[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

α,β-DIAMINO CARBINOLS FROM α,β-DIAMINOBUTYROPHENONES

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Certain α,β-diamino ketones, ethyleneimine ketones, and their carbinol derivatives have been successfully synthesized in this laboratory, notably in the benzalacetophenone (1) and benzalacetone series (2). It therefore seemed of interest to attempt the preparation of similar compounds in the ethylideneacetophenone series, especially in view of certain structural similarities which some of these α,β-diamino compounds bear to compounds of known pharmacological value as histamine antagonists and antispasmodics.

Previous studies (3) have indicated that the reaction of Grignard reagents with α,β-diamino ketones may result in considerable cleavage of the aliphatic side chain to give compounds of lower molecular weights, and low yields of the desired tertiary carbinols. Certain organolithium reagents have been reported (4) to be less subject to steric effects than the corresponding Grignard reagent. Thus it seemed reasonable that phenyllithium might prove useful in the preparation of diphenyl substituted tertiary carbinols from the α,β-diaminobutyrophenones. The fact that the reaction of phenyllithium with these carbonyl compounds proceeds smoothly with good yields seems to indicate that the steric requirements of phenyllithium actually are less than those of the phenyl Grignard reagent since phenylmagnesium bromide gave only traces of the desired compound. The mechanism of the reaction of phenyllithium with aryl ketones has been investigated and discussed by Swain (5).

Secondary α,β-diamino carbinols were prepared in fair yield by reduction of the corresponding ketone with lithium aluminum hydride.

α,β-Bis(dimethylamino)butyrophenone and α,β-dimorpholinobutyrophenone were prepared in fair yields by the reaction of α,β-dibromobutyrophenone (6) (prepared by the method of Dufraisse and Demontvignier) with dimethylamine and morpholine respectively. The α,β-dipiperidinobutyrophenone used in these studies had been reported previously (7). It is interesting to note that these α,β-diaminobutyrophenones all possess a characteristic light yellow color which is also found in the analogous diaminobenzylacetophenones (1) but which is lacking in the colorless α,β-diaminobenzylacetones (2).

An ethyleneimine derivative was prepared in this series by the reaction of α,β-dibromobutyrophenone with cyclohexylamine. A solid derivative of the oily product was prepared by reaction of the ketone oil with phenyllithium to give the tertiary carbinol, 1-cyclohexyl-2-methyl-4,4-diphenyl-4-hydroxypropyleneimine.

In the case of the α,β-dimorpholino compounds and the ethyleneimine derivative, two isomeric products possessing different melting points were obtained. These are probably the two possible racemic mixtures resulting from the asym-

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metric centers at the *alpha* and *beta* carbon atoms. The dipiperidino and bisdimethylamino compounds were isolated in but a single form.

Although the reduction of the ketone to the secondary alcohol involves the formation of a third asymmetric center in these molecules, no evidences of a third racemic mixture were detected in the case of the dimorpholino compound; the bisdimethylamino and the dipiperidino secondary alcohols like their corresponding ketones were isolated in but one form. This phenomenon is probably due to steric factors which predominately restrict the approach of the reagent to but one side of the carbonyl grouping.

EXPERIMENTAL[2]

α,β-Diaminobutyrophenones. A mixture of 10.00 g. (0.0327 mole) of α,β-dibromobutyrophenone, 100 ml. of dry ether, and 50 ml. of ethanol was cooled to −5°. To this mixture, (0.1308 mole) of the secondary amine was added rapidly with stirring. The reaction mixture was stirred for several hours while the temperature was held at 0°. The precipitated amine hydrobromide was removed and the filtrate was evaporated to give light yellow crystals. The product was washed with water, dried, and recrystallized from ether and petroleum ether mixtures.

Reduction of α,β-diamino ketones with lithium aluminum hydride. To a mixture of 0.017 mole of lithium aluminum hydride and 20 ml. of dry ether was added dropwise 5.00 g. (0.0157 mole) of the mixed racemates of α,β-dimorpholinobutyrophenone (m.p. 96–102°) dissolved in ether. After all of the ketone had been added the mixture was heated at reflux temperature for one hour. The excess hydride was hydrolyzed with water. The supernatant ether layer after separating, washing, and drying was evaporated to give 4.00 g. of the crude product. Recrystallization from ether and petroleum ether mixtures gave two colorless crystalline products, (IIIA) and (IIIB).

The procedure used in the preparation of the dipiperidino carbinol (IV) from α,β-dipiperidinobutyrophenone was similar.

Reaction of α,β-diamino ketones with phenyllithium. A dry ether solution containing four equivalents (0.1712 mole) of phenyllithium was prepared according to the method of Gilman (8). To this solution was added 10.00 g. (0.0428 mole) of α,β-bis(dimethylamino)butyrophenone (II) in ether solution, and the reaction mixture was heated at reflux temperature for two hours. The mixture was hydrolyzed with ice and ammonium chloride. The ether solution was separated, washed, and dried over calcium sulfate.

Evaporation of the ether solution gave 12.00 g. of the crude product (VII). Recrystallization was from petroleum ether.

The procedure used in the preparation of the dipiperidino carbinol (VI) and the mixture of the racemates of the dimorpholino carbinol (VA) and (VB) from the corresponding diamino ketones was similar.

