acid and corresponded to those of the oxonium ion (2). The hydroxyketone (5) was isolated in 76% yield from this reaction.



Scheme 1.

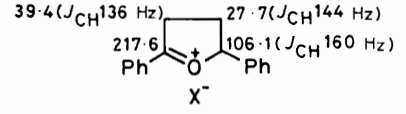
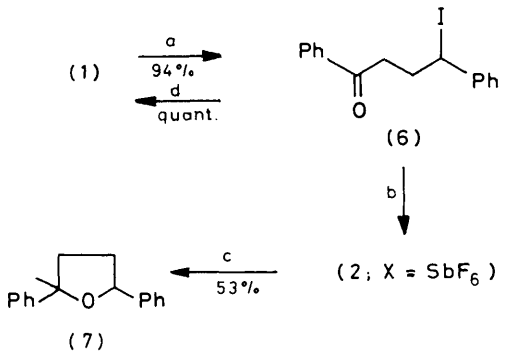


Figure.

It is noted that the open carbocation (3) could not be detected. This result was unexpected since the reaction media were highly polar and we had earlier concluded [3,6] that substituted forms of (3) must be involved in those reactions in which tetralones (4) were formed.

Direct chemical evidence for the structural assignment of (2) was next sought. This was undertaken as outlined in Scheme 2. The iodoketone (6) was prepared in high yield by treating the ketone (1) with trimethylsilyl iodide.[17] This iodide was rather unstable even in the dark and was best used immediately after isolation. The structure of (6) was proved chemically by its quantitative conversion into the cyclopropyl ketone (1) when heated with either ethanolic potassium hydroxide or 1,5-diazabicyclo[3.4.0.]non-5-ene in carbon tetrachloride. Treatment of the iodide (6) with silver hexafluoroantimonate [12] resulted in the immediate precipitation of silver iodide, which was then removed by filtration. The salt (2; X = SbF_6) was then isolated as a viscous oil. The ^1H and ^{13}C



Scheme 2. a, Me_3SI, CCl_4, −10 °C; b, $AgSbF_6$, CH_2Cl_2; c, MeMgI, C_6H_6; d, reflux 0.5 h in either alcoholic KOH or DBN, CCl_4

n.m.r. spectra were identical with those observed in both concentrated sulphuric acid and nitromethane–stannic chloride (see above). When this oxonium ion (2; X = SbF_6) was treated with methylmagnesium iodide in benzene, the tetrahydrofuran (7) was isolated as an approximately 1 : 1 mixture of stereoisomers. It is of note that no products were detected which could have resulted from either an S_N2 attack on C-5 of (2) or S_N1 attack on the corresponding carbocationic centre in (3). This result is doubtless due to a combination of the high activation of C-2 in (2) and the low equilibrium concentration of (3) (see above). It is probable that (5), as its hemiacetal, is formed from (2) by the same mechanism, *i.e.* attack on C-2 by water.

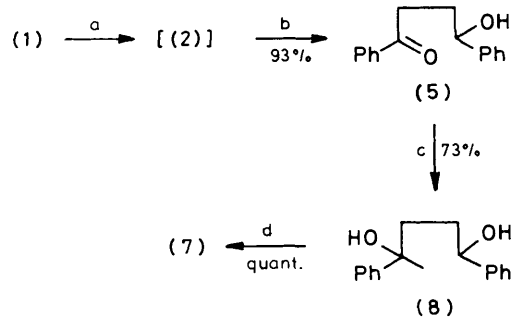
The physical and chemical evidence for the structure assigned to (2) is now complete. In conclusion, the structure of the tetrahydrofuran (7) was proved unequivocally by independent synthesis (Scheme 3). It was found that the glycol (8) was isolable. However, it was dehydrated smoothly when mixed with toluene-*p*-sulphonic acid or when stirred overnight with silica gel.

