TABLE II (*Continued*)

Yield (from free base)	M. p., °C.	Hydrochloride: Empirical formula	Analyses, %: Cl, Calcd.	Cl, Found	N, Calcd.	N[i], Found	Pharmacology: Toxicity[b]	Antispasmodic activity[c]
93	89–91	$C_{16}H_{30}O_2NCl$	11.66	11.59	4.61	4.51		−
94	95.5–98	$C_{17}H_{32}O_2NCl$	11.15	11.02	4.41	4.30		+
85	103–104.5	$C_{18}H_{34}O_2NCl$	10.68	10.60	4.22	4.14	250–275[h]	+
54[d]	70–76	$C_{17}H_{30}O_2NCl$	11.23	11.00			80–90	+++
95	126–128.5	$C_{20}H_{34}O_2NCl$	9.96	9.90	3.94	3.93		−
56[d]	129.5–132.5	$C_{20}H_{36}O_2NCl$	9.91	9.97	3.91	3.85		−
89[d]	130–135	$C_{21}H_{38}O_2NCl$	9.53	9.53	3.77	3.62	135–145	++
69[d]	99–107.5	$C_{22}H_{40}O_2NCl$	9.19	9.14	3.63	3.45	125–135	−
68[d]	119–125	$C_{21}H_{32}O_2NCl$	9.69	9.63	3.83	3.70	60–70	−
90	109–113	$C_{22}H_{34}O_2NCl$	9.33	9.45	3.69	3.42		+
74[d]	87–98	$C_{23}H_{34}O_2NCl$	9.05	9.00	3.57	3.49	45–55	−
60[d]	82–98[e]	$C_{19}H_{30}O_3NCl$	9.97	10.12	3.94	3.27		++
80	94.5–97	$C_{16}H_{32}O_2NCl$	11.59	11.59	4.58	4.53		−
88	108–110	$C_{18}H_{36}O_2NCl$	10.62	10.58	4.20	4.12	225–250[h]	+
70[d]	120–130	$C_{22}H_{42}O_2NCl$	9.15	9.17	3.61	3.80		−
84[d]	137–140.5	$C_{21}H_{34}O_2NCl$	9.64	9.74	3.81	3.96		−
45[f,d]	122–127[g]	$C_{23}H_{36}O_2NCl$	9.00	8.92	3.58	3.44	60–70	++

[a] See (a) Table I. [b] Intravenous LD_{50}, in mg./kg. in rats. [c] Relative antispasmodic activity tested on isolated muscle, at a dilution of 1:3,000,000. [d] Calcd. from starting acid. [e] Recrystallized from isopropanol and ether. [f] Yield of unrecrystallized material. [g] Recrystallized from methyl isobutyl ketone. [h] Intraperitoneal LD_{50} in mg./kg. in mice. [i] Nitrogen analysis by Elizabeth Beard in this Laboratory.

KANSAS CITY, MISSOURI RECEIVED SEPTEMBER 28, 1946

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Diamino Ketones. IV.[1] Addition and Cleavage with Grignard Reagents

BY NORMAN H. CROMWELL

Several years ago it was reported[2] from this Laboratory that α,β-dimorpholinobenzylacetone reacted with phenylmagnesium bromide to give a fair yield of the carbinol, 2,4-diphenyl-3,4-dimorpholinobutanol-2, and that the corresponding α,β-dimorpholinobenzylacetophenone reacted with methylmagnesium iodide to give the same carbinol, but in very low yields.

The present communication reports an extension of the investigation of the reactions of these more or less hindered carbonyl compounds with Grignard reagents. It was recognized in the earlier investigation[2] that lower molecular weight products were being formed in these reactions, resulting possibly from cleavage of the aliphatic chain of the diamino ketones. Since E. P. Kohler had reported cleavage reactions when 1,3-diketones[3] and epoxy ketones[4] were treated with Grignard reagents, it seemed important to attempt to relate the behavior of the diamino ketones to these compounds. Furthermore, since some of the diamino ketones which have been prepared in these studies have been found to possess mild avian antimalarial activity[5] it was important to search for ways to convert them into derivatives that might be expected to be more soluble and more active as antimalarials.

