

(77.5%) of crude phenanthridone. Recrystallization from glacial acetic acid, followed by washing with ethanol, yielded 35.6 g. of pure phenanthridone as fine white needles; m. p. 292.5–293.5° (293°).^{1b}

Anal. Calcd. for C₁₃H₉NO: C, 79.98; H, 4.65; N, 7.18. Found: C, 80.03; H, 4.58; N, 7.36.

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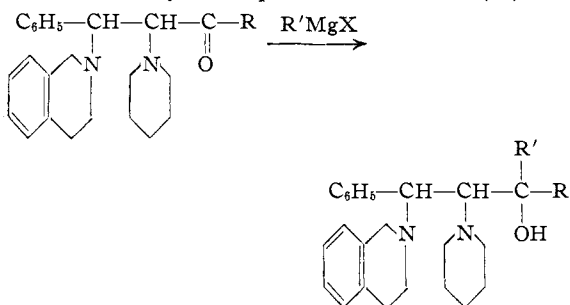
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α,β -Diamino Ketones. V.¹ Synthesis of α,β -Diamino Tertiary Carbinols

BY NORMAN H. CROMWELL AND DONALD J. CRAM²

Previous investigations^{1,3} had shown that it was possible to add Grignard reagents to the carbonyl group in certain α,β -diamino ketones to form α,β -diamino tertiary carbinols. Certain α,β -diamino ketones had been found to possess mild avian antimalarial activity.⁴ It was hoped that conversion of these α,β -diamino ketones to α,β -diamino tertiary carbinols would increase the antimalarial activity.

Methylmagnesium iodide was added to α -piperidino- β -tetrahydroisoquinolinobenzylacetone⁵ to give a low yield of 2-methyl-4-phenyl-3-piperidino-4-tetrahydroisoquinolinobutanol-2 (I). Phenylmagnesium bromide reacted with this same diamino ketone to give 2,4-diphenyl-3-piperidino-4-tetrahydroisoquinolinobutanol-2 (II).



I, R and R' = CH₃
II, R = CH₃; R' = C₆H₅
III, R = C₆H₅; R' = CH₃

The reaction of methylmagnesium iodide with α -piperidino- β -tetrahydroisoquinolinobenzylacetophenone⁶ led to racemate (III), a diastereoisomer of (II). Four racemates of 2,4-diphenyl-3-piperidino-4-tetrahydroisoquinolinobutanol-2 can exist. The starting α,β -diamino ketone in each case is undoubtedly one of the two possible racemates. It is not surprising that (II) and (III) should turn out to be different racemates.

(1) Previous paper in this series: Cromwell, *THIS JOURNAL*, **69**, 1857 (1947).

(2) Present address: Department of Chemistry, University of California, Los Angeles, Calif.

(3) Cromwell, *THIS JOURNAL*, **62**, 3470 (1940).

(4) 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," Vol. I and II, F. Y. Wiselogle, editor, Edwards Brothers, Ann Arbor, Michigan, 1946.

(5) Cromwell and Cram, *THIS JOURNAL*, **65**, 301 (1943).

(6) Cromwell, Harris and Cram, *ibid.*, **66**, 134 (1944).

Tiffeneau⁷ has shown that the action of Grignard reagents on ketones having an asymmetric carbon atom in the α -position with respect to the carbonyl group leads to only one of the two possible diastereoisomers; the other diastereoisomer can be obtained by inverting the order in which are introduced the substituted radicals of the tertiary alcohol function thus created. The present experiment is an example of the stereochemical specificity of the Grignard reaction with ketones containing two asymmetric carbon atoms.

The ultraviolet absorption spectra of (II) and (III) were quite similar and showed no pronounced maxima, as would be expected for these structures; see Fig. 1. Mixtures of (II) and (III) melted over a range of temperature beginning considerably below the melting point of either (II) or (III).

