[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

# The Reaction of Benzylmagnesium Chloride with Benzaldehyde—The Identification of the Abnormal Product

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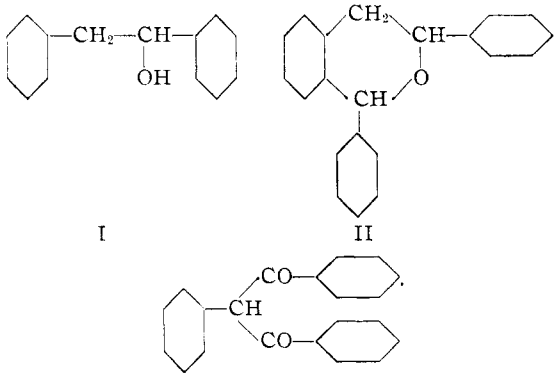
The reaction of benzylmagnesium chloride with benzaldehyde has been reinvestigated. The earlier study of Garcia-Banús[1] has been confirmed and supported by an independent synthesis of 1,3-diphenylisochromane, the so-called "abnormal" product. This work is consistent with the mechanism of the reaction previously proposed by Young and Siegel.[2]

The reaction of benzaldehyde with benzylmagnesium chloride has been reported to yield, under different conditions, benzylphenylcarbinol[1] (I), 1,3-diphenylisochromane[1] (II) and dibenzoylphenylmethane[3] (III).



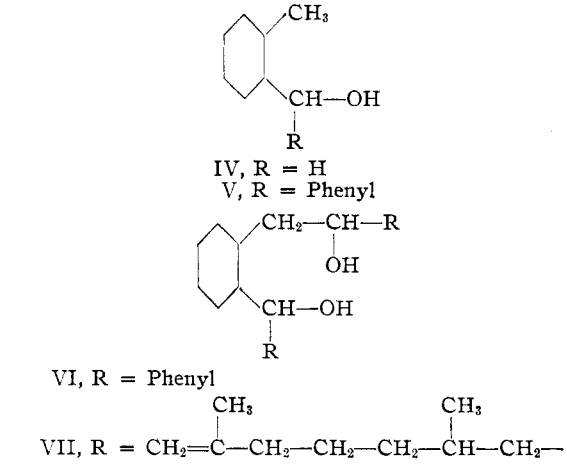
I II III

The first product may be made to predominate if the aldehyde is added to an excess of benzylmagnesium chloride, the second, if the Grignard reagent is added to the aldehyde at room temperature and the third compound is obtained if an excess of aldehyde is added to the Grignard reagent and the resulting mixture is heated for several hours.[4]

Despite the careful work of Garcia-Banús, *et al.*, there appears to be some uncertainty as to the course of this reaction[5a,b] with particular regard to the formation of II, a compound which may be classed as an "abnormal" product of the reaction. The structure of the latter was established by degradative methods. Attempts to establish its identity by synthesis were unsuccessful.[6]

The structure of II is not one which would have been predicted by analogy with the classical example of the "abnormal" reaction of benzylmagnesium chloride with carbonyl compounds.[7] Therefore, the reaction with benzaldehyde seemed to deserve further investigation. Certain salient studies of Garcia-Banús[1,4] have been confirmed in this Laboratory. In addition, the "abnormal" product 1,3-diphenylisochromane was synthesized by an independent method.

The reaction yields the primary products benzylphenylcarbinol (I) and 2-[2-hydroxy-2-phenylethyl]-benzhydrol (VI). Analysis for active hydrogen, measurement of molecular weight and oxidation with potassium permanganate to *o*-benzoylbenzoic acid and benzoic acids support the assigned structure. The glycol (VI) is readily dehydrated to the isochromane (III). This dehydration is acid catalyzed. Magnesium chloride, an acid according to the definition of Lewis,[8] is also an effective catalyst. There was no indication of the formation of *o*-tolylphenylcarbinol (V), which would be the expected "abnormal" product.[7] These results coincide with those obtained for the reaction of citronellal[2] with benzylmagnesium chloride in which the "abnormal" product is structurally analogous to VI but not to IV.