Ethylmagnesium bromide and methylmagne-

(1) Previous paper in this series: Cromwell and Hoeksema, THIS JOURNAL, **67**, 124 (1945).

(2) Cromwell, *ibid.*, **62**, 3470 (1940).

(3) Kohler and Erickson, *ibid.*, **53**, 2301 (1931).

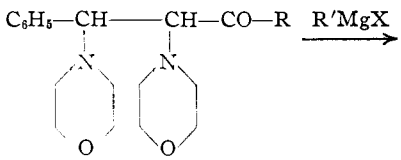
(4) Kohler, Richtmyer and Hester, *ibid.*, **53**, 205 (1931).

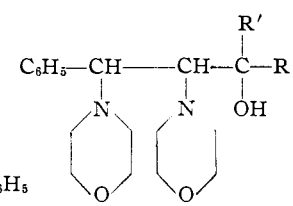
(5) For the antimalarial activities of the various amino ketones and derivatives that have been reported in these several series of papers, see "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor, to be published soon.

sium iodide both added rather readily to α,β-dimorpholinobenzylacetone[2] to give 50–60% yields of the corresponding carbinols, 3-methyl-5-phenyl-4,5-dimorpholinopentanol-3, (I) and 2-methyl-4-phenyl-4,5-dimorpholinobutanol-2, (II). When α,β-dimorpholinobenzylacetophenone[6] was treated with ethylmagnesium bromide, a 25% yield of the corresponding carbinol, 3,5-diphenyl-4,5-dimorpholinopentanol-3 (III), resulted along with some unidentified oily products. This same diamino ketone was treated with phenylmagnesium bromide to give only a 4% yield of the expected carbinol, 1,1,3-triphenyl-2,3-dimorpholinopropanol-1, (IV).

From this latter reaction mixture was isolated larger amounts of a lower molecular weight amino compound which was shown to be identical with benzhydryl morpholine (VI), synthesized from benzhydryl bromide. Since the other fragment from this apparent cleavage was suspected to be ω-morpholinoacetophenone, the residual reaction mixture was then treated with hydroxylamine to yield an oxime which was found to be identical with an authentic sample of the known oxime (VII) of ω-morpholinoacetophenone.[7] That this cleavage of the diamino ketone was probably not the result of a hydrolytic cleavage followed by reaction of the products with the Grignard reagent during decomposition of the Grignard reaction mixture was indicated by an experiment which showed that α,β-dimorpholinobenzylacetophenone is not readily cleaved under such conditions.

The nature of this cleavage of diamino ketones by Grignard reagents was further



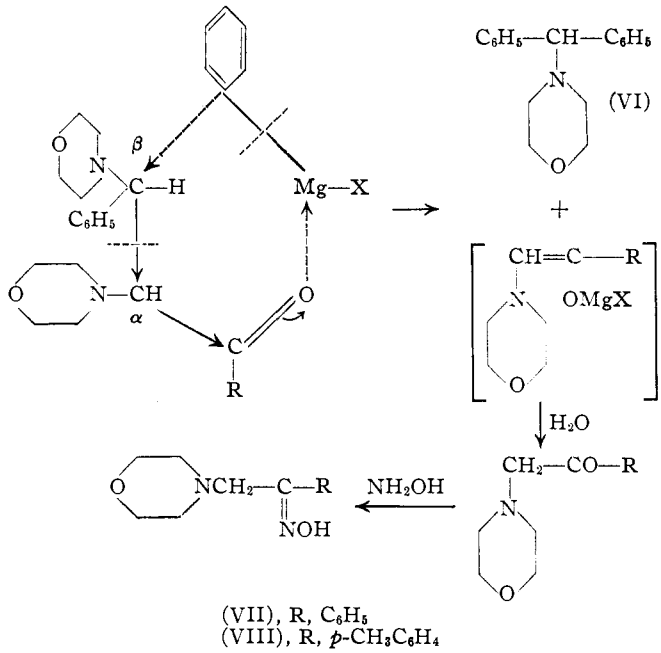


(I) R, CH_3; R′, C_2H_5
(II) R, CH_3; R′, CH_3
(III) R, C_6H_5; R′, C_2H_5
(IV) R, C_6H_5; R′, C_6H_5
(V) R, p-$CH_3C_6H_4$; R′, C_6H_5

