

Acid-catalysed Rearrangement of a Spirocyclohexadienone Involving an External Nucleophile

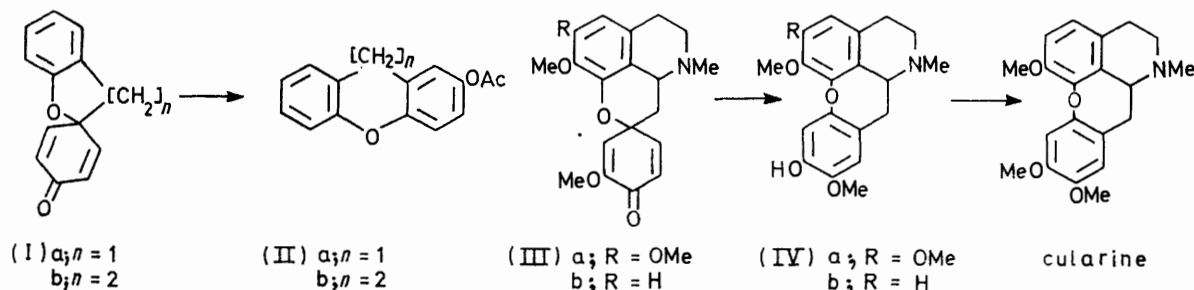
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3,4-Dihydro-3',8-dimethoxy-2*H*-benzo[*b*]pyran-2-spirocyclohexa-2',5'-dien-4'-one (VI) has been obtained in 13% yield by oxidation of 2',6-dimethoxy-2,4'-ethylenebisphenol with alkaline ferricyanide. With methanolic hydrogen chloride, the dienone undergoes ring opening to give 2-methoxy-6-(2,4,5-trimethoxyphenethyl)phenol (VIIa), 5'-chloro-2',6-dimethoxy-2,4'-ethylenebisphenol (VIIb), and 2-(2-chloro-4,5-dimethoxyphenethyl)-6-methoxyphenol (VIIc), whereas with methanol and a trace of concentrated sulphuric acid the product was only (VIIa). Under the conditions used, neither oxygen- nor alkyl-migration occurs. Syntheses of (VIIa) and (VIIc) are described.

In vitro experiments have already demonstrated the feasibility of the formation of many aporphine alkaloids from appropriate spirocyclohexadienones, either by dienone-phenol rearrangement or, after reduction, by dienol-benzene rearrangement;^{1,2} in such rearrangements aryl groups generally migrate in preference to aralkyl groups.

into the cularine-type structure (IVa), although a later communication reported that the dienone (IIIb)⁵ could not be rearranged to the cularine-type compound (IVb). The formation of (IVa) clearly involves aryloxy- rather than aralkyl-group migration.

It has been pointed out³ that the competition between the possible modes of rearrangement (aralkyl- or aryloxy-



The syntheses of the spirodienones (Ia and b), and their acid-catalysed rearrangements into 2-acetoxycularine (IIa) and 2-acetoxydibenz[*b,f*]oxepin (IIb), respectively, *via* aralkyl group migration have been reported.³ These findings were, at that time, in contrast with the reported rearrangement of the dienone (IIIa)⁴

group migration) may be sensitive to changes in conditions or to the presence of substituents (in particular methoxy-groups), or to both of these factors. In order to investigate such effects, the spirocyclohexadienone (VI) has been synthesised and its reactions under acidic conditions have been studied.

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¹ D. H. R. Barton and T. Cohen, 'Festchr. A. Stoll,' Birkhäuser, Basel, 1957, p. 117; A. R. Battersby, 'Oxidative Coupling of Phenols,' Arnold, London, 1968, p. 121.

² A. H. Jackson and J. A. Martin, *J. Chem. Soc. (C)*, 1966, 2222; D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *ibid.*, 1967, 2134; K. Bernauer, *Helv. Chim. Acta*, 1964, **42**, 2119, 2122; I. R. C. Bick, *Experientia*, 1964, **20**, 362.

