[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Abnormal Reactions of Benzylmagnesium Chloride. II. The Mechanism of the *o*-Tolyl Rearrangement[1]

BY JOHN R. JOHNSON

Studies of the behavior of benzylmagnesium chloride toward a variety of reactants[2,3] have shown that *o*-tolyl derivatives appear frequently among the products of the reaction. That such a rearrangement should occur in a Grignard reagent containing an allylic system is not unusual, but the experimental evidence indicates clearly that the reactant must likewise possess some structural characteristic that is also requisite for the rearrangement. It is the latter feature that has not been explained satisfactorily by any of the previously proposed mechanisms.

Two principal theories have been advanced to explain the mechanism of the rearrangement. One of these[4] involves the assumption of dynamic isomerism between the normal and an *o*-quinonoid form of the Grignard reagent; the other assumes that the change of structure occurs in the course of the reaction, through rearrangement of electrons in a free benzyl radical or ion. The first of these cannot be accepted since it assumes rearrangement to occur before the introduction of the reactant and does not explain the important relation between the nature of the reactant and the rearrangement. Furthermore, experiments of Gilman and Kirby[2] designed to detect the presence of a quinonoid form gave entirely negative results. The validity of the second hypothesis may be considered doubtful in the absence of experimental evidence indicating that a free benzyl radical or ion tends to undergo rearrangement. Indeed, failure to observe rearrangement of the benzyl group in other reactions (such as the Hofmann, Lossen or Curtius reaction and a variety of others) suggests that if free benzyl radicals or ions are produced in organic reactions they are not prone to undergo rearrangement.

An hypothesis which appears to give a satisfactory explanation of the experimental findings involves rearrangement of a coördination compound formed as the first stage of all Grignard reactions, in accordance with the general mechanism of Hess and Rheinboldt[5a] and of Meisenheimer.[5b] The subsequent transformations can be illustrated by the reaction between benzylmagnesium chloride and a reactant containing a carbonyl group,[6] A-CO-B, giving rise to the coördination compound I. The normal *and*

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[1] The reaction mechanism reported here was presented in a paper read at the Fourth Symposium on Organic Chemistry, Yale University, December, 1931.

[2] Gilman and Kirby, THIS JOURNAL, **54**, 345 (1932).

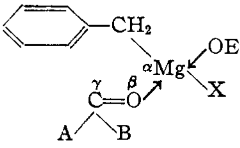
[3] Austin and Johnson, *ibid.*, **54**, 647 (1932).

[4] Schmidlin and Garcia-Banùs, *Ber.*, **45**, 3193 (1912).

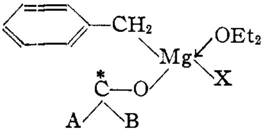
[5] (a) Hess and Rheinboldt, *Ber.*, **54**, 2043 (1921); (b) Meisenheimer, *Ann.*, **442**, 180 (1925).

[6] An analogous series of transformations can be invoked for reactants containing other reactive groups. For the sake of brevity, other cases are not given in detail.

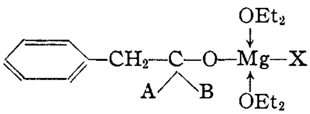
abnormal reactions result from subsequent transformations within this complex; both arise from a γ-α shift of electrons in the triad system, Mg ⟵ O=C, which would tend to leave the carbon atom (γ) with a sextet of electrons[7] (marked by an asterisk, formula II). In the normal reaction the $\gamma \longrightarrow \alpha$ shift of electrons is completed by $\alpha \longrightarrow \gamma$ migration of the benzyl group *with* its binding electrons, essentially as an anion, and is not accompanied by rearrangement within the benzyl group. The octet of the magnesium atom is simultaneously completed by coördination with ether, giving the stable normal product (III).



