23. *Studies in Stereochemical Structure. Part IX. The Stereochemical Relationship of the α- and the β-Forms of Substituted Hydrobenzoins.* (b) *Ethylhydrobenzoin (β-Form).*

By Robert Roger.

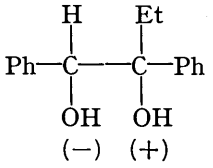
The α-form of (+)ethylhydrobenzoin has been oxidised to (+)ethylbenzoin (J., 1937, 1048) and it is now shown that the β-form of (−)ethylhydrobenzoin also can be oxidised to (+)ethylbenzoin. From the latter result the deduction can be made that the β-form of (+)ethylhydrobenzoin would undergo oxidation to (−)ethylbenzoin :

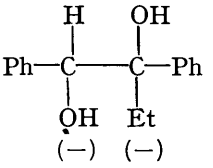
$$(-)\text{CHPh(OH)}\cdot\text{COEt} \xrightarrow{\text{PhMgBr}} (+)\text{ethylhydrobenzoin (α-form)} \longrightarrow (+)\text{COPh}\cdot\text{C(OH)PhEt}$$

and

$$(-)\text{CHPh(OH)}\cdot\text{COPh} \xrightarrow{\text{EtMgBr}} (+)\text{ethylhydrobenzoin (β-form)} \longrightarrow (-)\text{COPh}\cdot\text{C(OH)PhEt}$$

To those two α- and β-forms the configurations (I) and (II) respectively are assigned on the arguments previously outlined (*loc. cit.*) :

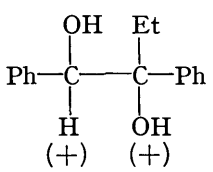
(I.) 

(II.) 

The compounds are thus diastereoisomeric, as also are the α- and the β-form of (−)ethylhydrobenzoin. The peculiar mode of synthesis of the α- and the β-forms of such glycols is discussed, and also the question whether the formation of the optically active ethylbenzoins can be regarded as examples of " asymmetric synthesis."

Roger (J., 1937, 1048) showed that the oxidation of (+)ethylhydrobenzoin (α-form) led to the formation of (+)ethylbenzoin, and the configuration (I) was provisionally assigned to that form of the glycol.

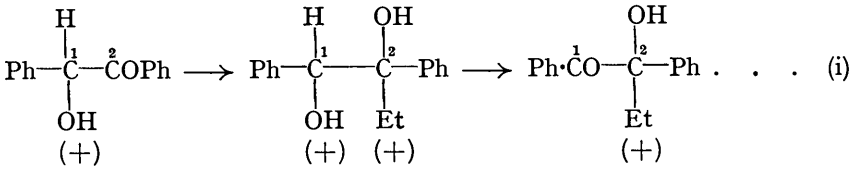
The oxidation of (−)ethylhydrobenzoin (β-form) was attended with great difficulty, possibly owing to steric hindrance, but was eventually achieved by a modification of the method previously described (*loc. cit.*). Thus the relationship $L(+)\text{CHPh(OH)}\cdot\text{CO}\cdot\text{OH} \longrightarrow L(+)\text{CHPh(OH)}\cdot\text{COPh} \longrightarrow (-)\text{CHPh(OH)}\cdot\text{C(OH)EtPh} \longrightarrow (+)\text{COPh}\cdot\text{C(OH)EtPh}$ was established and the β-form of (−)ethylhydrobenzoin would appear therefore to have the annexed configuration.



For the first time proof is brought forward that these α- and β-forms are the diastereoisomers predicted by McKenzie and Wren (J., 1910, **97**, 473) (cf. also the relationship of ephedrine and ψ-ephedrine; Leithe, *Ber.*, 1932, **65**, 660; Skita, Keil, and Meiner, *Ber.*, 1933, **66**, 974).

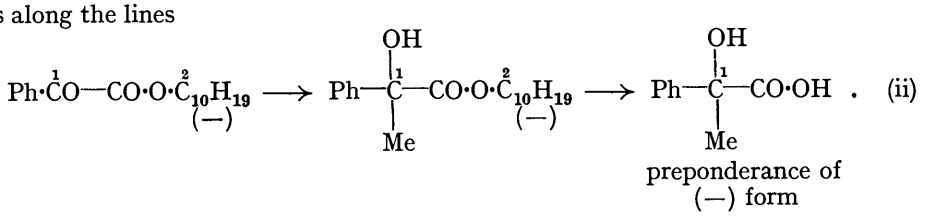
The new centres of asymmetry created during the synthesis of such substituted hydrobenzoins, therefore, are veritably active, *i.e.*, they actually contribute to the evident rotatory powers of the two forms (α- and β-) of the glycol. This eliminates the possibility

that one of the forms at least might be a partial racemate. The establishment of this important fact raises the question whether in such a change