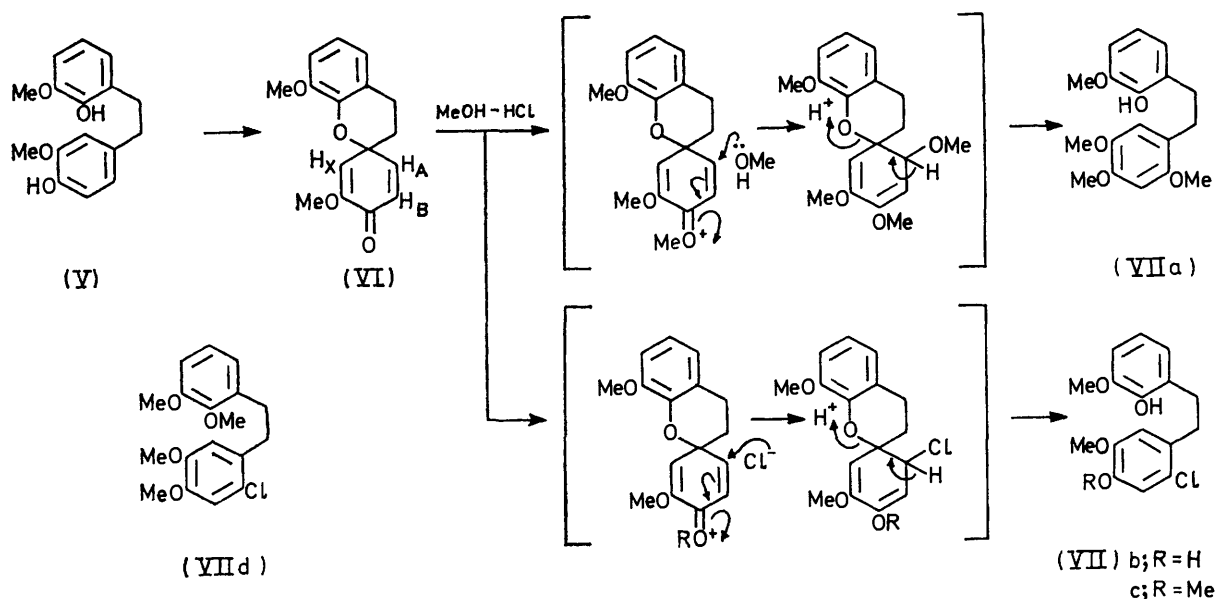
³ A. M. Choudhury, K. Schofield, and R. S. Ward, *J. Chem. Soc. (C)*, 1970, 2543.

⁴ T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1003; T. Kametani and K. Fukumoto, *Chem. Comm.*, 1967, 546; T. Kametani, H. Iida, T. Kikuchi, M. Mizushima, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 709.

⁵ T. Kametani, K. Fukumoto, and K. Fujihara, *Chem. Comm.*, 1971, 352.

The rearrangement reaction was brought about by treating the dienone (VI) with methanolic hydrogen chloride. The products, isolated by preparative thick-layer chromatography, were the phenols (VIIa–c), identified by mixed m.p. determinations and by comparison of spectra with those of authentic samples, synthesised as described later. The addition of one or two drops of concentrated hydrochloric acid to the reaction mixture accelerated the rearrangement and reduced the proportion of polymeric material formed.

With methanol and a trace of concentrated sulphuric



acid, the dienone (VI) gave only the phenol (VIIa). On treatment of (VI) with acetic anhydride and a trace of concentrated sulphuric acid³ a polymeric material was produced which was highly fluorescent under u.v. light and insoluble in most organic solvents; this behaviour was not further investigated.

The foregoing findings demonstrate that under these acidic conditions the dienone (VI) undergoes ring opening, and that this is preferred to ring expansion. This is possibly because migration to form the seven-membered ring system of the dibenz[*b,f*]oxepin-type (IIb) is less favourable sterically than the analogous and well established⁶ dienone rearrangements to form six-membered rings, and also possibly because a nucleophilic solvent system (MeOH–HCl) was used; the substituents of the spirodienone system must have a specific part to play in the direction taken by such rearrangements. Recently, Jackson *et al.*⁷ also observed ring opening in a system similar to (IIIb).