investigated by repeating this type of experiment using an α,β-dimorpholinobenzylacetophenone with one of the phenyl groups marked with a *p*-methyl group. When α,β-dimorpholinobenzyl-*p*-methylacetophenone was treated with phenylmagnesium bromide, the corresponding carbinol, 1,3-diphenyl-1-(*p*-tolyl)-2,3-dimorpholinopropanol-1 (V), resulted in low yields along with benzhydryl morpholine and ω-morpholino-*p*-methylacetophenone. This latter product was identified by comparing its oxime with an authentic sample (VIII), synthesized from the hydrochloride of ω-morpholino-*p*-methylacetophenone.

Neither phenyl *p*-tolyl ketone nor diphenyl-*p*-tolylcarbinol could be isolated from this reaction mixture, indicating there had been no significant amount of the α,β-diamino ketone cleaved between the carbonyl carbon and the α-carbon atom by the Grignard reagent.

A mechanism for this unique cleavage of the α,β-diamino ketones may be postulated diagrammatically as



(VII), R, C_6H_5
(VIII), R, p-$CH_3C_6H_4$

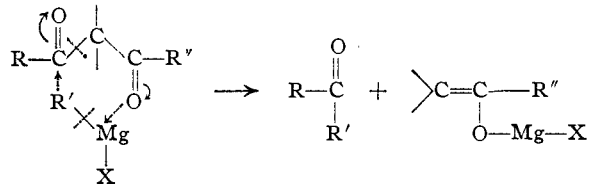
The Grignard reagent is attracted in the normal manner, as a result of the nucleophilic nature of the carbonyl oxygen toward the electrophilic metal portion of the reagent. Since the "normal" approach of the nucleophilic organic portion of the reagent toward the electrophilic carbonyl carbon atom is sterically hindered by large groups on both sides in some of these molecules, an alternative electrophilic carbon atom becomes a competitive reactive center. As is indicated in the diagram, the β-carbon atom is electrophilic and, moreover, the organic portion of the reagent may approach it *via* a quasi-six membered ring. The α-carbon–β-carbon bond had already been shown to be weak because of the presence of the several electron attracting groups and thus susceptible to cleavage by dilute acids.[6] As the organic portion of the Grignard reagent approaches the β-carbon atom the formal bonds are broken as indicated, and the electrons shifted to give the indicated products which are quite stable substances. This cleavage mechanism would not require actual ionization of the Grignard reagent.

It is interesting to compare the slow "normal"

(6) Cromwell, THIS JOURNAL, **62**, 2897 (1940).
(7) Cromwell and Hoeksema, *ibid.*, **66**, 870 (1944).

addition here with the rapid and rather complete addition of Grignard reagents to the related ethylene imine ketones,[8] with related β-amino ketones,[9] and with related α-amino ketones.[10] Another communication will discuss the effect on the reactivity of the carbonyl group as the nature and position of the amino groups in amino ketones are varied.

It is also of interest to point out that it is possible to write an analogous mechanism for the cleavage of the 1,3-diketones.



Such a mechanism might even operate in the cleavage of some strained cyclic 1,3-diketones,[11] and certainly should be considered as a possible parallel mechanism along with others that have been suggested for the cleavage of open-chain, non-enolizing 1,3-diketones.[3,12]

Acknowledgment.—The author appreciates a grant from the Research Council of the University of Nebraska which aided in the completion of this investigation.

Experimental

Reaction of Ethylmagnesium Bromide with α,β-Dimorpholinobenzylacetone.[2]—To the Grignard reagent prepared from 4.8 g. (4 equiv.) of magnesium and an equivalent amount of ethyl bromide, a dry benzene solution (240 ml.) of the diamino ketone (16 g., one equiv.) was added rapidly with stirring. After refluxing the mixture for two hours it was decomposed with ice and ammonium chloride and the benzene–ether layer washed several times with water and dried. Removal of part of the benzene and addition of petroleum ether caused colorless crystals to form, m. p. 175–178° (12 g.). Recrystallization from benzene and petroleum ether solutions gave 10 g. of colorless crystals (I), m. p. 180–181°; yield, 57%.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.90; H, 9.23; N, 8.04. Found: C, 68.53; H, 9.07; N, 7.95.