Preparation of 1-cyclohexyl-2-methyl-4,4-diphenyl-4-hydroxypropyleneimine (VIII). A mixture of 12.00 g. (0.1176 mole) of α,β-dibromobutyrophenone, and 35 ml. of dry ether was cooled to 15°. To this mixture was added rapidly with stirring 11.53 g. (0.1176 mole) of cyclohexylamine. The mixture was stirred for three hours at 15° and then was allowed to stand for one hour at room temperature. The precipitated cyclohexylamine hydrobromide was removed and the filtrate was evaporated to give 8.40 g. of a yellow oil which resisted all attempts at crystallization.

The ketone oil (0.0344 mole, assuming 100% purity) was dissolved in ether and added to 0.1376 mole of phenyllithium prepared by the method of Gilman (8). The mixture was

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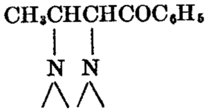
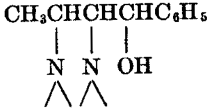
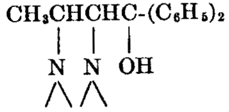
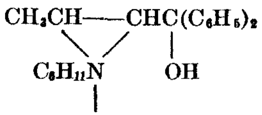
[2] Microanalyses for carbon, hydrogen, and nitrogen are by the Clark Microanalytical Laboratory, arranged for through the courtesy of the Smith, Kline, and French Laboratories, Philadelphia, Pa.

TABLE 1

Physical and Analytical Data

BUTYROPHENONE	NO.	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
					C		H		N	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
α,β-DIAMINO BUTYROPHENONES				 $\mathrm{CH_3}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\mathrm{COC_6H_5}$						
-Dimorpholino	(IA)	110–112	82	$C_{18}H_{26}N_2O_3$	67.90	68.24	8.23	8.10	—	—
	(IB)	96.5–97.5			67.90	67.79	8.23	8.28	—	—
-Bisdimethylamino	(II)	91.5–93.5	66	$C_{14}H_{22}N_2O$	71.75	71.70	9.46	9.17	11.96	11.97
DIAMINO SECONDARY ALCOHOLS				 $\mathrm{CH_3}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\underset{\substack{\vert\\ \mathrm{OH}}}{\mathrm{CH}}\mathrm{C_6H_5}$						
1-PHENYL-1-BUTANOL										
2,3-Dimorpholino	(IIIA)	105–107	80	$C_{18}H_{28}N_2O_3$	67.47	67.82	8.81	9.10	8.74	8.71
	(IIIB)	84–86			67.47	67.57	8.81	8.71	8.74	8.69
2,3-Dipiperidino	(IV)	78–79.5	85	$C_{20}H_{32}N_2O$	75.90	75.64	10.19	10.03	8.85	8.96
DIAMINO TERTIARY ALCOHOLS				 $\mathrm{CH_3}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\underset{\substack{\vert\\ \mathrm{N}\\ \wedge}}{\mathrm{CH}}\underset{\substack{\vert\\ \mathrm{OH}}}{\mathrm{C}}\text{-}\mathrm{(C_6H_5)_2}$						
1,1-DIPHENYL-1-BUTANOL										
2,3-Dimorpholino	(VA)	218–220	82	$C_{24}H_{32}N_2O_3$	72.69	73.03	8.13	8.13	7.07	6.94
	(VB)	168–180			72.69	72.43	8.13	8.07	—	—
2,3-Dipiperidino	(VI)	162.4–164	90	$C_{26}H_{36}N_2O$	79.54	79.30	9.24	9.02	7.14	7.36
2,3-Bisdimethylamino	(VII)	77.5–79.5	91	$C_{20}H_{28}N_2O$	76.88	76.62	9.03	9.01	8.97	8.85

1-CYCLOHEXYL-2-METHYL-4,4-DIPHENYL-4-HYDROXYPROPYLENE IMINE



$$\underset{C_6H_{11}N}{CH_3CH\text{---}CHC(C_6H_5)_2}\quad OH$$

	(VIIIA) (VIIIB)	114.5–116.5 85–87	79	$C_{22}H_{27}NO$	82.20 82.20	82.27 82.18	8.47 8.47	8.63 8.35	4.36 4.36	4.52 4.57

heated at reflux temperature for two hours. After hydrolysis with ice and ammonium chloride, the ether solution was separated, washed with water, and dried over calcium sulfate. Evaporation gave 9.90 g. (79% yield, calculated on the basis of the α,β-dibromobutyrophenone) of colorless crystals.

Fractional recrystallization from petroleum ether gave two fractions (VIIIA) and (VIIIB).

SUMMARY

1. Two new α,β-diamino derivatives of butyrophenone have been synthesized.
2. Several new diamino secondary alcohols were made by reduction of the carbonyl groups of the respective α,β-diamino ketones.
3. Three new diamino tertiary alcohols were synthesized by reacting the respective α,β-diamino ketones with phenyllithium.
4. Phenyllithium was found to give better yields of the tertiary carbinol than were obtained with phenylmagnesium bromide.
5. An ethyleneimine derivative of butyrophenone was synthesized.

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