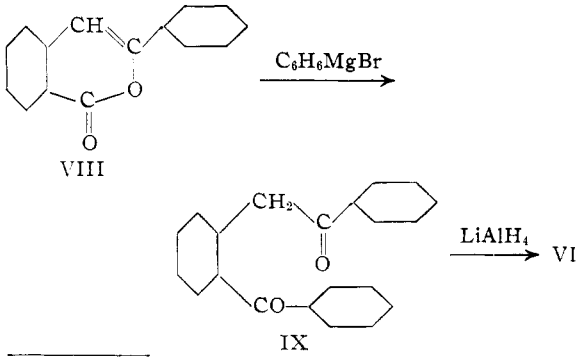


IV, R = H
V, R = Phenyl

VI, R = Phenyl

VII, R = $CH_2{=}C(CH_3){-}CH_2{-}CH_2{-}CH_2{-}CH(CH_3){-}CH_2{-}$

The structure of the abnormal product (II), was confirmed by a synthesis whose key step was the successful addition of phenylmagnesium bromide to 3-phenylisocoumarin (VIII) to yield 2-phenacylbenzophenone (IX). This diketone was



VIII IX

(1) J. Schmidlin and A. Garcia-Banús, *Ber.*, **45**, 3193 (1912).
(2) W. G. Young and S. Siegel, THIS JOURNAL, **66**, 354 (1944).
(3) J. Marshall, *J. Chem. Soc.*, **107**, 509 (1915).
(4) A. Garcia-Banús and L. Medrano, *Anales Soc. Espan. Fis. Quim.*, **21**, 436 (1923); *C. A.*, **18**, 2144 (1924).
(5) (a) H. Gilman and J. Kirby, THIS JOURNAL, **54**, 345 (1932); (b) P. R. Austin and J. R. Johnson, *ibid.*, **54**, 647 (1932).
(6) A. Garcia-Banús, *Anales Soc. Espan. Fis. Quim.*, **26**, 372 (1928); *C. A.*, **23**, 2178 (1929).
(7) From the reaction of benzylmagnesium chloride with formaldehyde is isolated mainly *o*-tolylcarbinol (IV) (M. Tiffeneau and Delange, *Compt. rend.*, **137**, 583 (1903)).
(8) G. N. Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., (Reinhold Publ. Corp.), New York, N. Y., 1923, p. 141f.

reduced with lithium aluminum hydride to the glycol (VI) which in turn was readily dehydrated to give 1,3-diphenylisochromane (II). The latter was identical with the dehydrated "abnormal" product.

Both the glycol (VI) and 1,3-diphenylisochromane obviously should form two racemic mixtures. Garcia-Banús, in his latter work,[6] was able to obtain two crystalline 1,3-diphenylisochromanes. In the present study only a single crystalline form of the isochromane was isolated. No attempt was made to isolate both modifications since the synthetic sample was identical with the "abnormal" product. The method of dehydration may well affect the proportion of the two isomers which are produced.[6]

This study, therefore, confirms the work of Garcia-Banús. It also supports the mechanism of this reaction which was previously proposed.[2] Of particular significance is the fact that the fraction of "abnormal" product which is formed is a function of the concentration of reactants. Furthermore the "abnormal" product can not form *via* the addition of a molecule of benzaldehyde to the magnesium salt of benzylphenylcarbinol (the normal product) since the per cent. of "abnormal" product is not increased when the reaction is allowed to take place in the presence of the preformed salt. Further discussion of the mechanism of this reaction will be reserved for a later date.[9]

## Experimental[10]

Benzylmagnesium chloride was prepared by the method described previously.[2] To the stirred reagent (0.40 mole in 400 ml. of ether), cooled by an ice-bath, freshly distilled benzaldehyde (0.38 mole) dissolved in five volumes of ether, was added dropwise. The reaction mixture was poured onto a mixture of ice and acetic acid. The ether layer was separated and washed repeatedly with aqueous sodium chloride, 10% sodium bicarbonate, a saturated solution of sodium chloride and then dried over potassium carbonate. The solvent was removed by distillation and the product distilled under reduced pressure. The first major fraction (64 g. 0.32 mole, b.p. 125–130° (2 mm.)) solidified on standing. This is the normal product, benzylphenylcarbinol. After recrystallization from ligroin–benzene mixtures the product melted at 65.5–66.5° (lit.[4] 67°). The compound (1.57 g.) was oxidized with potassium permanganate to yield an acid which was purified by sublimation (m.p. 121–122.5°, 0.98 g., 64% yield) and identified as benzoic acid by a mixed melting point determination with an authentic sample.