Some unreacted starting material (4 g.) was recovered.

Reaction of Methylmagnesium Iodide with α,β-Dimorpholinobenzylacetone.[2]—To the Grignard reagent prepared from 3.02 g. (4 equiv.) of magnesium and 7.8 ml. (4.01 equiv.) of methyl iodide, a dry benzene (150 ml.) solution of the diamino ketone (10 g., one equiv.) was added rapidly with stirring and the mixture refluxed for two hours. The reaction mixture was worked up as before to give 7.7 g. of a colorless crystalline product, m. p. 184–187°. Two recrystallizations from benzene and petroleum ether gave 5.5 g. of colorless crystals (II), m. p. 190–192°; yield, 53%.

Anal. Calcd. for $C_{19}H_{30}N_2O_3$: C, 68.22; H, 9.04; N, 8.38. Found: C, 67.90; H, 9.35; N, 8.35.

Some unreacted starting material (2 g.) was recovered.

Reaction of Ethylmagnesium Bromide with α,β-Dimorpholinobenzylacetophenone.[6]—To the Grignard reagent prepared from 1.28 g. (4 equiv.) of magnesium and 5.73 g. (4.1 equiv.) of ethyl bromide, a dry benzene (80 ml.) solution of 5.0 g. (one equiv.) of the diamino ketone was added rapidly with stirring. The solution was refluxed for one-half hour during which time a white precipitate formed. The reaction mixture was decomposed as usual and the benzene solution evaporated to leave an oil. After many manipulations from benzene and petroleum ether solutions, and from alcohol and water solutions it was possible to obtain 1.5 g. of colorless crystals (III), m. p. 158–160°; yield 25%. This compound was stable after boiling for one hour in hydrochloric acid solution.

Anal. Calcd. for $C_{25}H_{34}N_2O_3$: C, 73.13; H, 8.35; N, 6.83. Found: C, 72.81; H, 8.69; N, 6.85.

Treatment of this same diamino ketone with four equivalents of methylmagnesium iodide at −10° gave no reaction.

Reaction of Phenylmagnesium Bromide with α,β-Dimorpholinobenzylacetophenone.[6]—To the Grignard reagent prepared from 3.33 g. (4 equiv.) of magnesium and 21.69 g. (4.01 equiv.) of bromobenzene, a dry benzene (210 ml.) solution of the diamino ketone (13.05 g.) was run in slowly with stirring over a period of one-half hour. The solution was refluxed for one hour and decomposed as usual. The benzene solution was extracted several times with 0.5 *N* sulfuric acid. The acid solution was made basic and the precipitated semi-solid extracted with ether. From this ether solution was obtained on evaporation and addition of petroleum ether, two products. The most insoluble product was 0.5 g. of colorless crystals (IV); yield, 4%; m. p. 206–208° (recrystallized from benzene and petroleum ether).

Anal. Calcd. for $C_{29}H_{34}N_2O_3$: C, 75.94; H, 7.47; N, 6.12. Found: C, 76.00; H, 7.69; N, 6.17.

This product was isolated unchanged after boiling for two hours with dilute sulfuric acid.

The second product isolated from this reaction mixture was 2.0 g. of colorless crystals (VI), m. p. 74–76° (recrystallized from 85% alcohol, yield, 23%).

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.52. Found: C, 80.43; H, 7.76; N, 5.52.

This latter compound (VI), was identical with benzhydryl morpholine prepared as outlined below; mixed m. p. 74–77°.

An oil, obtained by evaporating the filtrates of (IV) and (VI), was treated with an excess of hydroxylamine in an alcohol-potassium hydroxide solution[7] to give colorless, granular crystals (VII), m. p. 146–148°; a mixture with authentic ω-morpholinoacetophenone oxime[7] gave m. p. 147–148°; yield 1.5 g., 20%.

