14. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part XII.* Friedel–Crafts Reactions of Camphoric Anhydride in Anisole and in Benzene.*

By William Bleazard and Eugene Rothstein.

The structure of the ketone resulting from the condensation of camphoric anhydride with anisole has been determined by the examination of the optical activities of the further condensation products.

" Phenylcamphoric acid " which is obtained by a similar condensation with benzene, and the phenylated acid produced when isolauronolic acid is also condensed with benzene, may be geometrical isomers. Possible structures for them are discussed.

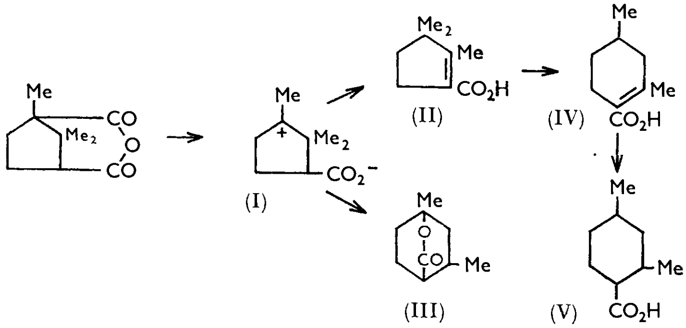
Condensations of camphoric anhydride with anisole and with benzene were described at the beginning of this century but the orientations of the products have not hitherto been satisfactorily determined. This is partly because the carbonyl group located on the tertiary carbon atom is often eliminated and the resulting carbonium ion (I) may rearrange to form isolauronolic acid (II) or give ring-expansion products such as the lactone (III) of 4-hydroxy-2,4-dimethylcyclohexanecarboxylic acid. Moreover, isolauronolic acid itself is slowly converted by aluminium chloride into 2,4-dimethylcyclohex-1-enecarboxylic acid (IV) or its dihydro-derivative (V).[1]

---

* Part XI, *J.*, 1958, 3789.

[1] Lees and Perkin, *J.*, 1901, **79**, 356; Perkin and Yates, *ibid.*, p. 1373.

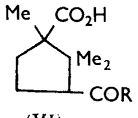
The foregoing rearrangements do not occur when ketones are formed because in these cases the carbonyl group is not eliminated and in consequence the structure of the products is more easily determined. The condensation of camphoric anhydride with anisole, first examined by Eykman [2] and subsequently by Rothstein and Saville,[3] yielded a ketone



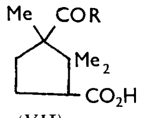
which was thought to be either (VI) or (VII) (R = $C_6H_4{\cdot}OMe$), but there was no attempt to distinguish between them. This was the case with the similar condensation with toluene but it appeared probable that the results of the anisole reaction would be directly applicable to those of toluene.

Consideration of analogous condensations with dibasic acid anhydrides showed that only the alkylated succinic anhydrides had been examined at all systematically [4] and in these cases electrophilic substitution into benzene was almost invariably by the carbonyl group attached to the least alkylated carbon atom. Although later experiments with substituted glutaric anhydrides carried out by Rothstein and Schofield [5] show that these compounds, which camphoric anhydride resembles in many respects, do not behave in altogether the same way as the lower homologue, the indication was that the ketones had the structure (VI) rather than (VII). The correctness of these conclusions has now been confirmed by examining the optical rotation of the initially formed ketonic acid (VI) and of the products which the further reactions of the latter compound afford.

It was shown in Part XI [6] that retention of optical activity in the Friedel–Crafts synthesis of ketones was associated with derivatives of tertiary acids only; in other cases racemization invariably occurred. In the present case, the substance is an anhydride of both a secondary and a tertiary acid and in consequence optical activity should be retained in any reaction which left the substituents on the tertiary carbon atom undisturbed. The condensation of (—)-camphoric anhydride with anisole yielded a ketonic acid (VI) which was optically active; Clemmensen reduction afforded an optically active acid (VIII) and the acid chloride of this in turn condensed with anisole to give an optically active ketone (IX).