I



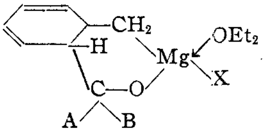
II



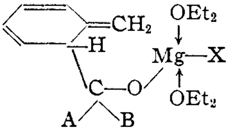
III

The abnormal reaction arises from a combination of several factors: (1) the presence of an allylic system (designated as α', β', γ') in the organic radical of the Grignard reagent, (2) the proximity of the γ-atom of the triad system Mg ⟶ O=C and the terminal atom of the allylic system present in the benzyl group, (3) the nature of the substituents A and B, attached to the carbonyl group. In the allylic system of the organic radical of the Grignard reagent, an $\alpha' \longrightarrow \gamma'$ shift of electrons makes possible an intramolecular chelation (1,6-cyclization)[8] with the production of an ephemeral ring structure (IV). The electronic shift is completed by rupture of the linkage between magnesium atom and the α'-atom of the allylic system (and coördination of the magnesium with ether), giving the product (V). This process constitutes the first step of the rearrangement.

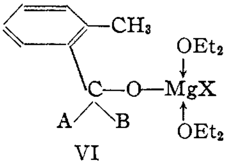
II ⟶



IV



V



VI

In the case of simple allylic systems the reaction may not proceed further, but with the benzyl group a migration of hydrogen[9] converts the *o*-quinonoid system into an *o*-tolyl group. The second step of the rearrangement has been discussed in some detail in an earlier paper.[3]

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[7] *Cf.* Carothers, THIS JOURNAL, **46,** 2226 (1924); Whitmore, *ibid.*, **54,** 3274 (1932).

[8] The formation of *p*-tolyl derivatives has been observed with a small group of reactants.[2] The more important of these, ethylene oxide and alkyl chloromethyl ethers, do not contain a carbonyl group, and it is not certain that the hypothesis presented above could be extended to these cases. Although the mechanism of the reaction of these substances with Grignard reagents is not entirely clear, it is possible that they give rise to a chelate system of *p*-quinonoid type instead of the *o*-quinonoid type.

[9] This migration may actually occur as an integral part of the ring opening of IV, converting it directly into the *o*-tolyl derivative (VI) without passing through the *o*-quinonoid intermediate (V).

This hypothesis possesses an advantage in that it offers a definite criterion for explaining or predicting the behavior of a given reactant. The rearrangement is postulated as an intramolecular addition or chelation (II ⟶ IV) and should be influenced to a marked degree by steric and chemical effects of substituents. Since these effects are apparent in other addition reactions, the tendency of a given reactant to produce rearrangement should parallel its behavior in other addition reactions.[10] This appears to be the case, since formaldehyde is more effective than other aldehydes[11] and ketones do not appear to be effective at all. Among the functional derivatives of organic acids, acid chlorides are more effective than anhydrides; typical esters, amides,[12] nitriles, and carbon dioxide do not give a detectable quantity of *o*-tolyl derivatives.

The main points of the hypothesis presented above may be summarized as follows: (1) formation of a primary addition product containing coördinate linkages; (2) transformation of the latter into a more stable system, (a) by α,γ-rearrangement or (b) by chelation and subsequent ring opening.

A survey of "abnormal" reactions involving Grignard reagents indicates that the factors associated with the abnormal reactions of benzylmagnesium chloride are operative in other important cases. Among these are the 1,4-addition reactions of α,β-unsaturated ketones and esters,[13] *o*-phenylation of benzophenone-anil through forced reaction with phenylmagnesium bromide[14] and allylic rearrangements observed by Prévost.[16] These examples illustrate strikingly the effect of steric relations in the primary addition complexes as well as the effect of substituents in modifying the abnormal reaction.

The hypothesis of intramolecular chelation is of rather general application and it may be offered as a possible mechanism for a variety of reactions which are currently explained by hypotheses which are not wholly adequate. Among these are the C-alkylation of metallic derivatives of enols and related reactions (the Reimer–Tiemann reaction, the Kolbe synthesis, etc.). The Kolbe synthesis, for example, may be explained by a mechanism entirely parallel to the benzyl ⟶ *o*-tolyl rearrangement.