A solution of 5.0 g. of pure α,β-dimorpholinobenzylacetophenone in benzene and ether was shaken with a water solution containing ammonium chloride and ammonium hydroxide for fifteen minutes. Evaporation of the dried benzene–ether solution and addition of petroleum ether gave 4.7 g. of the starting material. A trace of benzaldehyde was present in the filtrate as indicated by a positive Schiffs test.

Preparation of Benzhydryl Morpholine (VI).—Ten grams of crude benzhydryl bromide[13] was dissolved in 25 ml. of dry benzene and treated with 7.75 g. (2.2 equiv.) of morpholine and allowed to stand at room temperature for twelve hours. The precipitated morpholine hydrobromide was filtered off and the filtrate evaporated under vacuum on a water-bath. The residue was recrystallized from 85% alcohol to give 9.4 g. of colorless crystals, m. p. 76–78°.

Preparation of α,β-Dimorpholinobenzyl-*p*-methylacetophenone.—Twenty grams (0.0523 mole) of α,β-dibromobenzyl-*p*-methylacetophenone[14] was mixed with 50 ml. of absolute alcohol and treated with 18.7 g. (0.215 mole) of morpholine. The reaction mixture was handled as

(8) Cromwell, THIS JOURNAL, **69**, 258 (1947).

(9) Cromwell and Burch, *ibid.*, **66**, 872 (1944).

(10) Kohler and Bruce, *ibid.*, **53**, 1994 (1931).

(11) Erickson and Kitchens, *ibid.*, **68**, 492 (1946).

(12) Geissman and Tulagin, *ibid.*, **63**, 3352 (1941); *ibid.*, **66**, 719 (1944).

(13) Courtot, *Ann. chim.*, [9] **5**, 80 (1916).

(14) Weygand, *Ber.*, **57**, 416 (1924).

previously described for such reactions[6] to give 8.2 g. of pale, yellow needles, recrystallized from 95% alcohol, m. p. 166–167°.

Anal. Calcd. for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.67. Found: C, 72.85; H, 7.78.

Reaction of Phenylmagnesium Bromide with α,β-Dimorpholinobenzyl-*p*-methylacetophenone.—The Grignard reagent was prepared from 1.85 g. (4 equiv.) of magnesium and 12 g. (4.1 equiv.) of bromobenzene in 40 ml. of dry ether. To this solution was added in one minute 7.5 g. of the diamino ketone dissolved in 60 ml. of dry benzene. After refluxing for two hours the solution remained clear. The reaction mixture was decomposed as before and the benzene–ether solution washed with water, dried over anhydrous sodium sulfate and evaporated to leave a brown oil that would not crystallize from benzene–petroleum ether solutions.

The oily product was dissolved in warm 85% alcohol. From this solution was eventually obtained a high melting compound which gave, after four recrystallizations from benzene and petroleum ether mixtures, a slightly soluble, colorless, crystalline product (V), m. p. 217–220°; yield 1.1 g., 12%.

Anal. Calcd. for $C_{30}H_{36}N_2O_3$: C, 76.24; H, 7.68. Found: C, 75.96; H, 7.71.

Concentration and strong cooling of the 85% alcohol filtrates from (V) gave 0.8 g. (17% yield) of benzhydrylmorpholine (VI), m. p. 75–77°. Treatment of the residual oil from the evaporation of the filtrates of (VI) with hydroxylamine in alcohol–potassium hydroxide solutions[7] gave 0.60 g. (14% yield) of a flaky, colorless, oxime (VIII), m. p. 149–153°, identical with ω-morpholino-*p*-methylacetophenone oxime.

The filtrate from (VIII) was evaporated and the residual oil dissolved in dry ether. Gaseous hydrogen chloride was added to this solution to precipitate all of the remaining basic products. The ether solution was washed with water, dried over anhydrous calcium sulfate and evaporated to leave 0.51 g. of a brown oil. This oil was crystallized from 85% alcohol to give only traces of biphenyl. No trace of phenyl *p*-tolyl ketone nor diphenyl *p*-tolyl carbinol was obtained.