(VI)



(VII)

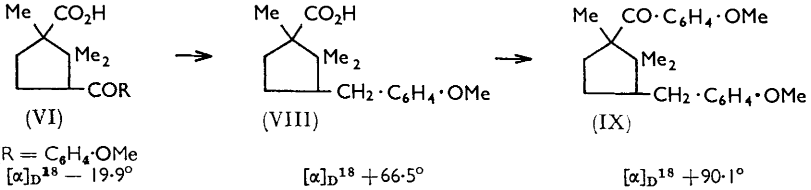
These reactions did not in themselves provide evidence in favour of either of the structures (VI) and (VII), but they did show that optical stability was preserved under fairly vigorous conditions. Clearly, the reaction at the secondary carboxyl residue would destroy the asymmetry of the adjacent carbon atom, but the molecule as a whole

---

[2] Eykman, *Chem. Weekblad*, 1907, **4**, 727.
[3] Rothstein and Saville, *J.*, 1949, 1961.
[4] Rothstein and Saboor, *J.*, 1943, 425.
[5] Rothstein and Schofield, unpublished work.
[6] Bleazard and Rothstein, *J.*, 1958, 425.

would still be optically active because of the undisturbed asymmetric tertiary carbon atom carrying the other carboxyl group. On the other hand, ketone formation at the tertiary carboxyl residue would not affect the optical activity of the carbon atom to which it was attached though in all probability the catalyst would racemize the other active carbon atom during the reaction. Experimentally it was found that a mixture of the optically active acid chloride of the acid (VIII) in benzene solution with aluminium chloride evolved carbon monoxide with the formation of an optically inactive product. This proved that the chlorocarbonyl group was attached to the optically active tertiary carbon atom and that the acids (VI) and (VIII) had the structures suggested above.

It is necessary to consider whether these heavily alkylated cyclopentane derivatives might not eliminate carbon monoxide by decomposition of the secondary chlorocarbonyl group. This so far has been encountered mainly with aromatic acid derivatives[3] but otherwise there has not been any systematic investigation of this possibility. Analogy with the examples cited below indicates that the acid chloride, (X; CN replaced by $CH_2{\cdot}C_6H_4{\cdot}OMe$) would yield the corresponding ketone (XI; CN replaced by $CH_2{\cdot}C_6H_4{\cdot}OMe$). Thus the nitrile (X), prepared by unambiguous methods, afforded the ketone (XI) whilst the isomeric compound (XII) eliminated carbon monoxide correspondingly to the acid chloride of (VIII);[7] and similarly, dihydroisolauronoyl chloride yielded 3-benzoyl-1,1,2-trimethylcyclopentane.[8]



(VI) (R = $C_6H_4{\cdot}OMe$) $[\alpha]_D^{18}$ − 19·9°

(VIII) $[\alpha]_D^{18}$ +66·5°

(IX) $[\alpha]_D^{18}$ +90·1°

The elimination of carbon monoxide from the acid chloride of (VIII) was not accompanied by condensation with benzene, and in this respect it differed from the corresponding reaction of (XII). The structure of the product was not definitely ascertained but it appeared to be either (XIII) or (XIV). Intense infrared absorption at 1625 cm.$^{-1}$ together with the C–H deformation absorption at 849 cm.$^{-1}$ suggested the cyclopentyl olefin (XIV), but its resistance to catalytic hydrogenation indicated a tetrasubstituted ethylenic bond. This resistance to reduction was a major obstacle to the identification of the compound, because the ketone (XV) obtained by condensing isolauronoyl chloride with anisole, gave on reduction, not the methoxybenzyl derivative (XIII), but the dihydro-compound which also resulted from a Clemmensen reduction of the condensation product of dihydroisolauronoyl chloride with anisole.

The structure of " phenylcamphoric acid " obtained in the Friedel–Crafts condensation of camphoric anhydride with benzene has been re-examined. The substance, m. p. 140°, first prepared by Burcker[9] was considered to be 2,2,3-trimethyl-3-phenylcyclopentanecarboxylic acid (XVI), the tertiary carbonyl group having been replaced by phenyl. We have now found the substance to be optically inactive so that there is no doubt that this carbonyl group has been eliminated. No real evidence is available about the position of the phenyl group. It could be on the 3-position as in (XVI) but equally, if a primary rearrangement to the isolauronolic acid structure preceded combination with benzene, it might be either of the acids (XVII) and (XVIII). Other structures derived from the xylic acids (*e.g.*, IV) are also possible. It can be assumed, however, that structure (XVIII) and others with a tertiary acid group are improbable because their acid chlorides would almost certainly lose their carbonyl group in a Friedel–Crafts reaction. We have, on the

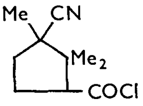
---

[7] Salmon-Legagneur, *Ann. Chim. (France)*, 1927, **8**, 5.