The second major fraction distilled at 185–195° (2 mm.) and was a yellow glassy material (5.4 g., 0.018 mole). It could not be made to crystallize. This was the "abnormal" product. A portion of the material was fractionally sublimed ($1 \times 10^{-4}$ mm. and a bath-temperature of 110–120°).

*Anal.* Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.37; H, 6.61.

The "abnormal" product (1.8 g.) was oxidized with potassium permanganate in pyridine.[2] The mixture of acids (1.56 g.) isolated from the reaction mixture was separated by sublimation. Benzoic acid (0.57 g.) and *o*-benzoylbenzoic acid (0.71 g.) were identified by their melting points and mixed melting points with authentic samples.

The molecular weight of the "abnormal" product was determined by the Rast method[11] (calcd., 304, found, 289). A Zerewitinoff[12] analysis indicated 1.6 active hydrogen atoms per molecule.

**Formation of 1,3-Diphenylisochromane from the "Abnormal" Product.**—The "abnormal" product (2.0 g.) was dissolved in 10 ml. of glacial acetic acid. Water was added to induce separation of a second phase. Six drops of concentrated sulfuric acid was added. A deep blue coloration appeared at the point where the acid met the solution and within five minutes needle-like crystals began to separate from the solution. The mixture was allowed to stand for one hour and then was filtered. From the filtrate an additional quantity of the same material was obtained following dilution of the solution with water. The combined yield was 1.7 g. (m.p. 109–110°) and corresponds to the "abnormal" product isolated by Garcia-Banús.

**Factors which Affect the Ratio of Normal to "Abnormal" Products.**—(a) Benzylmagnesium chloride (0.40 mole) was added to benzaldehyde (0.38 mole). The yield of normal product was 33.9 g. (0.17 mole) whereas the yield of "abnormal" product amounted to 20.3 g. (0.067 mole).

(b) To benzylmagnesium chloride (0.40 mole in 400 ml. of ether) was added benzylphenylcarbinol (40.0 g., 0.20 mole). This reaction should produce an equivalent amount of the magnesium alcoholate. To the solution was added benzaldehyde (0.20 mole). The reaction products were isolated in the usual manner. The normal product, *dl*-benzylphenylcarbinol (55.7 g.) as well as a yellowish-brown viscous material (3.4 g.) were isolated by distillation. Treatment of the latter fraction with acid as described above for the "abnormal" product yielded 0.5 g. of 1,3-diphenylisochromane.

This experiment shows that the alcoholate of *dl*-benzylphenylcarbinol is not an intermediate for the formation of the "abnormal" product.

**3-Phenylisocoumarin (V).**—This was prepared from 40 ml. of purified thionyl chloride and 10 g. (0.040 mole) of *o*-phenacylbenzoic acid.[13] The solution was refluxed for two hours after which the excess thionyl chloride was removed at reduced pressure. The product was purified by vacuum sublimation (0.3 mm. at 135°). The yield was 5 g. (54%), m.p. 89–90° (lit.[13] 90°).

**2-Phenacylbenzophenone.**—Fifty milliliters of an ethereal solution containing 0.0077 mole of phenylmagnesium bromide was added to 50 ml. of an ethereal solution of 3-phenylisocoumarin (1.55 g., 0.007 mole). A cream-colored precipitate formed during the addition of the Grignard reagent. Stirring was continued for 25 minutes following the addition. The reaction mixture was hydrolyzed with ammonium chloride (25 ml. of a 15% solution). The ether layer was separated, dried over anhydrous sodium sulfate and concentrated. The product was fractionally sublimed at $1 \times 10^{-4}$ mm. at a bath temperature of 110–120°. The product was a viscous, amber, glassy mass (1.21 g., 57%).

*Anal.* Calcd. for $C_{21}H_{16}O_2$: C, 83.97; H, 5.37. Found: C, 83.90; H, 5.33.