(i)

an asymmetric synthesis has been effected. In this sequence of operations there is a certain resemblance to the well-known asymmetric syntheses of McKenzie and his co-workers along the lines



(ii)

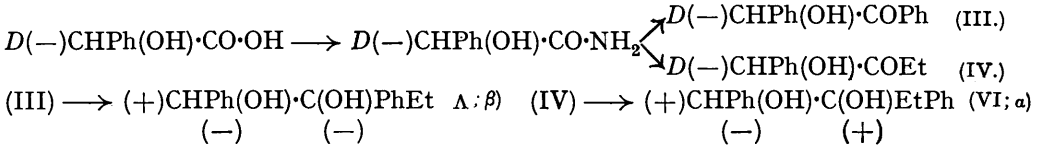
preponderance of (−) form

(for a résumé of work, see Asymmetric Synthesis, McKenzie, " Ergebnisse der Enzymforschung," Band V, s. 4, Leipzig, 1936). The main differences between schemes (i) and (ii) are: (*a*) In (i) the original asymmetric inducing centre is not removed unchanged by a simple process such as saponification (as in ii), but is converted *in situ* into a centre of symmetry and does not separate from the original molecule. (*b*) The (+)ethylbenzoin in (i) arises in an optically pure state, whereas in many of the syntheses of the atrolactinic acid type there is finally only a preponderance of one optically active form over the other. In only one or two cases have such acids been isolated immediately in a state approaching optical purity (Christie, McKenzie, and Ritchie, J., 1935, 153; McKenzie and Christie, *Biochem. Z.*, 1935, **227**, 426).

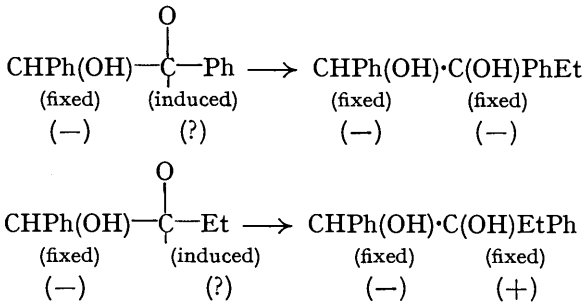
The reason for difference (*b*) probably is this. In the formation of (+)ethylbenzoin (i) the inducing centre C^1 is directly linked to the induced centre C^2 and the induced effect is at a maximum. In the synthesis of atrolactinic acid (ii), however, the inducing centre, the (−)menthyl group[2], is separated from the induced centre[1] which is about to become the new centre of fixed asymmetry, by a buffer carbon atom, that of the carboxyl group. As a result the induced centre[1] does not attain a state of maximum induction and a partly racemised product ensues. On such grounds the production of pure (+)ethylbenzoin by the above method justly could be termed a " unilateral internal asymmetric synthesis."

In Part VIII (*loc. cit.*) the configuration adduced for the α-form of (+)ethylhydrobenzoin was qualified by the condition " provided that no inversion of the mandelyl complex has occurred either during the conversion of *D*(−)mandelic acid into (+)ethylhydrobenzoin or in the solution of the glycol in the ethylmagnesium iodide preparatory to oxidation." It has not been found possible to obtain any proof of inversion during the syntheses of the glycols from mandelic acid and, indeed, this would be of little importance, since both forms of the glycol might be expected to be correspondingly affected. Much more important is the possibility of inversion arising during the process of solution of the glycol in the ethereal ethylmagnesium iodide. A simple proof that this does not happen was found by dissolving a sample of each form of the glycol in portions of the Grignard reagent, boiling the solutions, and decomposing them. In each case the glycol was recovered unchanged both in sign and in rotatory power.

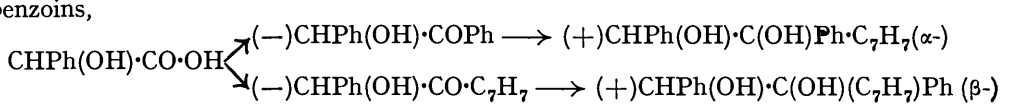
The peculiar method of synthesis of the two forms of the glycol is also interesting. The α- and the β-form are both prepared from one optically active form of mandelic acid,



from which it will be seen that, whilst the mandelyl complex in each case retains the same configuration throughout, the new centres of asymmetry created in the stages III ⟶ V and IV ⟶ VI are enantiomorphic. A natural interpretation of the creation of the new centres in active conditions is found on the grounds of asymmetric induction. In (−)benzoin and (−)phenylpropionylcarbinol there are two centres of asymmetry, one "fixed" and one "induced," and in the syntheses of the two forms of the glycol the two induced centres become fixed, *e.g.*