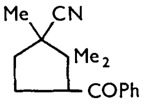
[8] Shive, Horeczy, and Lochte, *J. Amer. Chem. Soc.*, 1940, **62**, 2744.

[9] Burcker, *Bull. Soc. chim. France*, 1895, **13**, 901.

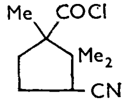
contrary, obtained ketones both in benzene and in anisole solution. The elimination of carbon monoxide from the acid chloride (XII), to which reference has already been made, affords in benzene solution the nitrile which on hydrolysis gives " phenylcamphoric acid "[7] but this has little bearing on its structure because in chloroform rearrangement of the chloride (XII) to isolauronolonitrile accompanied by loss of carbon monoxide occurs[10] and so is analogous to the corresponding reaction of camphoric anhydride.



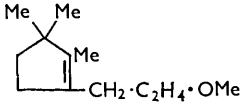
(X)



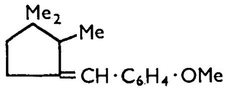
(XI)



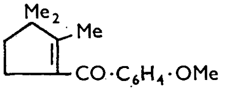
(XII)



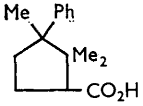
(XIII)



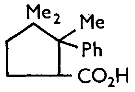
(XIV)



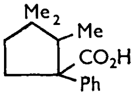
(XV)



(XVI)



(XVII)



(XVIII)

It was reported by Eykman[2] that isolauronolic acid itself undergoes a slow aluminium chloride-catalysed reaction with benzene, yielding a phenylated acid, m. p. 119°, isomeric with " phenylcamphoric acid," m. p. 140°. His suggested structure was (XVII) for the new acid, and therefore (XVI) for the acid, m. p. 140°. This seemed very likely, provided that the acid, m. p. 119°, had the structure assigned to it, and this could easily be tested by carrying out a Friedel–Crafts condensation with its acid chloride. When the preparation of this acid was repeated, it became evident that it was possibly a geometrical isomer of the acid, m. p. 140°, since a mixture of the two had an intermediate melting point, whilst their infrared spectra were all but identical. The respective acid chlorides condensed with benzene to furnish ketones which differed by 6° in their melting points and also gave an intermediate melting point when mixed. The infrared absorption spectra were again virtually identical. The identity of the two " phenylcamphoric acids " as regards their main skeletal structure necessitates the conclusion that rearrangements of the camphoric, the isolauronolic, or both structures had taken place.

EXPERIMENTAL

Optical rotations were measured for chloroform solutions with $l = 1$, and $c = 2{\cdot}5$. The aluminium chloride was either prepared from aluminium foil or was " free flowing " aluminium chloride supplied by Messrs. British Drug Houses.

Condensations based on (—)-*Camphoric Anhydride.—Camphoric anhydride and anisole.* Aluminium chloride (45 g.) was slowly added to a stirred solution of (—)-camphoric anhydride (30 g.) in anisole (200 c.c.). Stirring was continued for 2 hr. during which a brilliant red colour developed; then the mixture was decomposed with ice and dilute sulphuric acid and extracted with ether, and the extract in turn extracted with dilute hydroxide solution. Acidification afforded (—)-3-p-*anisoyl*-1,2,2-*trimethylcyclopentanecarboxylic acid* (30 g., 60%), m. p. 178° (from benzene), $[\alpha]_D^{18}$ $-19{\cdot}9°$ [this m. p. was considerably higher than that found by Rothstein and Saville[3] (165°) for the inactive isomer, but there was no depression of the m. p. when the two were mixed] (Found: C, 70·4; H, 7·6. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). Clemmensen reduction of the above acid yielded (+)-3-4′-*methoxybenzyl*-1,2,2-*trimethylcyclopentanecarboxylic acid* (VIII), m. p. 133° (from aqueous methanol), $[\alpha]_D^{18}$ $+66{\cdot}5°$, in 90% yield (Found: C, 73·8; H, 8·7. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%). Here again large variations in the m. p. indicated the presence of a geometrical isomer. A sample obtained by alkaline hydrolysis of the methyl ester had m. p. 173° and gave an intermediate m. p. when mixed with the lower-melting isomer (Found: C, 74·0; H, 8·8%). The infrared spectra were practically identical.

---

[10] Salmon-Legagneur, *Compt. rend.*, 1935, **200**, 1222.

Excess of thionyl chloride at room temperature yielded the acid chloride (70%), b. p. 168—169°/0·3 mm.