Compounds (VI), (VIIa), and (VIIc) were prepared by the routine procedures described in the Experimental section.

EXPERIMENTAL

Light petroleum used had b.p. 40–60°. N.m.r. spectra were obtained with a Varian HA-100 instrument with tetramethylsilane as internal standard. I.r. and u.v.

spectra were recorded with Perkin-Elmer instruments. R_F Values refer to chromatography by the ascending solvent method. Anhydrous sodium sulphate was used as drying agent for organic solutions.

2-Benzyloxy-3-methoxybenzyl Alcohol.—A solution of 2-benzyloxy-3-methoxybenzaldehyde (48.4 g) in methanol–benzene (400 ml; 3:1 v/v) was treated with portions of sodium borohydride (7.0 g). The solvents were evaporated off and the residual oil was extracted with chloroform. The extract was washed with dilute alkali and water, dried, and evaporated. Crystallisation of the residue from ether–light petroleum gave the alcohol (48.0 g), m.p. 59–60°

(Found: C, 73.7; H, 6.5. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.55%).

2-Benzyloxy-3-methoxybenzyltriphenylphosphonium Chloride.—(a) A solution of the foregoing alcohol (40.0 g) in anhydrous ether (50 ml) was treated slowly with distilled thionyl chloride (40.0 g) and the mixture was boiled gently for 45 min. The solvents were evaporated off and the residual oil distilled to give the corresponding benzyl chloride (37.4 g) as a pale yellow oil, b.p. 146–149° at 0.02 mmHg (Found: C, 68.65; H, 5.8. $C_{15}H_{15}ClO_2$ requires C, 68.55; H, 5.7%).

(b) The benzyl chloride (37.2 g), triphenylphosphine (52.6 g), and dry benzene (50 ml) were heated under reflux for 1 h. The mixture was cooled and diluted with light petroleum, yielding a product which afforded the phosphonium chloride as white crystals (95%), m.p. 234–235° (from benzene–light petroleum) (Found: Cl, 0.7. $C_{33}H_{30}ClO_2P$ requires anionic Cl, 0.65%).

2',6-Dimethoxy-2,4'-ethylenebisphenol (V).—(a) To a stirred solution of sodium (2.3 g) in absolute ethanol (125 ml) were added simultaneously solutions of 2-benzyloxy-3-methoxybenzyltriphenylphosphonium chloride (52.5 g) in absolute ethanol (75 ml) and *O*-benzylvanillin (24.2 g) in absolute ethanol (50 ml). The mixture was stirred overnight. The precipitate was collected, washed with water,

⁶ B. Miller, 'Mechanisms of Molecular Migration,' ed. B. S. Thyagarajan, Interscience, New York, 1968, p. 247 and references cited therein.

⁷ A. H. Jackson and G. W. Stewart, *Tetrahedron Letters*, 1971, 4941.

dried, and crystallised from benzene–light petroleum to give 2,4'-bisbenzyloxy-3,3'-dimethoxystilbene (30.7 g) as a white silk, m.p. 100° (Found: C, 79.7; H, 6.0. $C_{30}H_{28}O_4$ requires C, 79.65; H, 6.2%).

(b) The stilbene (30.0 g) in acetic acid (500 ml) was hydrogenated over 10% palladised charcoal for 3 h (uptake 3 mol. equiv.). Filtration, evaporation, and crystallisation from benzene–light petroleum gave the *diphenol* (V) (17.8 g), m.p. 78–79°, as needles (Found: C, 70.7; H, 6.85. $C_{16}H_{16}O_4$ requires C, 70.75; H, 6.55%), ν_{\max} (KBr) 3350 and 3400 cm^{-1} ; *diacetate*, m.p. 112–113° (from ethanol) (Found: C, 67.15; H, 6.05. $C_{20}H_{22}O_6$ requires C, 67.05; H, 6.15%).