Experimental

^1H N.m.r. spectra were obtained in $CDCl_3$, unless otherwise stated, on a Perkin-Elmer R20A instrument at 60 MHz. ^{13}C N.m.r. spectra were recorded in $CDCl_3$, unless otherwise stated, on a JEOL FX60 instrument. Spectra obtained in concentrated sulphuric acid had a 5 mm capillary tube containing $CDCl_3$ and Me_4Si. I.r. spectra were recorded as KBr discs or as thin films. *trans*-2-Phenylcyclopropyl phenyl ketone (1) was prepared as detailed previously.[6]

Reactions of the Cyclopropyl Ketone (1).—(a) *Sulphuric acid.* A solution of cyclopropyl ketone (1) (100 mg) in concentrated sulphuric acid (0.8 ml) had the following spectral characteristics: δ 3.15 (lit.,[15] 3.19) (2 H, m, broad, CH_2CH), 4.56 (lit.,[15] 4.49) (2 H, m, broad, $CH_2C{=}O$), 6.96br (lit.,[15] 6.91) (1 H, t, CHC_6H_5), and 7.76—8.44 (10 H, m, ArH); δ_C 27.74 (t, J_{CH} 144 Hz), 39.44 (t, J_{CH} 136 Hz), 106.10 (d, J_{CH} 160 Hz), 125.01, 127.54, 129.47, 130.73, 131.31, 132.87, 135.67, 144.56, and 217.53 (s).

The cyclopropyl ketone (1) (2.0 g, 9 mmol) was added in portions to concentrated sulphuric acid (10 ml) with stirring until it dissolved (0.3 h); the solution was reddish brown. It was poured onto ice (100 g), extracted with ether (3 × 100 ml), and the combined extracts washed with brine (3 × 100 ml), dried ($MgSO_4$), and evaporated to dryness to give 3-hydroxy-3-phenylpropyl phenyl ketone (5) (2.02 g, 93%), m.p. 84—86 °C (lit.,[18] 92—93 °C) (Found: C, 80.1; H, 7.0. Calc. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7%).



Scheme 3. a, Conc. H_2SO_4; b, H_2O, 0 °C; c, MeMgI; d, toluene-*p*-sulphonic acid or SiO_2

(b) *Stannic chloride–perdeuterionitromethane.* To a solution of the cyclopropyl ketone (1) (0.22 g, 1 mmol) in trideuterionitromethane (5 ml) was added stannic chloride (0.15 ml, 13 mmol). The reaction mixture was stirred at room temperature for 18 h. The ^1H and ^{13}C spectra corresponded precisely with those observed in sulphuric acid in addition to traces of side products. The reaction mixture was poured onto water (50 ml), extracted with chloroform (2 × 50 ml), and the combined extracts washed with brine (2 × 50 ml), dried ($MgSO_4$), and evaporated to give an oil from which the ketoalcohol (5) was isolated (0.18 g, 76%) by preparative t.l.c. [silica gel, ether–light petroleum (b.p. 60—80 °C), 2 : 3]. On one occasion only, the tetralone (4) was detected (^1H n.m.r.) and isolated (17%).

(c) *Trimethylsilyl iodide.* To a solution of the cyclopropyl ketone (1) (0.80 g, 3.6 mmol) in dry carbon tetrachloride (9 ml) was added freshly distilled trimethylsilyl iodide (0.51 ml, 36 mmol) at −10 °C under nitrogen. The solution was stirred at 10 °C for 1 h and at 25 °C for 1 h. The solution was then diluted with ether (100 ml) and washed with a saturated solution of sodium sulphite (50 ml). The ethereal solution was dried ($MgSO_4$) evaporated to give white, solid 3-*iodo*-3-*phenylpropyl phenyl ketone* (6) (1.19 g, 94%), m.p. 88—89 °C (Found: C, 54.9; H, 4.4; I, 36.9. $C_{16}H_{15}IO$ requires C, 54.9; H, 4.3; I, 36.2%); $\nu_{max.}$ 1 675 cm^{-1}; δ 2.56 (2 H, m, CH_2CH), 3.06 (2 H, m, $CH_2C{=}O$), 5.26 (1 H, t, *J* 7.8 Hz, CHC_6H_5), and 7.25—7.98 (10 H, m, ArH); δ_C 33.47, 35.55, 38.60, 127.09, 128.0, 128.13, 128.65, 128.85, 133.27, 136.58, 143.6, and 198.37.