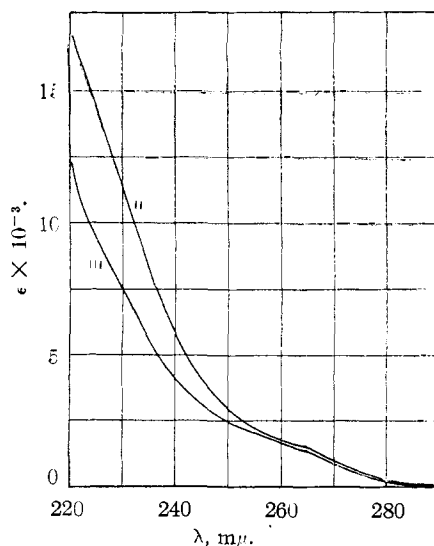


Fig. 1.—Absorption spectra in heptane of II and III.

Apparently a tetrahydroquinolino group in the β -position of an α,β -diamino ketone offers considerably more hindrance than does the tetrahydroisoquinolino group to the addition of the Grignard reagent. Methylmagnesium iodide gave no apparent reaction with either α -morpholino- β -tetrahydroquinolinobenzylacetone⁶ or the α -piperidino analog.⁵

Phenylmagnesium bromide reacted with α,β -dipiperidinobenzylacetone⁸ to give a low yield of 2,4-diphenyl-3,4-dipiperidinobutanol-2 (IV). The carbonyl group in these diamino ketones is hindered, especially by the amino group located at the β -position.

Acknowledgment.—The assistance of Mr. K. C. Tsou of the Chemistry Department, University of Nebraska, who carried out the absorption spectra studies, is gratefully acknowledged.

(7) Tiffeneau and Levy, *Bull. soc. chim. France*, [5] **2**, 1848 (1935).

(8) Cromwell and Witt, *THIS JOURNAL*, **65**, 308 (1943). This preparation of carbinol (IV) was carried out by Dr. Ivan H. Witt.

TABLE I
 PHYSICAL AND ANALYTICAL DATA FOR α,β -DIAMINO TERTIARY CARBINOLS

Compound	No.	M. p., °C.	Yield, %	Formula	Percentage composition					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
3-Piperidino-4-tetrahydroisoquinolino- butanol-2										
2-Methyl-4-phenyl	(I)	141-143	14	C ₂₅ H ₃₄ N ₂ O	79.32	78.92	9.05	9.09	7.41	7.35
2,4-Diphenyl	(II)	194-197	47	C ₃₀ H ₃₆ N ₂ O	81.77	81.69	8.24	8.01	6.36	6.57
2,4-Diphenyl	(III)	206-209	20	C ₃₀ H ₃₆ N ₂ O	81.77	81.94	8.24	8.33	6.36	6.09
2,4-Diphenyl-3,4-dipiperidinobutanol-2	(IV)	145-147	13	C ₂₆ H ₃₆ N ₂ O	79.54	79.66	9.26	9.32

Experimental

Reaction of Grignard Reagents with the Ketones.—Four equivalents of the corresponding Grignard reagent were prepared in dry ether solution in the usual manner. To these solutions, one equivalent of the corresponding α,β -diamino ketone dissolved in the minimum amount of dry benzene was added all at once. The reaction mixtures were refluxed for two hours, cooled, and then decomposed with ice and ammonium chloride. The benzene-ether layer was washed several times with water, dried and evaporated to give the crude oily products. Recrystallization of these products from 95% ethanol gave as a first crop, mainly unchanged starting material. The second crop contained most of the carbinol product. These crude carbinol products were purified further by boiling with 5% sulfuric acid to destroy by hydrolysis any remaining unchanged α,β -diamino ketone.⁹ Neutralization of the acid solutions with sodium hydroxide precipitated the diamino carbinols, which were again recrystallized from a chloroform-alcohol mixture and finally from a benzene-petroleum ether mixture, see Table I.

(9) Cromwell, *THIS JOURNAL*, **62**, 2897 (1940).