3,4-Dihydro-3',8-dimethoxy-2H-benzo[b]pyran-2-spiro-cyclohexa-2',5'-dien-4'-one (VI).—The diphenol (V) (685 mg) in 2M-sodium hydroxide (300 ml) was added dropwise during 1.5 h to a stirred mixture of ether (300 ml) and a solution of potassium ferricyanide (4.1 g) in water (410 ml). The mixture was then stirred for another 3 h. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined, dried, ethereal extracts were evaporated and the residue was eluted with benzene through a short column of alumina (grade III). Evaporation of the eluate and crystallisation of the residue from ether–light petroleum gave the *spirodienone* (86 mg), m.p. 154–155° (Found: C, 70.45; H, 6.25. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%), m/e 272, ν_{\max} (KBr) 1695, 1650, and 1625 cm^{-1} , λ_{\max} (MeOH) 234, 274.5, and 282.5 nm, τ ($CDCl_3$) 2.80–3.10 (3H, m), 4.09 (1H, d, J_{AX} 3 Hz, H_X), 3.88 (1H, d, J_{AB} 10 Hz, H_B), 3.20 (1H, q, H_A), 6.16 and 6.33 (each 3H, s), and 7.07 and 7.90 (each 2H, t).

Rearrangement of the Spirodienone (VI).—(a) A solution of the dienone (200 mg) in methanol (60 ml) was stirred together with methanolic hydrogen chloride (5 ml) and concentrated hydrochloric acid (2 drops) in the dark at room temperature for 1 h, then neutralised with saturated sodium hydrogen carbonate solution, and extracted with chloroform (4 × 25 ml). The extracts were washed with water, dried, and evaporated to give an oily solid (186 mg), which t.l.c. (Kieselgel DC-Karten SIF; chloroform–benzene, 1 : 2 v/v) showed to consist of three components (R_F 0.30, 0.39, and 0.46). The solid was loaded onto three thick-layer plates (20 × 20 cm; Kieselgel GF₂₅₄) and eluted with chloroform–benzene (R_F value of the dienone in the same system, 0.28). The bands were removed and extracted with methanol–chloroform to give three fractions.

Fraction (i), R_F 0.30 (50 mg, 21%), had m.p. 76–77° (from benzene–light petroleum), mixed m.p. with the phenol (VIIa) 76–77° (Found: C, 68.0; H, 6.8. Calc. for $C_{18}H_{22}O_5$: C, 67.9; H, 6.9%), m/e 318, ν_{\max} (KBr) 3550 cm^{-1} , τ ($CDCl_3$) 3.30 (3H, s), 3.34 (1H, s), 3.48 (1H, s), 4.24 (1H, s, OH), 6.19 (6H, s), 6.24 (3H, s), 6.27 (3H, s), and 7.16 (4H, s).

Fraction (ii), R_F 0.39 (60.2 mg, 26.5%), had m.p. 84–85° (from benzene–light petroleum) (Found: C, 62.35; H, 5.7. $C_{16}H_{17}ClO_4$ requires C, 62.5; H, 5.5%), m/e 308, ν_{\max} (KBr) 3575 cm^{-1} , τ ($CDCl_3$) 3.19 (1H, s), 3.28 (3H, s), 3.43 (1H, s), 4.31 (2H, d, OH), 6.17 (3H, s), 6.21 (3H, s), and 7.16 (4H, s). The *O*-methyl derivative had m.p. 116°, mixed m.p. with 1-(2-chloro-4,5-dimethoxyphenethyl)-2,3-dimethoxybenzene (VIIId) 116°, and spectra identical with those of synthetic (VIIId). Hence fraction (ii) was identified as 5'-chloro-2',6-dimethoxy-2,4'-ethylenebisphenol (VIIb).