Condensation of the acid chloride of (VIII) *with anisole.* The reaction was carried out at room temperature with a solution of the acid chloride (2 g.) in anisole (50 c.c.) and aluminium chloride (2 g.). No carbon monoxide was evolved, and the product, (+)-1-p-*anisoyl*-3-4′-*methoxybenzyl*-1,2,2-*trimethylcyclopentane* (IX), b. p. 180°/0·5 mm. (yield, 1·5 g.), crystallised. Recrystallisation from ethanol gave the ketone, m. p. 96°, $[\alpha]_D^{18}$ +90·1° (Found: C, 78·8; H, 8·4. $C_{24}H_{30}O_3$ requires C, 78·7; H, 8·2%).

Condensation of the acid chloride of (VIII) *with benzene.* A solution of the acid chloride (4 g.) in benzene (10 c.c.) was slowly added to a stirred suspension of aluminium chloride (3 g.) in benzene (40 c.c.) at room temperature. Carbon monoxide (200 c.c., 85%) was evolved and the liquid became deep maroon in colour. After 2 hr. it was decomposed as usual. The *product*, either 1-4′-methoxybenzyl-2,3,3-trimethylcyclopentene (XIII) or 3-4′-methoxybenzylidene-1,1,2-trimethylcyclopentane (XIV), had b. p. 112°/0·4 mm. (Found: C, 83·6; H, 9·6. $C_{16}H_{22}O$ requires C, 83·5; H, 9·6%). It was optically inactive. Aqueous permanganate and bromine water were decolorised by the substance which was, however, unchanged when shaken at room temperature with hydrogen in the presence of 5% palladium–charcoal. Use of platinum oxide catalyst in glacial acetic acid at 5 atm. yielded a mixture of three fractions which could not be identified: (i) b. p. 85—86°/0·11 mm. (Found: C, 74·6; H, 10·7%); (ii) b. p. 94°/0·11 mm. (Found: C, 81·8; H, 10·9%); and (iii) b. p. 110°/0·11 mm. (Found: C, 81·7; H, 10·4%).

Camphoric anhydride and benzene. Under the same reaction conditions as with anisole, carbon monoxide was evolved, and the phenyl derivative, "phenylcamphoric acid," m. p. 139—140° (yield, 70%), was obtained (Found: C, 77·4; H, 8·7. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·6%). It was optically inactive. Reaction with cold thionyl chloride afforded the acid chloride, b. p. 107°/0·05 mm. (85%), which slowly crystallised.

Condensation of "phenylcamphoroyl chloride" with anisole. Aluminium chloride (10 g.) was added in small portions to a vigorously stirred solution of the acid chloride (16 g.) in anisole (100 c.c.). Carbon monoxide was not evolved and the usual deep-red colour developed. The resulting p-*methoxyphenyl ketone* (3-*p*-anisoyl-1,1,2-trimethyl-2-phenylcyclopentane?) separated from ethanol and had m. p. 151° (yield, 16 g., 78%) (Found: C, 81·5; H, 7·9. $C_{22}H_{26}O_2$ requires C, 82·0; H, 8·1%). The ketone (10 g.) was reduced by amalgamated zinc and hydrochloric acid to the corresponding 4-*methoxybenzyl derivative* (3-4′-methoxybenzyl-1,1,2-trimethyl-2-phenylcyclopentane?), b. p. 172°/0·05 mm. (yield, 8 g., 95%) (Found: C, 85·6; H, 9·1. $C_{22}H_{28}O$ requires C, 85·7; H, 9·1%).

Condensation of the acid chloride with benzene. Repetition of the above reaction with benzene in place of anisole afforded a pale yellow liquid which on decomposition yielded the *phenyl ketone* (3-benzoyl-1,1,2-trimethyl-2-phenylcyclopentane?), as a viscous liquid, b. p. 107°/0·05 mm. (yield, 71%). It gradually crystallised and separated from aqueous ethanol as colourless crystals, m. p. 96°. Further recrystallisations from ligroin (b. p. 40—60°) raised the m. p. to 102° (Found: C, 85·8; H, 8·0. $C_{21}H_{24}O$ requires C, 86·3; H, 8·2%).