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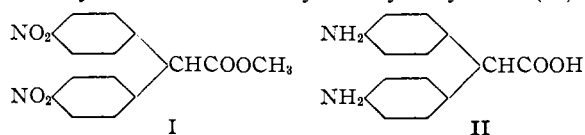
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4,4'-Diaminodiphenylacetic Acid

BY L. HASKELBERG AND D. LAVIE

The interesting therapeutical properties of 1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane, of di-(*p*-aminophenyl)-sulfone and of di-(*p*-aminophenyl) ketone¹ led us to an investigation in the series of di-(*p*-aminophenyl)-acetic acid (II). Heller's² method, the condensation of dichloroacetic acid with aniline, gave no reliable results. The easily available diphenylacetic acid³ was, therefore, selected as starting material. Whilst the products of its direct nitration could neither be crystallized nor purified by vacuum distillation, the methyl ester gave a crystalline dinitro-derivative, if only in 23% yield.⁴ Formula (I) for the nitration product could be derived from the observation that, upon treatment with alkali, not only hydrolysis, but also decarboxylation took place, leading in quantitative yield to the known 4,4'-dinitrodiphenylmethane of m. p. 187°, which was oxidized to 4,4'-dinitrobenzophenone of the

same melting point.⁵ Hydrolysis of (I) could only be effected (in 95% yield) in acid medium, and both the free acid and the methyl ester (I) could be hydrogenated catalytically without difficulty. The 4,4'-diaminodiphenylacetic acid (II) (yield, 71%) had the melting point (204.5°) indicated by Heller²; its methyl ester was oily, but could be characterized by its dihydrochloride, its diacetyl derivative and by the hydrolysis to (II).



Experimental

Methyl 4,4'-Dinitrodiphenylacetate (I).—At a temperature of -15° , 20 g. of methyl diphenylacetate was slowly added to 130 cc. of fuming nitric acid, with vigorous stirring. The clear solution was poured onto crushed ice and the solid which separated triturated with water and sodium carbonate solution and finally with alcohol. From glacial acetic acid, one obtained transparent platelets of m. p. 162°; yield, 23%. *Anal.* Calcd. for C₁₅H₁₂O₆N₂: C, 56.9; H, 3.8. Found: C, 57.2; H, 3.5.

4,4'-Dinitrodiphenylmethane.—To a solution of 1.6 g. of (I) in 7 cc. of methanol, one added gradually a solution of 0.2 g. of sodium hydroxide in 7 cc. of water. The violet solution (aci-salt) was refluxed for two hours, whereupon the color disappeared and crystals separated which were filtered, washed with dilute hydrochloric acid and water and recrystallized from petroleum ether: m. p. 187°; yield, quantitative.⁶ Oxidation of 1 g. with 1.5 g. of chromic acid in boiling glacial acetic acid gave, after recrystallization from the same solvent, pure 4,4'-dinitrobenzophenone which was identified by mixed melting point with an authentic specimen.

Methyl 4,4'-Diaminodiphenylacetate.—When 4.7 g. of (I) in 100 cc. of ethyl acetate was shaken with hydrogen in presence of 0.5 g. of Raney nickel, the theoretical quantity of hydrogen was absorbed in two hours. The reaction product distilled without substantial decomposition at 252-258° under 1.5 mm. pressure; it was converted into its dihydrochloride by treatment of its ethereal solution with gaseous hydrogen chloride. The crude product which separated, was triturated with light petroleum ether and several times suspended in anhydrous methanol and brought to dryness. From alcohol, one obtained slight pinkish crystals of m. p. 245° (dec.). *Anal.* Calcd. for C₁₅H₁₈O₂N₂Cl₂: C, 54.7; H, 5.5. Found: C, 54.7; H, 5.8. **Diacetyl derivative.** The mixture of 1 g. of the oily diamino-ester and 5 cc. of acetic anhydride was refluxed

(1) R. Kuhn, *et al.*, *Ber.*, **75**, 711 (1942).

(2) Heller, *Ann.*, **375**, 261 (1910).

(3) "Organic Syntheses," Coll. Vol. I, 2nd Edition, New York, N. Y., 1944, p. 224.

(4) Werner (*Ber.*, **39**, 1290 (1906)) described the tetra-nitration of ethyl diphenylacetate.

(5) The facile decarboxylation of similar substances has been reported before: 2,4-dinitrophenylacetic acid (Radiszewski, *Ber.*, **3**, 648 (1870)); 5-bromo-2,4-dinitro-phenylacetic acid (Jackson and Robinson, *Am. Chem. J.*, **11**, 549 (1889)); 2,4,6-trinitrophenylacetic acid (Jackson and Phinney, *ibid.*, **21**, 430 (1899); *Ber.*, **28**, 3067 (1895)).

(6) Stadel, *Ber.*, **27**, 2110 (1894).