Since the inducing centre is of the same sign in both cases, it might reasonably be expected that the direction of induction in the induced centres would be the same. Yet, when these two induced centres become fixed, they are of opposite signs, *i.e.*, the same negative inducing centre has apparently caused a negative induction effect in one case and a positive effect in the other: this would appear to be illogical. The fact that the phenyl and the ethyl radical directly attached to the induced centres (the CO groups) in the two ketols are very different in character may cause a relatively different arrangement in space of the two centres of induced asymmetry with regard to the centre of fixed asymmetry (the mandelyl complex in each case). When the radicals directly attached to the ketonic carbon atoms in the ketols are similar in character, as occurs in the synthesis of the α- and β-*p*-tolylhydrobenzoins,



the new centres of asymmetry contribute very little to the evident rotatory powers of the two forms of the glycol (Roger and McKay, J., 1931, 2229; McKenzie and Kelman, J., 1934, 412), as is shown by comparison with the rotatory powers of triphenylethylene glycol (which has only one centre of asymmetry).

From these considerations it would seem that the configurations of the new centres of asymmetry in the α- and the β-form of ethylhydrobenzoin are definitely fixed at the moment of addition of the Grignard reagents to the ketonic groups of the ketols. Since the fundamental actions of the two Grignard reagents must be similar, the respective configurations of the two new centres must depend on the nature or size of both the entrant radicals and also the alkyl or aryl radicals directly attached to the ketonic groups of the ketols. No definite law can be formulated regarding this point until the relative configurations of a number of such diastereoisomeric pairs have been determined. This study is in progress.

Experimental.

(−)Ethylhydrobenzoin (β-form), prepared by the action of ethylmagnesium bromide on *L*(+)benzoin, had m. p. 96—97° and $[\alpha]_{5461}^{17°}$ −31·5° (*c* = 2·352 in acetone, *l* = 1, $\alpha_{5461}^{17°}$ −0·74°). McKenzie and Wren (*loc. cit.*) give m. p. 96·5—97·5°, $[\alpha]_{D}^{11·7°}$ + 27·4° in acetone.

The glycol (7 g.) was added in dry ethereal solution to the Grignard reagent prepared from ethyl iodide (23 g.), and the mixture boiled for 15 minutes. Most of the ether was then removed by distillation, and benzaldehyde (12 g., twice distilled) in 30 c.c. of pure dry benzene added gradually. The mixture was kept overnight and then boiled for 8 hours. After decomposition with ice and dilute sulphuric acid and extraction with ether, an oil was obtained from the ethereal layer and distilled in a vacuum. The fraction, b. p. 140—190°/0·5 mm., solidified

when seeded with *r*-ethylbenzoin. It separated from light petroleum, containing a small amount of ethyl alcohol, in coarse needles (1·8 g.), m. p. 71—72° after two recrystallisations from the same solvent, $[\alpha]_{5461}^{18°}$ + 254° (c = 2·422 in ethyl alcohol, l = 1, $\alpha_{5461}^{18°}$ + 6·16°). The m. p. was not depressed by (+)ethylbenzoin obtained by the oxidation of (+)ethylhydrobenzoin (α-form) (Roger, *loc. cit.*; McKenzie and Ritchie, *Ber.*, 1937, **70**, 23).

In order to ensure that no change in either form of the glycol had taken place during the act of solution in the ethereal ethylmagnesium iodide two similar control experiments were carried out in which samples of the two forms were heated for several hours in solutions of ethylmagnesium iodide. Thus, (+)ethylhydrobenzoin (β-form, m. p. 96—97°, 6 g., $[\alpha]_{5461}^{16°}$ + 31·3° in acetone) was added in dry ethereal solution to the Grignard reagent prepared from ethyl iodide (22 g.), and the mixture boiled for 3 hours. After decomposition with ice and dilute sulphuric acid the ethereal layer yielded a solid, which was recrystallised from light petroleum and a little ethyl alcohol. The solid then obtained had m. p. 96·5—97° and $[\alpha]_{5461}^{17°}$ +30·7° (c = 2·044 in acetone, l = 1, $\alpha_{5461}^{17°}$ +0·62°) and was identical with the initial glycol.

A similar experiment with partly racemised (−)ethylhydrobenzoin (α-form, $[\alpha]_{5461}^{18°}$ −29·8°, c = 2·284° in chloroform, l = 1, m. p. 88—90°) yielded unchanged glycol ($[\alpha]_{5461}^{17°}$ −29·7°, c = 2·202 in chloroform, l = 1, m. p. 88—89°).

The author thanks the Carnegie Trust for grants for the purchase of material.

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