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SUBSTITUTED 6,7-BENZOCOUMARAN-2-ONES FROM THE STOBBE REACTION OF BENZYL KETONES

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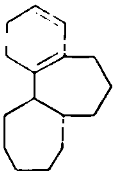
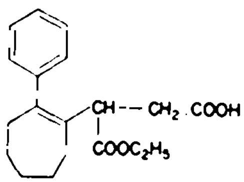
Abstract A new type of ring closure, characterized by the formation of a naphthalene nucleus condensed to a γ-lactone ring, is described. It appears to be general for acid-esters, acid-lactones and dicarboxylic acids derived from the Stobbe products of benzyl ketones.

For the preparation of tricyclic compounds of type I, starting material II is available by the Stobbe reaction of 2-phenylcycloheptanone (III).

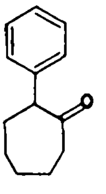

I



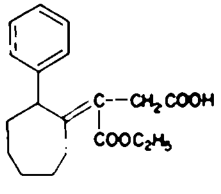
II

This ketone is easily prepared from 2-chlorocycloheptanone and phenylmagnesium bromide.[1,2] Its condensation with diethyl succinate is best carried out with sodium hydride as catalyst in *boiling* benzene. Sodium t-pentoxide gives lower yields and does not permit the recovery of unchanged III, which probably undergoes self-condensation. With sodium hydride, a 30–40 per cent yield of acidic products (expectedly IV) is obtained and 40 per cent of III is recovered.

From the oily acidic products, a solid acid of the expected composition and m.p. 144° was obtained in 7 per cent yield. The spectrum (233 mμ, log 3·89) appears to confirm structure II, as the isomer IV would be expected to absorb at 220–225 mμ.[3] The hypsochromic shift in the spectrum of II as compared with styrene (245 mμ), may be ascribed to steric hindrance,[4] which may also explain the relatively low extinction coefficient.



III



IV

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[1] M. S. Newman and M. D. Farbman, *J. Amer. Chem. Soc.* **66**, 1550 (1944).

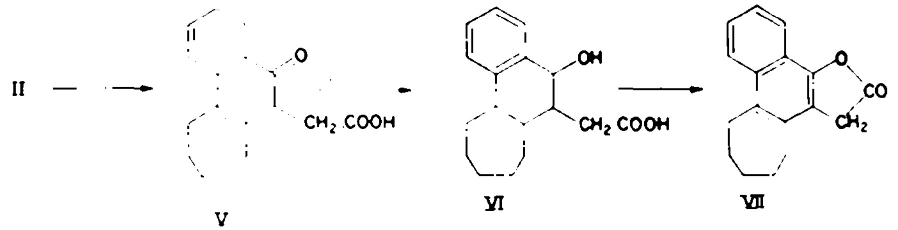
[2] R. T. Arnold, J. S. Buckley and R. M. Dodson, *J. Amer. Chem. Soc.* **72**, 3153 (1950).

[3] H. E. Ungnade and I. Ortega, *J. Amer. Chem. Soc.* **73**, 1564 (1951).

[4] R. B. Carlin and H. P. Landerl, *J. Amer. Chem. Soc.* **75**, 3969 (1953).

Cyclization of II with polyphosphoric acid gave a neutral product of the formula $C_{17}H_{16}O_2$, which is not a ketone. Its ultra-violet spectrum resembles closely that of naphthalene; in the infra-red, a pronounced maximum was observed at 1823 cm^{-1}, pointing to the presence of a β,γ-unsaturated γ-lactone system[5,6] for which a value of 1800 cm^{-1} is accepted.

The following mechanism for the formation of $C_{17}H_{16}O_2$ is proposed, leading to the structure of 6,7-benzo-4,5-cycloheptenocoumaran-2-one (VII).



Compound II cyclizes to V which isomerizes immediately to the α-naphthol derivative VI in the manner known from the classical α-naphthol synthesis from 3-benzylidenepropionic acid.[7] Compound VI, a derivative of *o*-hydroxyphenylacetic acid, is incapable of independent existence and forms the corresponding coumaran-2-one (VII).[9]

When the crude acidic product of the Stobbe reaction of III is heated with hydrobromic and acetic acids, in order to hydrolyse the ester group in (II) and cause decarboxylation,[10] an oily product is obtained, which upon treatment with polyphosphoric acid again yields VII. The oily product has an infra-red band at 1778 cm^{-1}, and thus appears to be a saturated γ-lactone.[5,6] Formula VIII is in agreement with this and explains the transformation into VII.