**2-[2-Hydroxy-2-phenylethyl]-benzhydrol.**—The above ketone (0.8 g., 0.0027 mole) was added to an ethereal solution of lithium aluminum hydride (0.75 g.) according to the description of Nystrom and Brown.[14] A minimum amount of water was added to the rapidly stirred reaction mixture to hydrolyze it. The ether layer was separated and combined with several ethereal washings of the precipitated hydroxides. The solution was dried over potassium carbonate and concentrated. The product was fractionally sublimbed at $1 \times 10^{-4}$ mm. and a bath temperature of 120°. A central fraction of a very viscous material (0.35 g.) was obtained and a portion analyzed.

*Anal.* Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.67; H, 7.12.

**Conversion of the Synthetic Glycol to 1,3-Diphenylisochromane.**—The above glycol (0.26 g.) was dissolved in 1.5 ml. of glacial acetic acid and treated in the manner described for the dehydration of the "abnormal" product. The phenomenon of halochromism with concentrated sulfuric acid and the appearance of the product were identical

(9) S. Siegel, W. M. Boyer and R. Jay, THIS JOURNAL, **73**, Aug. (1951).

(10) Micro analyses by Charles Beazley, Micro-Tech Laboratories, Skokie, Ill.

(11) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 50.

(12) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 44.

(13) C. Graebe and F. Trumpy, *Ber.*, **31**, 375 (1898).

(14) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

with that of the "abnormal" product. After two recrystallizations from ethanol, the melting point was 109–110°. The melting point was not depressed by admixture with the 1,3-diphenylisochromane obtained previously.

*Anal.* Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 87.45; H, 6.12.

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[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

# Some β-(2-Pyridyl)- and β-(2-Piperidyl)-propionamides*

BY FREEMAN H. MCMILLAN AND JOHN A. KING

Series of the substances named in the title were prepared for pharmacological evaluation of their central stimulant action. 3-(2-Pyridyl)-propanol-1 was oxidized to 3-(2-pyridyl)-propionic acid which was converted to 17 amides. Eight of these were catalytically hydrogenated to the corresponding piperidyl amides.

Although the physiological actions of N,N-diethylnicotinamide, assigned the non-proprietary name nikethamide by the Council on Pharmacy and Chemistry of the American Medical Association,[1] were first reported in 1924[2,3] and this compound has subsequently enjoyed considerable use in medical practice as a respiratory stimulant and analeptic, there has been relatively little study of its homologs, analogs and isosteres. In the pyridine series amides of pyridine-2,3- and -3,4-dicarboxylic acid are claimed[4] as analeptics, as are the amides of N-substituted - 2,3 - dimethylpiperidine - 4,4 - dicarboxylic acid,[5] and N,N-diethylpyridine-3-acetamide.[6] Several furyl carboxylic and acetic acid amides[5,7,8] and amides of a pyranyl malonic acid[5] and pyrone carboxylic acids[9,10] are reported to have stimulant properties. Other amides so reported are those of several isoxazole[11–16] and benzisoxazole[17] carboxylic acids, of methyl-β-(1-morpholinyl)-ethylmalonic acid,[5] and of nuclear carboxylic acids of the pyrazole,[18] pyrazine[19] and thiazole[20] series. It is noteworthy that in practically all of the amides claimed to have analeptic properties the carboxyl group is attached directly to the heterocyclic nucleus; the few exceptions are a small number of substituted malondiamides, a few furan derivatives, a single pyridine derivative,[6] and, as the only mention of heterocyclic substituted alkanamides higher than acetamides as analeptics, a series of ω-(3,5-dimethylisoxazolyl)-alkanamides.[13] It seemed desirable to us to learn if this neglect of higher alkanamides was justified and, particularly, to learn if the 3-carboxylic and -acetic amides were unique in the pyridine series in their display of stimulant properties.

