Tetrahedron. Vol. 25, pp. 2661 to 2666. Pergamon Press 1969. Printed in Great Britain

REARRANGEMENTS OF BICYCLIC δ-HYDROXY-α,β-ENONES—III[1,2]

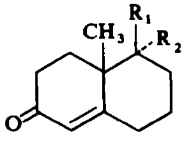
SYNTHESES OF SUBSTITUTED 1,2-BENZOCYCLOOCT-1-EN-6-ONES

J. P. John, K. G. Srinivasan, P. S. Venkataramani and S. Swaminathan
Department of Organic Chemistry, University of Madras, Madras 25, India

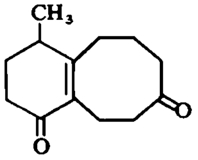
(*Received in the UK* 15 *January* 1969; *Accepted for publication* 23 *January* 1969)

Abstract—The earlier structural assignment as **2** for the dione obtained by the base treatment of **1a** or **1b** is confirmed. Syntheses of substituted 1,2-benzocyclooct-1-en-6-ones are reported.

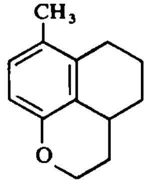
Earlier work[1,2] from our laboratories has shown that the epimeric vinyl carbinols **1a** and **1b** when treated with base yield a dione for which structure **2** has been assigned on the basis of its light absorption properties. The dione (**2**) has also been obtained in addition to the benzopyran (**3**) when the same carbinols are treated with *p*-toluenesulphonic acid.



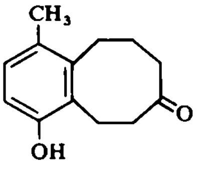
1a: $R_1 = -OH$, $R_2 = -CH{=}CH_2$
1b: $R_1 = -CH{=}CH_2$, $R_2 = -OH$.



2



3



4

We report here further work which confirms the structure **2**; it relates to (a) the transformation of the dione (**2**) to 3′-methyl-1,2-benzocyclooct-1-ene (**6**) and (b) an unequivocal synthesis of the phenol (**4**) obtained by dehydrogenation of the dione (**2**).

Treatment of the dione (**2**) with sodium borohydride caused selective reduction of the non-conjugated carbonyl group and the crude alcohol obtained was dehydrated to the dienone (**5**) (Fig. 1). Further transformations of this purified dienone were carried out as indicated without purification of the intermediate compounds which had the expected IR absorptions. The hydrocarbon (**6**) thus obtained was found to be identical (TLC and IR) with an authentic sample of 3′-methyl-1,2-benzocyclooct-1-ene obtained by Wolff–Kishner reduction of the known[3] ketone (7).

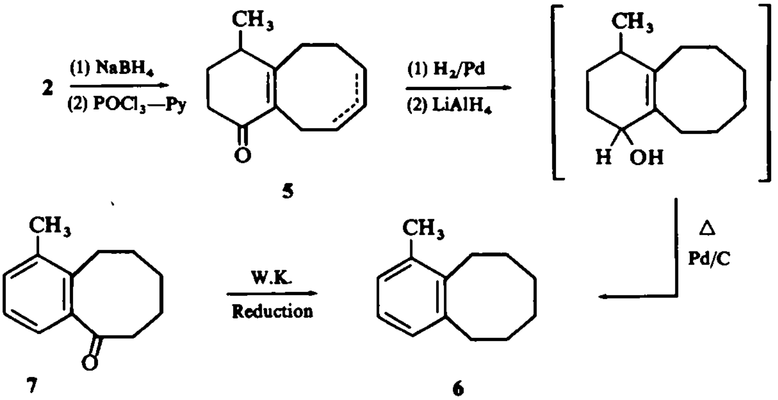
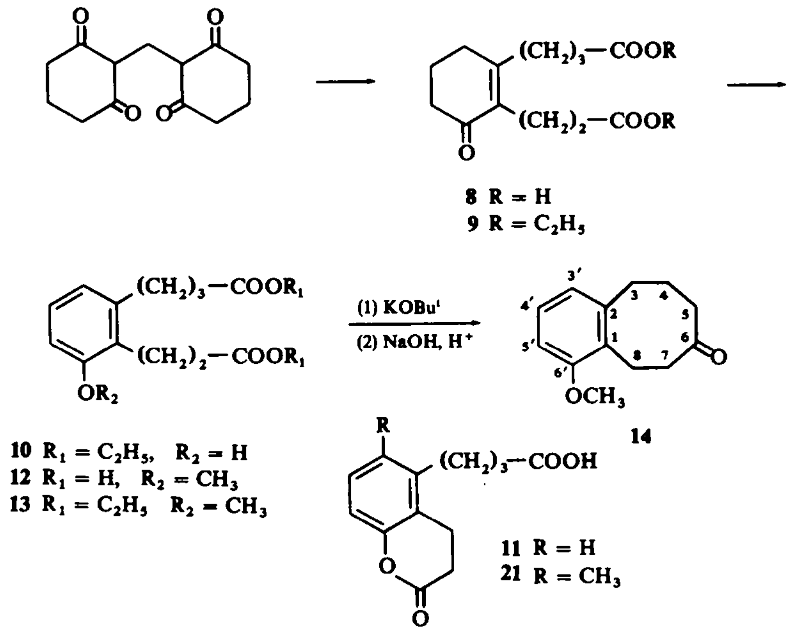