The mechanism proposed for the formation of VII suggests that benzyl ketones would undergo in the Stobbe reaction, the same sequence of transformations. Indeed, analogous observations have been made with 2-phenylcyclohexanone and phenylacetone.

The condensation of 2-phenylcyclohexanone with diethyl succinate in the presence of sodium hydride in boiling benzene give a 61 per cent yield of oily acidic products, but only a 9 per cent yield of a defined acid m.p. 115°, to which according to the spectrum (which is similar to that of benzene) formula IX of 3-carbethoxy-3-(3-phenylcyclohex-1-en-2-yl)-propionic acid is ascribed.[11] Polyphosphoric acid gave X, which has infra-red and ultra-violet spectra (see Table 1) almost identical with VII.

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[5] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).

[6] R. S. Rasmussen and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1073 (1949).

[7] R. Fittig and H. Erdmann, *Ber. Dtsch Chem. Ges.* **16**, 43 (1883); *Liebigs Ann.* **227**, 242 (1885); R. Fittig, *Ber. Dtsch. Chem. Ges.* **20**, 3182 (1887); R. Fittig and L. Liebmann, *Liebigs Ann.* **255**, 257 (1889); R. Fittig and H. Salomon, *Ibid.* **314**, 73 (1901).

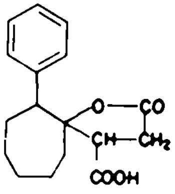
[8] A. v. Baeyer and P. Fritsch, *Ber. Dtsch. Chem. Ges.* **17**, 973 (1884).

[9] In the above scheme, it has been tacitly assumed that in the first step (II → V) the ester group is used directly for cyclization. It is possible that initially ester exchange takes place [C. D. Gutsche and K. L. Seligman, *J. Amer Chem. Soc.* **75**, 2579 (1953); C. D. Gutsche, M. W. Wendt and K. L. Seligman, *Ibid.* **80**, 3711 (1958); W. S. Johnson and A. Goldman, *Ibid.* **67**, 430 (1945)], that the intermediates V and VI contain a carbethoxy, and not a free carboxyl group, and that the molecule of ethyl alcohol is lost in the formation of the coumaran-2-one system (VI → VII).

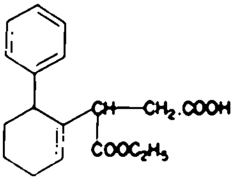
[10] W. S. Johnson, J. W. Petersen and W. P. Schneider, *J. Amer. Chem. Soc.* **69**, 74 (1947).

[11] C. D. Gutsche and K. L. Seligman, *J. Amer. Chem. Soc.* **75**, 2579 (1953); C. D. Gutsche, M. W. Wendt and K. L. Seligman, *Ibid.* **80**, 3711 (1958).

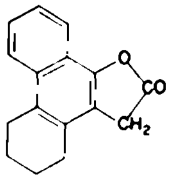
The condensation of phenylacetone with diethyl succinate has been studied by Dice and Allen[12]. The use of sodium hydride in boiling benzene (no reaction takes place in the cold) results in a 80–90 per cent yield of a mixture of two half-esters XI and XII (R = C_2H_5), exhibiting a broad absorption band between 225 and 240 mμ. The mixture of the corresponding acids XI and XII (R = H), obtained by hydrolysis with barium hydroxide, also shows this band. Treatment of the mixture of either these half-esters or acids with polyphosphoric acid gives the same product, which according to analysis, infra-red absorption at 1823 cm^{-1} and the ultra-violet spectrum (Table 1) is 4-methyl-6,7-benzocoumaran-2-one (XIII).



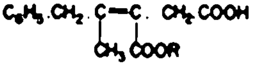
VIII



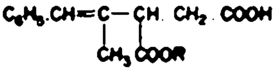
IX



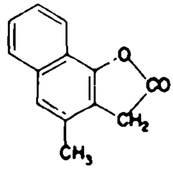
X

XI 

$C_6H_5.CH_2.\underset{CH_3}{C}=\underset{COOR}{C}.CH_2COOH$

XII 

$C_6H_5.CH=\underset{CH_3}{C}-\underset{COOR}{CH}.CH_2.COOH$



XIII

Table 1. Spectra of 6,7-benzocoumaran-2-ones, mμ [log ε]; in chloroform[13]

Compound				
VII	294 (3·72)	304 (3·70)	318 (3·63)	334 (3·43)
X	291 (3·74)	302 (3·19)	316 (3·62)	331 (3·40)
XIII	284 (3·73)	291 (3·75)	301 (3·43)	327 (3·20)
Naphthalene	267 (3·70)	278 (3·70)	287 (3·60)	311 (3·40)

EXPERIMENTAL

2-Chlorocycloheptanone.[14] A vigorous current of chlorine was bubbled through a suspension of 224 g cycloheptanone in 600 ml water until the weight of the mixture had increased by 140 g (about ½ hr). The heavy layer of 2-chlorocycloheptanone was separated, washed well with water, dried over magnesium sulphate and distilled, yielding 2-chlorocycloheptanone, b.p. 115–116° (30 mm), 175 g (60%).