1,4-*Diphenylpentane*-1,4-*diol* (8).—The hydroxyketone (5) (1.44 g, 6 mmol) in dry ether (20 ml) was added dropwise to methylmagnesium iodide (24 mmol) in dry ether (20 ml). The temperature was maintained at or below 0 °C during the addition. The reaction mixture was then heated under reflux for 2 h, quenched by pouring onto 0.05% hydrochloric acid (200 ml) at 0 °C, extracted with ether (3 × 100 ml), and the combined extracts washed with brine, dried ($MgSO_4$), and evaporated to dryness to give a crude oil (1.32 g) which was purified by preparative t.l.c. [silica gel, ethyl acetate–light petroleum (b.p. 60—80 °C) 1 : 1] to yield 1,4-*diphenylpentane*-1,4-*diol* (1.13 g, 73%), m.p. 104—105 °C (Found: C, 79.9; H, 7.9. Calc. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.9%), $\nu_{max.}$ 3 320 and 3 260 cm^{-1}; δ 1.46 (3 H, s, CH_3), 1.62—1.85 (4 H, m, CH_2CH_2), 2.95 (2 H, s, 2 × OH), 4.50 (1 H, t, *J* 6 Hz, CHC_6H_5) and 6.82—7.60 (10 H, m, ArH); δ_C 30.21(q), 33.53(t), 39.83(t), 74.20(d), 74.99(s), 124.88(d), 125.85(d), 126.50(d), 127.25(d), 128.19(d), 128.39(d), 144.63(s), and 148.01(s). Additional absorptions due to a second stereoisomer in low concentration appeared at 30.99, 40.54, 74.40, and 74.91.

2-*Methyl*-2,5-*diphenyltetrahydrofuran* (7).—(a) *From* 3-*iodo*-3-*phenylpropyl phenyl ketone* (6). To a solution of the

iodoketone (6) (0.84 g, 2.4 mmol) in dichloromethane (8 ml) was added silver hexafluoroantimonate (0.89 g, 2.6 mmol) under nitrogen at room temperature; a yellow precipitate of silver iodide appeared immediately. The reaction mixture was stirred for a further 0.5 h and then filtered through a sintered glass frit (porosity 4) under nitrogen. The solvent was removed under reduced pressure to leave a viscous brownish yellow oil. Dry benzene (5 ml) was added to this followed by the dropwise addition of methylmagnesium iodide (0.01 mol) in dry benzene (10 ml) at −10 to 0 °C. The reaction mixture was stirred for 2 h at room temperature and then poured onto hydrochloric acid (0.5%, 100 ml) at 0 °C. Work-up led to a crude oil from which, as well as traces of unidentified side-products, 2-methyl-2,5-diphenyltetrahydrofuran [19] (7) was isolated by preparative t.l.c. [silica gel, ethyl acetate–light petroleum (b.p. 60—80 °C), 1 : 4] as an oil (0.30 g, 53%). (Found: C, 85.8; H, 7.9. $C_{17}H_{18}O$ requires C, 85.7; H, 7.6%); $\nu_{max.}$ 3 000 and 1 610 cm^{-1}; δ 1.57 (3 H, s, CH_3), 1.72—2.37 (4 H, m, CH_2CH_2), 4.85—5.2 (1 H, t, CHC_6H_5), and 6.95—7.57 (10 H, m, ArH); the second stereoisomer was indicated by the presence of absorptions at 1.60 (3 H, s, CH_3) and a superimposed triplet (4.85—5.20); δ_C 30.02(g), 34.57(t), 40.02(t), 80.57(d), 84.79(s), 124.68(d), 124.94(d), 125.79(d), 126.18(d), 126.37(d), 127.22(d), 128.06(d), 128.26(d), 143.66(s), and 148.72(s). The second stereoisomer had separate absorptions at 30.67, 35.09, 39.44, 85.18, 142.88, and 148.40. The ratio of stereoisomers was variable, but averaged 5 : 7.

(b) *From* 1,4-*diphenylpentane*-1,4-*diol* (8). A solution of 1,4-diphenylpentane-1,4-diol (8) (400 mg, 1.6 mmol) in ether (20 ml) was heated under reflux for 0.5 h with toluene-*p*-sulphonic acid (40 mg, 0.2 mmol). Tetrahydrofuran (7) was formed quantitatively (t.l.c.) and was isolated as a pure oil. There were no side-products. The spectra were identical with those from the sample prepared from the iodoketone (6). It was also noted that cyclisation of diol (8) occurred on silica gel within 15 h, during which time the solvent had evaporated. When the diol (8) was stirred overnight in chloroform with silica gel, conversion into the tetrahydrofuran (7) was not complete.

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