FIG. 1

A survey of the literature reveals that while completely alicyclic compounds of the type **2** containing an eight atom ring have not been synthesized, a few benzocyclooct-1-ene derivatives are known. The methods that have been employed for their synthesis include (a) the condensation[4] of 2-hydroxymethylene cyclooctanone with ethyl acetone dicarboxylate followed by hydrolysis and decarboxylation to give 4′-hydroxybenzocyclooct-1-ene (b) treatment of α-tetralone with diazomethane to give a product believed[5] to be benzocyclooct-1-en-4-one (c) cyclization[6] of a α,ω-dinitrile to give after hydrolysis and decarboxylation benzocyclooct-1-en-5-one and (d) Friedel–Crafts cyclization,[3, 7–10] under high dilution conditions of 6-arylhexanoic acid chloride. Dieckmann cyclization itself does not appear to have been applied to the preparation of 1,2-benzocyclooct-1-enones or for that matter any compound containing an eight membered carbon ring other than cyclooctanone itself.[11]

The ready availability of the diacid (**8**) obtained[12] by alkaline cleavage of methylene *bis*-cyclohexane-1,3-dione prompted us to study as a model system, the Dieckmann cyclization of its diester (**9**) and also the pyrolysis of its heavy metal salts. No useful products could be obtained in these experiments and its was concluded that the α,β-enone function present in these compounds perhaps hampered the desired cyclization. The diester (**9**) was therefore aromatized catalytically to the phenolic ester (**10**) which when treated with dimethyl sulphate and alkali gave the methoxy diacid (**12**) which was reesterified to the desired diester (**13**) (Fig. 2). Incidentally, saponification of the phenolic ester (**10**) gave only the lactonic acid (**11**).

Cyclization of the diester (**13**) under conditions of high dilution in the presence of potassium tertiary butoxide furnished in a 26% yield a mixture, possibly, of the expected β-keto esters. Saponification of the crude product gave 6′-methoxy benzocyclooct-1-en-6-one (**14**) as a liquid characterized by its oxime and 2,4-dinitrophenyl hydrazone. The above cyclization was then carried out with the homologous diester (**20**) prepared in a similar way from the diacid (**16**) which in turn was obtained in excellent yields by alkaline cleavage of the known[13] dione (**15**) (Fig. 3).