ω-Morpholino-*p*-methylacetophenone Oxime (VIII).—From 4.0 g. of ω-morpholino-*p*-methylacetophenone hydrochloride[15] was obtained 3.6 g. of colorless, flaky crystals, m. p. 150–154°, using the method previously described for ω-morpholinoacetophenone oxime.[7] The product was recrystallized from 85% alcohol.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.81; H, 7.88.

Summary

1. α,β-Dimorpholinobenzylacetone reacts readily with Grignard reagents to give the expected α,β-diamino carbinols in fair yields.

2. α,β-Dimorpholinobenzylacetophenones contain a hindered carbonyl group. Addition to the carbonyl group is slowed, so that the expected α-β-diamino carbinol is accompanied by considerable amounts of lower molecular weight products resulting from cleavage by the Grignard reagent of the bond between the *alpha* and *beta* carbon atoms. An explanation of this type of cleavage is presented and compared with a similar cleavage of open chain 1,3-diketones.

(15) German Patent 667,356, Nov. 9, 1938; *C. A.*, **33**, 2287[8] (1939).

LINCOLN, NEBRASKA RECEIVED FEBRUARY 27, 1947

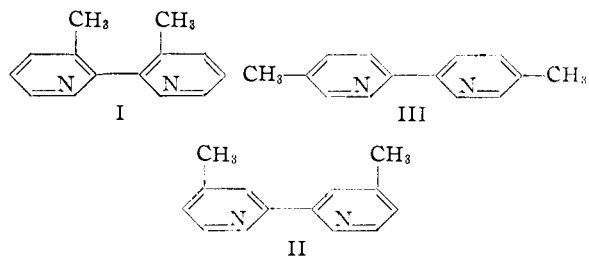
[CONTRIBUTION FROM THE WILLIAM ALBERT NOYES LABORATORY, UNIVERSITY OF ILLINOIS]

Effect of the Symmetrical Situation of Methyl Groups on the Property of Dimethyl-2,2′-bipyridyl to Complex the Ferrous Ion

BY F. WM. CAGLE, JR., AND G. FREDERICK SMITH

The complex 2,2′-bipyridyl ferrous ion $Fe(C_{10}H_8N_2)_3^{++}$ has long been known.[1] Salts of this ion and their solutions are intensely red, and this color together with the observation that the solutions conform closely to Beer's law have made 2,2′-bipyridyl a very desirable reagent for colorimetric iron determinations.[2] For an extended discussion and bibliography of the analytical uses of 2,2′-bipyridyl, the reader is referred to two monographs containing this material.[3,4]

The purpose of this investigation was to compare and contrast, in so far as possible, the ferrous complexes of three symmetrically substituted dimethyl 2,2′-bipyridyls. These were 3,3′-dimethyl-2,2′-bipyridyl (I), 4,4′-dimethyl-2,2′-bipyridyl (II) and 5,5′-dimethyl-2,2′-bipyridyl (III).[5] Previous work on 6,6′-dimethyl-2,2′-bipyridyl has shown that this compound does not form a ferrous iron complex[6] so it may be eliminated from this investigation. An analogous condition is met with 2,2′-biquinolyl.[7] In fact, the substitution of only one of the 6 positions on 2,2′-bipyridyl suffices to much weaken the ability to



(1) F. Blau, *Ber.*, **21**, 1077 (1888); *Monatsh.*, **10**, 375 (1889).

(2) J. T. Woods and M. G. Mellon, *Ind. Eng. Chem., Anal. Ed.*, **13**, 551 (1941).

(3) G. F. Smith and F. P. Richter, "Phenanthroline and Substituted Phenanthroline Indicators," The G. Frederick Smith Chemical Co., Columbus, Ohio, 1944.

(4) "Organic Reagents for Metals," Hopkin and Williams Ltd., London, 1944, ed. 4, pp. 66–69.

(5) These compounds were furnished by Professor Francis H. Case of Temple University, THIS JOURNAL, **68**, 2574 (1946).

(6) F. Feigl, *Ind. Eng. Chem., Anal. Ed.*, **8**, 406 (1936).

(7) A. P. Smirnoff, *Helv. Chim. Acta*, **4**, 802 (1921).