In connection with other work[21] which required the preparation of β-(2-piperidyl)-propionic acid dimethylamide and cyclic lactam (3-ketoöctahydropyrrocoline) it was desirable to have a ready source of the requisite corresponding acid or its pyridyl precursor. The most frequently mentioned synthesis of β-(2-pyridyl)-propionic acid consists[22] of the condensation of chloral with α-picoline, followed by hydrolysis, dehydration and reduction; this method was used by us at the start of our work and, while the over-all yield of 30 to 40% was considered satisfactory, the initial condensation reaction was somewhat troublesome. Other methods which have been described in the literature for the preparation of the acid are: condensation of α-picoline with mesoxalic ester, giving a 40% yield of ethyl β-(2-pyridyl)-acrylate which could be reduced to the propionate[23]; preparation of β-(2-pyridyl)-ethyl bromide, its metathesis with sodium cyanide, then hydrolysis to the acid[24]; and the addition of hydrogen cyanide to 2-vinylpyridine followed by hydrolysis, giving the acid in 30% over-all yield.[25]

Because objections were to be had to each of the above methods, a more convenient synthesis of β-(2-pyridyl)-propionic acid was sought and was found in the acid permanganate oxidation of the

* Presented before the Division of Medicinal Chemistry at the 119th meeting of the American Chemical Society, Cleveland, Ohio, April 9, 1951.

(1) "New and Nonofficial Remedies," J. B. Lippincott Company, Philadelphia, Pa., 1950, p. 239.

(2) E. S. Faust, *Schweiz. med. Wochschr.*, **54**, 229 (1924); *Lancet*, **208**, 1336 (1925); *C. A.*, **19**, 3114 (1925).

(3) S. J. Thannhauser and W. Fritzel, *ibid.*, **54**, 232 (1924); *C. A.*, **19**, 3114 (1925).

(4) M. Hartmann and H. Ensslin (to Society of Chemical Industry in Basle), U. S. Patent 2,136,502, November 15, 1938.

(5) H. Martin and H. Gysin (to J. R. Geigy A.-G.), U. S. Patent 2,447,194, Aug. 17, 1948.

(6) M. Hartmann and W. Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

(7) H. Martin, W. Baumann and H. Gysin (to J. R. Geigy A.-G.), U. S. Patent 2,317,286, April 20, 1943.

(8) J. R. Geigy A.-G. Swiss Patent 226,786; *C. A.*, **43**, 2643 (1949).

(9) H. Martin, W. Baumann, H. Zaeslin and H. Gysin (to J. R. Geigy A.-G.), U. S. Patent 2,364,304, Dec. 5, 1944.

(10) J. R. Geigy A.-G. Swiss Patent 215,240, Sept. 1, 1941; *C. A.*, **42**, 3782 (1948).

(11) M. Hoffer (to Hoffmann-La Roche Inc.); U. S. Patent 2,115,-681, April 26, 1938.

(12) M. Hoffer and M. Reinert, *Arch. intern. pharmacodynamie*, **56**, 211 (1937); *C. A.*, **32**, 1326 (1938).

(13) F. Hoffmann-La Roche and Co. A.-G., German Patent 673,111, Mar. 16, 1939; *C. A.*, **33**, 4380 (1939).

(14) F. Hoffmann-La Roche and Co. A.-G., Swiss Patent 194,109, Feb. 1, 1938; *C. A.*, **32**, 7214 (1938).

(15) F. Hoffmann-La Roche and Co. A.-G., Swiss Patent 194,368, Feb. 16, 1938; *C. A.*, **32**, 7214 (1938).

(16) F. Hoffmann-La Roche and Co. A.-G., Swiss Patent 215,778, Nov. 1, 1941; *C. A.*, **42**, 4613 (1948).

(17) U. P. Basu and S. P. Dhar, *J. Indian Chem. Soc.*, **23**, 189 (1946).

(18) C. Musante and P. Pino, *Gazz. chim. ital.*, **77**, 199 (1947).

(19) O. Dalmer and E. Walter (to Merck and Co., Inc.), U. S. Patent 2,149,279, March 7, 1939.

(20) H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **28**, 362 (1945).

(21) J. A. King, V. Hofmann and F. H. McMillan, *J. Org. Chem.*, in press.

(22) (a) A. Einhorn and A. Liebrecht, *Ber.*, **20**, 1593 (1887); (b) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 2969 (1932); (c) K. Winterfeld and F. W. Holschneider, *Arch. Pharm.*, **277**, 192 (1939); (d) C. W. Tullock and S. M. McElvain, THIS JOURNAL, **61**, 961 (1939).

(23) S. M. McElvain and H. G. Johnson, THIS JOURNAL, **63**, 2213 (1941).

(24) L. A. Walter, W. H. Hunt and R. J. Fosbinder, *ibid.*, **63**, 2771 (1941).

(25) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).