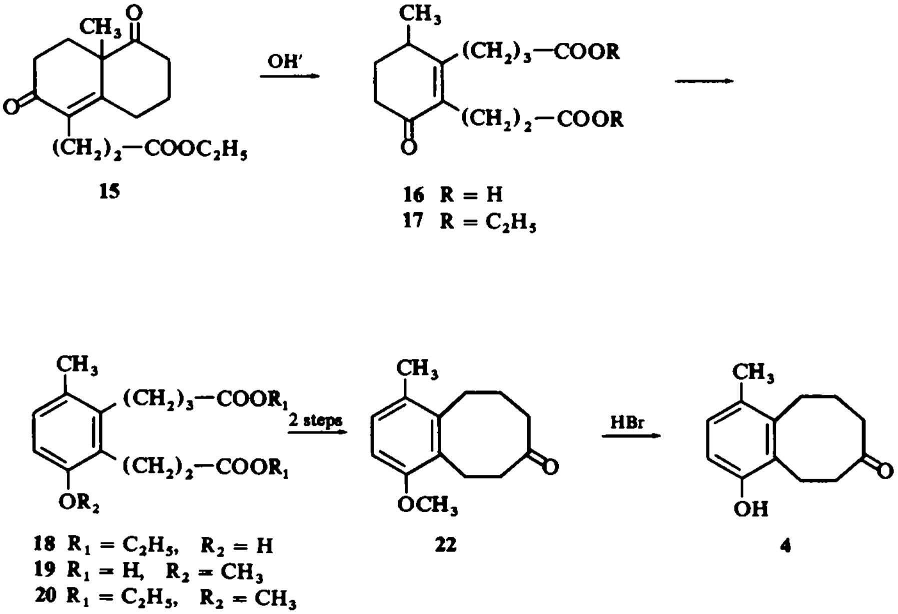
8 $R = H$
9 $R = C_2H_5$

10 $R_1 = C_2H_5$, $R_2 = H$
12 $R_1 = H$, $R_2 = CH_3$
13 $R_1 = C_2H_5$ $R_2 = CH_3$

14

11 $R = H$
21 $R = CH_3$

FIG. 2



15

16 $R = H$
17 $R = C_2H_5$

18 $R_1 = C_2H_5$, $R_2 = H$
19 $R_1 = H$, $R_2 = CH_3$
20 $R_1 = C_2H_5$, $R_2 = CH_3$

22

4

FIG. 3

The phenolic ketone (4) thus obtained was identical in all respects with a sample obtained by dehydrogenation of (2) obtained by rearrangement of the vinyl carbinol (1a) or (1b).

EXPERIMENTAL

Rearrangement of 1-*vinyl*-1-*hydroxy*-6-*oxo*-8*a*-*methyl*-1,2,3,4,6,7,8,8*a*-*octahydronaphthalene to compound* **2**

A mixture of **1a** or **1b** (5 g), methanol (50 ml) and potassium hydroxide solution (50 ml, 5·6%) was refluxed for 1 hr. The dark red reaction mixture was freed of solvent and extracted with ether. The ether extract was washed with water, dried and concentrated to give a solid (2·25 g) m.p. 57–59°. An additional amount of the same solid (1·35 g) was obtained by chromatography of the ethereal filtrate over alumina. A crystallization from ether furnished* colourless crystals m.p. 58·4–59·4°.

The dione (2) furnished a dioxime, m.p. 182–183° (aqueous ethanol). (Found: C, 66·4; H, 8·7. $C_{13}H_{20}N_2O_2$ requires: C, 66·1; H, 8·5).

Dehydrogenation of the dione (**2**)

A solution of the dione (**2**) (750 mg) in *p*-cymene (5 ml) was heated with Pd/C (100 mg, 30%) for 3 hr at 220° and then filtered while hot. The filtrate when cooled gave a solid (600 mg). A crystallization from benzene–petroleum (60–80°) gave* colourless needles of the phenol (**4**), m.p. 148–149°. The methyl ether obtained by treatment with dimethyl sulphate and potassium hydroxide solution had a m.p. 62·6–63·6° (ether–petroleum (60–80°)).* The phenol (**4**) also furnished a bromoacetyl derivative m.p. 114·5–115·5° (ethyl acetate). (Found: C, 55·6; H, 5·3. $C_{15}H_{17}O_3Br$ requires: C, 55·7; H, 5·2.)