Fraction (iii), R_F 0.46 (32.8 mg, 13.9%), had m.p. 106–

107° (from benzene–light petroleum), mixed m.p. with (VIIc) 106–107° (Found: C, 63.15; H, 6.0. Calc. for $C_{17}H_{19}ClO_4$: C, 63.35; H, 5.9%), m/e 322, ν_{\max} (KBr) 3600 cm^{-1} , τ ($CDCl_3$) 3.17 (1H, s), 3.30 (3H, s), 3.40 (1H, s), 4.32 (1H, s, OH), 6.17 (3H, s), 6.21 (3H, s), 6.28 (3H, s), and 7.10 (4H, s).

(b) The dienone (75 mg), methanol (25 ml), and concentrated sulphuric acid (2 drops) were stirred together in the dark at room temperature for 1.5 h. The mixture was neutralised with saturated sodium hydrogen carbonate solution, methanol was evaporated off, and the aqueous layer was extracted with chloroform (3 × 25 ml). The extracts were washed with water, dried, and evaporated to give an oily solid (67 mg), which t.l.c. (Kieselgel DC-Karten SIF; chloroform–benzene, 1 : 2 v/v) showed to consist of a fast-running component (R_F 0.30), along with polymeric material of much lower R_F value. The former was isolated by thick-layer chromatography to give material (25 mg, 28.8%) of m.p. 75–76°, mixed m.p. with (VIIa) was 74–76°. Two crystallisations from benzene–light petroleum gave almost colourless needles, m.p. 76–77°, spectra identical with those of synthetic (VIIa).

2-Methoxy-6-(2,4,5-trimethoxyphenethyl)phenol (VIIa).—Solutions of 2-benzyloxy-3-methoxybenzyltriphenylphosphonium chloride (17.0 g) in absolute ethanol (25 ml) and 2,4,5-trimethoxybenzaldehyde⁸ (6.3 g) in absolute ethanol (35 ml) were added simultaneously to a stirred solution of sodium (750 mg) in absolute ethanol (50 ml) and the mixture was stirred at room temperature for 2 days. The precipitate was collected, washed with water, dried, and crystallised from acetic acid to give 2-benzyloxy-2',3,4',5'-tetramethoxystilbene as white crystals (5.9 g), m.p. 144–145° (Found: C, 73.95; H, 6.3. $C_{25}H_{26}O_5$ requires C, 73.9; H, 6.4%).

The stilbene (5.6 g) in acetic acid (300 ml) was hydrogenated over 10% palladised charcoal for 3 h. Filtration, evaporation, and crystallisation from benzene–light petroleum gave (VIIa) (3.3 g) as needles, m.p. 76–77° (Found: C, 68.0; H, 6.85. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.9%).

2-(2-Chloro-4,5-dimethoxyphenethyl)-6-methoxyphenol (VIIc).—The corresponding stilbene was obtained as white needles, m.p. 135–136° (from benzene–light petroleum), by Wittig reaction between 2-benzyloxy-3-methoxybenzyltriphenylphosphonium chloride and 2-chloro-4,5-dimethoxybenzaldehyde⁹ (see similar method above). Hydrogenolysis over palladised charcoal in acetic acid gave the phenol (VIIc) (60%), m.p. 107–108° (Found: C, 63.4; H, 5.85. $C_{17}H_{19}ClO_4$ requires C, 63.35; H, 5.9%).

1-(2-Chloro-4,5-dimethoxyphenethyl)-2,3-dimethoxybenzene (VIIId).—The phenol (VIIc) (400 mg) in dilute sodium hydroxide was treated with dimethyl sulphate at room temperature and the precipitate was crystallised from benzene–light petroleum to give (VIIId) (400 mg) as white feathers, m.p. 116° (Found: C, 64.25; H, 6.1. $C_{18}H_{21}ClO_4$ requires C, 64.2; H, 6.25%), m/e 336, τ ($CDCl_3$) 3.10–3.42 (5H, m), 6.22 (9H, t), 6.28 (3H, s), and 7.11 (4H, s).

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⁸ F. S. H. Head and A. Robertson, *J. Chem. Soc.*, 1930, 2441.

⁹ D. Ginsburg, *J. Amer. Chem. Soc.*, 1951, **73**, 702.