2-Phenylcycloheptanone. To a solution of phenylmagnesium bromide (1·5 moles; from 36 g magnesium and 235 g bromobenzene in 400 ml dry ether), a solution of 146·5 g (1 mole) 2-chlorocycloheptanone in 300 ml dry ether was added with stirring keeping the mixture boiling gently. Stirring was continued for 1 hr more, the ether distilled off and replaced by 400 ml dry benzene, and

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[12] J. R. Dice and G. R. Allen, *J. Amer. Chem. Soc.* 74, 1231 (1952).

[13] The spectra were examined only above 250 mμ.

[14] M. S. Newman, M. D. Farbman and H. Hipsher, *Organic Syntheses* Coll. Vol. III, p. 188. John Wiley, New York (1955).

the mixture refluxed for 8 hr. After cooling, ice and water were added, and the benzene layer washed with dil. sodium carbonate and water, dried and distilled yielding 2-phenylcycloheptanone (56 g; 30%); b.p. 130–134° (3–4 mm).[16] The 2,4-dinitrophenylhydrazone after recrystallization from ethanol had m.p. 138° (lit.[16] 138°).

3-*Carbethoxy*-3-(2′-*phenylcyclohept*-1-*en*-1-*yl*)-*propionic acid* (II)

To a suspension of 12 g (0·5 mole) sodium hydride in 300 ml dry benzene, 87 g (0·5 mole) diethyl succinate, 62 g (0·33 mole) 2-phenylcycloheptanone and 0·5 ml absolute ethanol were added. After refluxing 3 hr with vigorous stirring, the mixture was cooled and acidified with 35 g acetic acid. Ether and water were added and the organic layer extracted several times with 5% sodium carbonate yielding an "acidic fraction". The organic layer was then washed with water, dried and concentrated yielding a "neutral fraction".

Neutral fraction. The residue was triturated with pet ether (40–60°) and yielded 5–6 g diethyl succinosuccinate, from ethanol m.p. 126°. From the filtrate, 24 g (40%) 2-phenylcycloheptanone was recovered.

Acidic fraction. The alkaline extract was acidified with dil. hydrochloric acid and the oily product extracted with ether. The ethereal solution was washed with water and sodium chloride solution, dried and evaporated leaving 31 g (30%) of an oil, which slowly crystallized. Trituration with methanol and two recrystallizations from cyclohexane gave 7 g (7%) of II as colourless crystals, m.p. 143–144°. λ_{max}^{EtOH} 233 mμ (3·89). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1715 cm^{-1}. (Found: C, 72·1; H, 7·2. $C_{19}H_{24}O_4$ requires: C, 72·1; H, 7·6%).

6,7-*Benzo*-4,5-*cycloheptenocoumaran*-2-*one* (VII)

(a) A mixture of 2 g II and 50 g polyphosphoric acid was heated with stirring at 100° for 3 hr. After the addition of ice and water, the product recrystallized from butanol yielding 1·3 g (82%) of VII, m.p. 168°. $\lambda_{max}^{CHCl_3}$ 294 (3·72), 304 (3·70), 318 (3·63), 334 mμ (3·43). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1823 cm^{-1}. (Found: C, 80·5; H, 6·7. $C_{17}H_{14}O_2$ requires: C, 80·9; H, 6·3%).

(b) The same product is obtained in better yield as follows: The acidic fraction (5 g), 50 ml hydrobromic acid (48%), 75 ml acetic acid and 25 ml water were refluxed for 14 hr. The volatile products were removed *in vacuo* and the residue treated with water and a mixture of ether and ethyl acetate (1 : 1). Removal of the organic solvents left an oily residue which after distillation yielded 2·5g (53%) of an oil, perhaps VIII, exhibiting two strong carbonyl bands in the infra-red at 1717 and 1778 cm^{-1}.

The distillate (2 g) was heated with 50 ml polyphosphoric acid at 100° for 3 hr. The product after addition of ice and water, was recrystallized from butanol yielding 1·2 g (70%) of VII, m.p. and mixed m.p. 168°.