Conversion of the dione (**2**) *to* 3′-*methyl*-1,2-*benzocyclooct*-1-*ene* (**6**)

(a) 3′,4′,5′,6′-*Tetrahydro*-3′-*methyl*-1,2-*benzocycloocta*-$\Delta^{1,x}$-*dien*-6′-*one* (5). To a stirred solution of dione (2) (4·2 g) in ethanol (200 ml) was added a solution of sodium borohydride (1·09 g) in ethanol (200 ml) dropwise over 1 hr, the mixture stirred for another 3 hr and then decomposed with acetic acid. Excess alcohol was removed and the product (4·1 g) extracted with chloroform. It was a viscous liquid having a camphor-like odour and IR absorptions at 2·85 and 6·0 μ. To a solution of this alcohol (3 g) in pyridine (5 ml) was added with stirring a solution of phosphorus oxychloride (3 ml) in pyridine (3 ml). The mixture was then heated on a steam bath for 1 hr, poured on ice and the organic product extracted with ether. The ether extract furnished a pleasant smelling liquid; b.p. 98–100°/1 mm; yield 1 g. (Found: C, 82·6; H, 9·2. $C_{13}H_{18}O$ requires: C, 82·1; H, 9·5. $\lambda_{max}^{CHCl_3}$ 6·05, 6·2 μ and no —OH absorption. The position of the double bond in (5) was not established.

(b) *Reduction and aromatization of dienone* (5). A solution of the dienone (5) (2·4 g) in ethanol (50 ml) when hydrogenated with $Pd/BaCO_3$ (240 mg) for 2 hr furnished a liquid (2 g) having conjugated carbonyl absorption at 6·0 μ. Without purification, this liquid (1·5 g) was reduced as usual with lithium aluminium hydride (750 mg) in ether (125 ml) to give *ca.* 1 g of a viscous liquid showing no IR absorption for carbonyl and only —OH absorption at 2·75 μ. This material (1 g) was heated at 260–275° for 3 hr with Pd/C (100 mg, 30%). Extraction with ether followed by distillation furnished a colourless pleasant smelling liquid, b.p. 110–112°/14 mm, n_D^{30} 1·5336 having identical IR absorptions with those of an authentic sample of (6) as obtained below.

3′-*Methyl*-1,2-*benzocyclooct*-1-*ene* (**6**)

A mixture of the ketone (7) (3·75 g) obtained as described in the literature,[3] hydrazine hydrate (5 g) and ethylene glycol (40 ml) was heated at 140° for 3 hr. Solid potassium hydroxide (5 g) was then added and the reaction mixture heated at 210° for 4 hr. The mixture was cooled, diluted with water and extracted with ether. The ether extract was concentrated and the residual liquid distilled; b.p. 101–102°/2 mm. A redistillation furnished the analytical sample. (Found: C, 89·7; H, 10·3. $C_{13}H_{18}$ requires: C, 89·6; H, 10·4.)

2-(2′*Carboxyethyl*)-3-(3′-*carboxypropyl*)*cyclohex*-2-*en*-*one* (**8**) *and its diethyl ester* (**9**)

2,2′-Methylene biscyclohexane-1,3-dione (30 g) was dissolved in a solution of barium hydroxide (180 g) in water (750 ml) and the mixture refluxed for 20 hr. The hot yellow solution was saturated with CO_2 and filtered from the precipitated barium carbonate. The precipitate was washed with some hot water and the combined filtrate evaporated to dryness to give the barium salt of the ketoacid (**8**). This Salt was acidified

---

* The analytical and light absorption data on these compounds have been reported in ref. 1.

with conc. HCl and the free acid extracted with ether. After removal of ether a syrupy liquid was obtained which solidified when cooled, yield 18 g; m.p. 85–86° (ether–petroleum (60–80°)) lit[12] m.p. 77°. $\lambda_{max}^{CHCl_3}$ 5·85, 6·03 and 6·13 μ λ_{max}^{EtOH} 244 mμ. (ε 14,730).

Pyrolysis of the barium salt did not give any useful product.