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(10) The selection of an addition reaction for this comparison offers some difficulty. With the reactants examined thus far the tendency to undergo rearrangement appears superficially to parallel the reactivity of the carbonyl group toward simple alcohols. Since this reaction was selected empirically and not from theoretical deduction, it is given merely as a tentative suggestion.

(11) In the case of formaldehyde, none of the normal product has been reported. Unpublished studies of Mr. L. G. Davy in this Laboratory have shown that other aliphatic aldehydes, such as acetaldehyde and *n*-butyraldehyde, induce the *o*-tolyl rearrangement to an appreciable extent.

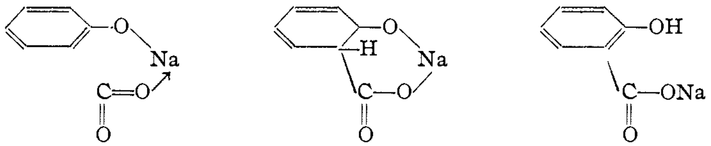
(12) Jenkins, THIS JOURNAL, **55**, 703 (1933).

(13) Kohler, *Am. Chem. J.*, **31**, 642 (1904); **33**, 21, 35, 153, 333 (1905); **34**, 132 (1905); and later papers.

(14) Gilman, Kirby and Kinney, THIS JOURNAL, **51**, 2252 (1929). A related reaction involving *o*-phenylation of an α,β-unsaturated ketone has also been reported.[15]

(15) Kohler and Nygaard, THIS JOURNAL, **52**, 4128 (1930).

(16) Prévost, *Ann. chim.*, [10] **10**, 121 (1928); Prévost and Daujat, *Bull. soc. chim.*, [4] **47**, 588 (1930); see also, Carothers and Berchet, THIS JOURNAL, **55**, 2807 (1933).



The specific applications of this hypothesis to such reactions will be discussed in a subsequent communication.

Summary

An hypothesis is presented to account for the abnormal reactions of benzylmagnesium chloride, without the assumption of rearrangement of free benzyl ions or radicals. This explanation is derived from the postulation of primary addition complexes in which certain definite factors are operative and lead, through chelation and ring opening, to abnormal products.

It is suggested that similar explanations may be used for a number of reactions which are not adequately elucidated by the conventional mechanisms.

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Rotenone. XXV. The Synthesis of Tetrahydrotubanol and Tetrahydrotubaic Acid

BY H. L. HALLER

In a brief note recently published[1] in THIS JOURNAL it was reported that the synthesis of tetrahydrotubanol[2] (2,6-dihydroxyisoamylbenzene) had been accomplished. The present paper presents the experimental evidence for this statement and also records the conversion of the synthetic tetrahydrotubanol into tetrahydrotubaic acid[2] (2,4-dihydroxy-3-isoamylbenzoic acid).

The synthesis of tetrahydrotubanol was effected through the following sequence of reactions: 2,6-dimethoxybenzonitrile ⟶ 2,6-dimethoxyphenyl isobutyl ketone ⟶ 2,6-dimethoxyisoamylbenzene ⟶ 2,6-dihydroxyisoamylbenzene.

The 2,6-dimethoxybenzonitrile was prepared from 2-nitro-6-methoxybenzonitrile, which was obtained from *m*-dinitrobenzene by a modification of the procedure described by Lobry de Bruyn.[3] In the preparation of the nitromethoxybenzonitrile it was found preferable to extract the crude

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[1] Haller, THIS JOURNAL, **54**, 4755 (1932).

[2] Haller and LaForge, *ibid.*, **53**, 4460 (1931); **54**, 1988 (1932).

[3] Lobry de Bruyn, *Rec. trav. chim.*, **2**, 210 (1883).