4-*Methyl*-6,7-*benzocoumaran*-2-*one* (XIII)

(a) A mixture of 67 g (0·5 mole) phenylacetone, 130 g (0·75 mole) diethyl succinate and 1 ml absolute ethanol was added to a suspension of 18 g (0·75 mole) sodium hydride in 300 ml dry benzene and the mixture refluxed for 6 hr. After cooling, 50 ml glacial acetic acid, ether and water were added. The acidic product was extracted from the benzene layer with sodium carbonate (5%), acidified with dil. hydrochloric acid and again ether extracted. The product (110 g; 84%) distilled at 200–210° (0·5 mm). The ultra-violet absorption [in ethanol broad band from 225 mμ (log ε 4·16) to 240 mμ (log ε 4·15)] indicated the presence of a mixture of 3-carbethoxy-4-methyl-5-phenyl-3- and -4-pentenoic acid (XI, XII; $R = C_2H_5$). This mixture (10 g) treated with 150 g polyphosphoric acid, yielded 5·7 g (75%) of XIII which recrystallized from butanol, m.p. 158°. $\lambda_{max}^{CHCl_3}$ 284 (3·73), 291 (3·75), 301 (3·43), 327 mμ (3·20). $\tilde{\nu}_{C=O\,max}^{KBr}$ 1823 cm^{-1}. (Found: C, 78·9; H, 5·4. $C_{13}H_{10}O_2$ requires: C, 78·8; H, 5·1%).

(b) Isolation of the dicarboxylic acids XI and XII ($R = H$). To a solution of 400 g barium hydroxide in 1 l. 50% ethanol, 20 g of the half-esters XI and XII ($R = C_2H_5$) was added and the mixture boiled for 5 hr. After cooling, the barium salts were collected and acidified with dil. hydrochloric acid. The free organic acids separated as a white solid, which after two recrystallizations from toluene had m.p. 148–152° and, according to Dice and Allen[17], was a mixture of the two dicarboxylic

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[16] C. D. Gutsche, *J. Amer. Chem. Soc.* **71**, 3513 (1949).

acids. The ultra-violet spectrum showed a broad band from 210 mμ (log ε 4·07) to 242 mμ (log ε 3·84), indicating the presence of such a mixture. (Found: C, 66·8; H, 6·3. $C_{13}H_{14}O_4$ requires: C, 66·7; H, 6·0%).

Cyclization of 2 g of this product with 50 g polyphosphoric acid yielded 1·2 g (82%) of XIII, m.p. and mixed m.p. 158°. $\lambda_{\max}^{\mathrm{CHCl_3}}$ 283 (3·77), 291 (3·77), 301 (3·56), 327 mμ (3·34). $\tilde{\nu}_{\mathrm{CO}\,\max}^{\mathrm{KBr}}$ 1823 cm^{-1}.

3-*Carbethoxy*-3-(3′-*phenylcyclohexen*-1-*en*-2-*yl*)-*propionic acid* (IX)

To a suspension of 4·2 g (0·175 mole) sodium hydride in 100 ml dry benzene, 30·5 g (0·175 mole) diethyl succinate, 20 g (0·115 mole) 2-phenylcyclohexanone[11] and 0·3 ml absolute ethanol were added, and the mixture boiled for 6 hr. After cooling, 12 ml glacial acetic acid, ether and water were added. The organic layer was extracted several times with sodium carbonate and the alkaline extract acidified with dil. hydrochloric acid. The oily material, which separated, was extracted with ether and the ether dried and evaporated leaving an oily residue (21 g; 61%). Upon trituration with a mixture of benzene and methanol it yielded 3 g (9%) of IX as colourless crystals, m.p. 115° after recrystallization from cyclohexane. $\lambda_{\max}^{\mathrm{EtOH}}$ 242 (2·45), 247 (2·42), 254 (2·43), 259 l mμ (2·45). (Found: C, 71·0; H, 7·4. $C_{18}H_{22}O_4$ requires: C, 71·5; H, 7·3%).

6,7-*Benzo*-4,5-*cyclohexenocoumaran*-2-*one* (X)

Cyclization of 2 g IX with 60 g polyphosphoric acid yielded 1·9 g (80%) X, from butanol m.p. 182°. $\lambda_{\max}^{\mathrm{CHCl_3}}$ 291 (3·73), 302 (3·79), 316 (3·62), 331 mμ (3·40). $\tilde{\nu}_{\mathrm{C-O}\,\max}^{\mathrm{KBr}}$ 1823 cm^{-1}. (Found: C, 80·4; H, 5·8. $C_{16}H_{14}O_2$ requires: C, 80·7; H, 5·9%).