The acid (8) (15 g) was esterified in the usual way to give the diester (9) (11 g); b.p. 160–170°/0·3 mm. lit[12] b.p. 235–240°/24 mm $\lambda_{max}^{CHCl_3}$ 5·80, 6·05 and 6·2 μ λ_{max}^{EtOH} 244 mμ (ε 13,110).

2-(2′-*Carboxyethyl*)-3-(3′-*carboxypropyl*)*anisole* (**12**)

A mixture of the ester (**9**) (4 g) and Pd/C (0·4 g, 30%) was heated at 290° until the evolution of hydrogen stopped (0·75 hr). The mixture was cooled and ether extracted to furnish the phenolic ester (**10**) (2·1 g); b.p. 126–130°/3 mm. $\lambda_{max}^{CHCl_3}$ 2·80, 5·85 and 6·275 μ.

To a solution of the ester (10) (1 g) in 10% aq sodium hydroxide (10 ml), dimethyl sulphate (1 ml) was added and the mixture heated on a water bath for 6 hr. At the end of the first 2 hr period, an additional amount of sodium hydroxide solution (5 ml, 10%) was added. The mixture was finally diluted with water and extracted with ether to remove any neutral material. The aqueous layer was acidified and extracted with chloroform. The chloroform extract furnished the diacid (**12**), (0·89 g) m.p. 124·4–125° (ether). (Found: C, 63·1, H, 6·9. $C_{14}H_{18}O_5$ requires: C, 63·2, H, 6·8.) NE Found: 132 (calc. 133) λ_{max}^{KBr} 5·87, 5·95 and 6·33 μ. NMR: ($CDCl_3$) (τ) 6·17 (3H, —$OC\underline{H}_3$), 2·7–3·2 (3H, ar. protons) −1·25 (2H, 2-$COO\underline{H}$) 6·8–8·4 (10 H, methylene protons).

Direct saponification of the phenolic ester (**10**) (2 g) by refluxing for 2 hr with a solution of potassium hydroxide (1 g) in aqueous methanol (75%, 20 ml) followed by acidification and extraction with chloroform gave 0·7 g of the lactonic acid (11), m.p. 191–191·5° (ethyl acetate–ethanol). (Found: C, 66·9; H, 5·8. $C_{13}H_{14}O_4$ requires: C, 66·7; H, 6·0) λ_{max}^{KBr} 5·6 (sh), 5·85 and 6·275 μ.

2-(2′-*Carbethoxyethyl*)-3-(3′-*carbethoxypropyl*)*anisole* (**13**)

The acid (12) (15 g) was esterified in the usual way to afford 13 g of the diethyl ester (**13**). A sample for analysis was obtained by chromatographic purification over alumina. (Found: C, 67·5, H, 8·4. $C_{18}H_{26}O_5$ requires: C, 67·1, H, 8·1.) λ_{max}^{neat} 5·75 and 6·25 μ. NMR (CCl_4) (τ): 2·8–3·5 (3H, ar. protons), 5·71–6·1 (4H, 2-$COOC\underline{H}_2$—CH_3), 6·2 (3H, —$OC\underline{H}_3$), 8·67–8·9 (6H, 2$COOCH_2$—$C\underline{H}_3$) 6·9–8·3 (10H, methylene protons).

6′-*Methoxy*-1,2-*benzocyclooct*-1-*en*-6-*one* (**14**)