Condensations Based in Isolauronolic Acid.—*Condensation of isolauronoloyl chloride with anisole.* The acid chloride, b. p. 89°/0·05 mm., was obtained in 90% yield from the acid and excess of cold thionyl chloride. A solution of it (15 g.) in anisole (15 c.c.) was added to a stirred solution of aluminium chloride (15 g.) in the same solvent (60 c.c.). After 3 hr. the mixture was decomposed and worked up as usual, furnishing 1-p-*anisoyl*-2,3,3-*trimethylcyclopentene*, b. p. 134—135°/0·11 mm. (14 g., 66%) (Found: C, 78·7; H, 8·3. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). Clemmensen reduction yielded a product (b. p. 98—100°/0·11 mm.; yield, 57%), the infrared spectrum of which showed it to be the benzyl derivative (compare below) but the hydrogen content was too low (Found: C, 83·4; H, 9·2. Calc. for $C_{16}H_{24}O$: C, 82·8; H, 10·3%). It was accompanied by a fraction, the b. p. of which (195—200°/0·10 mm.) indicated that it might be a bimolecular reduction product (Found: C, 83·5; H, 9·8%); the infrared spectrum indicated the presence of a carbonyl group and possibly hydroxyl.

Condensation of dihydrolisolauronoloyl chloride with anisole. Dihydroisolauronolic acid was obtained as an oil, b. p. 81°/0·2 mm., by catalytic reduction (platinum oxide) of isolauronolic acid in alcohol (yield, 65%) (Found: C, 69·7; H, 10·2. Calc. for $C_9H_{16}O_2$: C, 69·2; H, 10·3%). It gave the acid chloride, b. p. 87°/16 mm. (yield, 96·5%), on reaction with cold thionyl chloride. A mixture of the acid chloride (2·7 g.), aluminium chloride (3 g.), and anisole (30 c.c.) was stirred for 2 hr. From this was isolated 3-p-*anisoyl*-1,1,2-*trimethylcyclopentane*, b. p. 122°/0·8 mm. (3·3 g., 86%) (Found: C, 78·5; H, 9·2. $C_{16}H_{22}O_2$ requires C, 78·1; H, 8·9%). Clemmensen reduction yielded 3-4′-*methoxybenzyl*-1,1,2-*trimethylcyclopentane*, b. p. 110—111°/0·15 mm. (Found: C, 83·0; H, 10·6. $C_{16}H_{24}O$ requires C, 82·8; H, 10·3%).

Condensation of isolauronolic acid with benzene.[2] A mixture of isolauronolic acid (26 g.), benzene (100 c.c.), and aluminium chloride (30 g.) was left at room temperature for a week. The syrupy product was esterified by saturating its methanolic solution with dry hydrogen chloride. Fractionation of the ester yielded *methyl isolauronolate*, b. p. 87°/12 mm. (8 g.) (Found: C, 71·2; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%), and *methyl* 2,3,3-*trimethyl*-2-*phenylcyclopentanecarboxylate* (4 g.), b. p. 106°/0·2 mm., prisms, m. p. 94—95° (from aqueous methanol) (Found: C, 78·0; H, 9·0. $C_{16}H_{22}O_2$ requires C, 78·1; H, 8·9%). Hydrolysis with alcoholic potassium hydroxide afforded the corresponding acid, m. p. 117—119° after two recrystallisations from aqueous ethanol (Found: C, 77·3; H, 8·4. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·6%). Mixtures of this acid with the acid (m. p. 139—140°) obtained from benzene and camphoric anhydride had intermediate m. p. As already mentioned, the infrared spectra (KCl discs) were nearly identical over the whole range (5000—625 cm.$^{-1}$). The acid chloride was left as a crystalline residue when a mixture of the acid and excess of cold thionyl chloride was left overnight and the excess of reagent removed at room temperature in a vacuum.

Condensation of the above acid chloride with benzene. This was carried out with the acid chloride (2·0 g.), benzene (25 c.c.), and aluminium chloride (2 g.). Two products were obtained: (i) a substance, b. p. 115—118°/0·12 mm., which might have been a ketone (infrared absorption at 1678 cm.$^{-1}$) though a satisfactory analysis was not obtained; and (ii) a *ketone* (40%), b. p. 181°/0·12 mm., flat prisms, m. p. 106—108° [from ligroin (b. p. 40—60°)] (Found: C, 86·5; H, 8·3. $C_{21}H_{24}O$ requires C, 86·3; H, 8·2%). The latter substance appears to be a geometrical isomer of the ketone prepared by two successive condensations of camphoric anhydride with benzene.

The Chemical Society is thanked for a Research Grant (E. R.) and the Department of Scientific and Industrial Research for a Maintenance Allowance (to W. B.).

THE UNIVERSITY, LEEDS. [*Received, May* 18*th*, 1960.]