The Dieckmann cyclization of the ester (**13**) was carried out in the special high dilution apparatus described in the literature.[14] The dry apparatus was flushed with nitrogen and dry xylene (450 ml) and dry *t*-butanol (35 ml) were added. Potassium (6·2 g) cut into small pieces was added gradually. After the potassium had reacted completely excess *t*-butanol was distilled off. The ester (13) (11 g) in dry xylene (125 ml) was then introduced dropwise over a period of 18 hr. During this period, a nitrogen atmosphere was maintained with stirring and refluxing. After all the ester had been added, the reaction mixture was refluxed for an additional hour with continued stirring, then cooled and acidified with acetic acid. The xylene layer was separated and washed successively with water, sodium bicarbonate solution and water, dried and freed of solvent to give 2·8 g of liquid with $\lambda_{max}^{CH_2Cl}$ 5·73, 5·81 and 6·35 μ. This liquid (2·5 g) was heated with 10% sodium hydroxide solution (25 ml) in a water-bath for 4 hr, cooled and extracted with ether. The ether extract furnished 1·2 g of liquid which was chromatographically purified over alumina. (Found: C, 76·0, H, 8·2. $C_{13}H_{16}O_2$ requires: C, 76·4; H, 7·9.) $\lambda_{max}^{CHCl_3}$ 5·83, 6·23 μ. λ_{max}^{EtOH} 275–283 mμ (ε 1338). NMR (CCl_4) (τ): 2·8–3·5 (3H, ar. protons) 6·25 (3H, —$OC\underline{H}_3$) 6·8–8·4 (10H, methylene protons).

2,4-Dinitrophenylhydrazone: m.p. 199·4–200°. (ethanol ethyl acetate). (Found: C, 59·0; H, 5·3. $C_{19}H_{20}N_4O_5$ requires: C, 59·4; H, 5·2.) Oxime: m.p. 126–126·8°, petroleum (60–80°). (Found: C, 70·5; H, 8·0; N, 6·3; $C_{13}H_{17}NO_2$ requires: C, 71·0; H, 7·8; N, 6·4).

2-(2′-*Carboxyethyl*)-3-(3′-*carboxypropyl*)-4-*methylcyclohex*-2-*enone* (**16**) *and its diethyl ester* (**17**)

The dione (15) (10 g)[13] was mixed with a saturated solution of barium hydroxide (600 ml) and the mixture heated over a water bath in an atmosphere of nitrogen for 6 hr and then kept overnight. After an extraction with ether to remove any neutral material, the alkaline solution was acidified with conc. hydrochloric acid, saturated with sodium chloride and extracted with chloroform. The chloroform extract furnished a semisolid which when triturated with ether gave a solid; this was collected and crystallized from ethyl acetate to give 4 g of the acid (16); m.p. 141–143°. (Found: C, 63·1, H, 7·5. $C_{14}H_{20}O_5$ requires: C, 62·7; H, 7·5.)

NE Found: 134 (calcd. 134). $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5·85, 6·01 and 6·15 μ. $\lambda_{\max}^{\mathrm{EtOH}}$ 243 mμ (ε 14,130). Pyrolysis of barium or cerium salt did not give any useful product.

The acid (**16**) (15 g) was esterified in the usual way to give the diethyl ester (17) (9 g); b.p. 181–185°/1 mm. (Found: C, 67·2; H, 8·6. $C_{18}H_{28}O_5$ requires: C, 66·8; H, 8·6.) $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5·77, 6·02 and 6·175 μ. $\lambda_{\max}^{\mathrm{EtOH}}$ 248 mμ (ε 19,050). NMR (CCl_4) (τ): 5·62–6·1 (4H, 2-$OC\underline{H}_2$—CH_3), 8·66–9·0 (9H $C\underline{H}_3$—CH— and 2-OCH_2—$C\underline{H}_3$), 7–8·5 (15 H, methylene and methine protons.)

2-(2′-Carboxyethyl)-3-(3′-carboxypropyl)-4-methylanisole (**19**) *and its ethyl ester* (**20**)

The diester (**17**) (3·5 g) and Pd/C (0·3 g, 30%) were heated together at 290° for 0·75 hr when the evolution of hydrogen stopped. Ether extraction furnished 2 g of the crude phenolic ester (**18**) as a liquid with $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2·8, 5·8 and 6·3 μ. There was a weak absorption at 5·72 μ indicating some lactonic impurity.

The phenol ester (**18**) (2 g) was methylated as in the case of ester (**10**) to furnish the methylated acid (**19**) (0·5 g); m.p. 132·8–134·2° (ethyl acetate). (Found: C, 64·0; H, 7·3. $C_{15}H_{20}O_5$ requires: C, 64·3 and H, 7·2). $\lambda_{\max}^{\mathrm{KBr}}$ 5·81 (sh), 5·88 and 6·25 μ NMR ($CDCl_3$) (τ): 7·75 (3H, ar. $C\underline{H}_3$) 6·27 (3H, —$OC\underline{H}_3$) 2·9–3·23 (2H, ar. protons), −0·88 (2H, 2$COO\underline{H}$) 6·8–8·3 (10 H, methylene protons).

Direct saponification of the ester (**18**) (1·5 g) followed by acidification furnished crystals (700 mg), m.p. 141–142° believed to be the lactonic acid (**21**). (Found: C, 68·2°, H, 6·2. $C_{14}H_{16}O_4$ requires: C, 67·7; H, 6·5.) $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5·83, 5·9 (sh) and 6·3 μ.

3′-Methyl-6′-hydroxy-1,2-benzocyclooct-1-en-6-one (**4**)

The diacid (**19**) (7 g) was esterified as usual to give the ethyl ester (20) (5 g) with $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 5·75 and 6·25 μ. Without further purification, this ester was cyclized with potassium-*t*-butoxide (from 1·7 g of potassium and 15 ml of *t*-butanol) in xylene (450 ml) as in the case of ester (**13**). The cyclized product (1·85 g) obtained as a liquid had $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 5·75 5·82 and 6·25 μ and was hydrolysed with aqueous sodium hydroxide to give crude (**22**) obtained as a liquid and with $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 5·82 and 6·33 μ. This ketone (**22**) was then refluxed with hydrobromic acid (48%) (2 ml) for 2 hr. The reaction mixture was cooled and extracted with ether to furnish 0·5 g of a dark viscous liquid. This was adsorbed on a column of acid washed alumina and eluted with a mixture of 30% ether–70% petroleum (60–80°) when the phenol (4) (0·35 g) was obtained as colourless crystals m.p. 148–149° undepressed by a sample obtained via the rearrangement of **1a** and having identical IR absorptions.

Acknowledgements—The authors are grateful to Professor T. R. Govindachari, CIBA research centre, Bombay for providing NMR and IR data and to Mr. R. Balasubramanian for analyses. JPJ and PSV are thankful to the UGC, New Delhi for the award of Research Fellowships and KGS to the Government of India for the award of a scholarship.

REFERENCES

[1] Part I. S. Swaminathan, Joseph P. John and S. Ramachandran, *Tetrahedron Letters*, 729 (1962).
[2] Part II. S. Swaminathan, R. K. Natarajan, S. Ramachandran and S. K. Sankarappa, *J. Org. Chem.* **31**, 656 (1966).
[3] R. Huisgen, I. Ugi, E. Rauenbusch, V. Vossius and H. Oertel, *Chem. Ber.* **90**, 1946 (1957).
[4] V. Prelog, L. Ruzika and O. Metzler, *Helv. Chim. Acta* **30**, 1883 (1947).
[5] R. B. Thompson, *J. Am. Chem. Soc.* **66**, 156 (1944).
[6] E. M. Fry and L. F. Fieser, *Ibid.* **62**, 3489 (1940).
[7] R. Huisgen and W. Rapp, *Chem. Ber.* **85**, 826 (1952).
[8] R. Huisgen, W. Rapp, I. Ugi, H. Walz and E. Mergenthaler, *Liebigs Ann.* **586**, 1 (1954).
[9] W. M. Schubert, W. A. Sweeney and H. K. Latourette, *J. Am. Chem. Soc.* **76**, 5462 (1954).
[10] N. L. Allinger and E. S. Jones, *J. Org. Chem.* **27**, 70 (1962).
[11] J. P. Schaefer and J. J. Bloomfield, *Org. Reactions* **15**, 10 (1967).
[12] D. Vorlander and F. Kalkow, *Liebigs Ann.* **309**, 356 (1899).
[13] P. Wieland, H. Uberwasser, G. Anner and K. Mischer, *Helv. Chim. Acta* **36**, 376 (1953).
[14] N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.* **23**, 1708 (1958).