[Contribution from the Avery Laboratory of the University of Nebraska]

DERIVATIVES OF α,β-DIAMINO KETONES

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Certain α,β-diamino ketones had been found to possess mild avian antimalarial activity.[1] It seemed possible that conversion of these α,β-diamino ketones to more soluble derivatives might increase the interest in them for various types of pharmacological screen testing. Previous investigations in this laboratory have indicated that the carbonyl group in the α,β-diamino ketones is not readily reduced to a secondary alcohol function[2] (1). Other studies have shown the addition of Grignard reagents to such ketones results in the formation of the tertiary alcohols in low yields (2, 3, 4). It has been postulated (3) that the low reactivity of the carbonyl group in the α,β-diamino ketones results from the steric effects of the *alpha* and *beta* amino groups. It thus seemed reasonable that the new and versatile reducing agent (5), lithium aluminum hydride, might be especially well suited for the reduction of these sterically hindered ketones. The fact that these compounds are readily reduced by this reagent indicates that the steric requirement of lithium aluminum hydride in such hydrogenations is considerably less than that of the surface active catalysts, and less than that of aluminum isopropoxide. The mechanism of such related hydrogenations has been investigated and discussed by Trevoy and Brown (6).

α,β-Bis-dimethylaminobenzylacetone was prepared in fair yield by the reaction of α,β-dibromobenzylacetone with dimethylamine. The other α,β-diamino ketones used in these studies were selected as representative types from the lists of such compounds which have been reported previously (7). The α,β-diamino alcohols which were prepared are described in Table I. In several cases two isomeric products, presumably different racemic mixtures, were isolated from these reaction mixtures. The benzoyl and acetyl derivatives of some of these alcohols are listed in Table II.

One of the diamino alcohols, 3,4-dimorpholino-4-phenyl-2-butanol (IA) was

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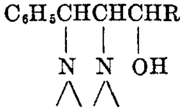
[1] For the antimalarial activities of the various amino ketones and derivatives that have been reported in the early papers in these series see, *A Survey of Antimalarial Drugs, 1941–1945*, Vol. I and II, F. Y. Wiselogle, editor, Edwards Brothers, Ann Arbor, Michigan, 1946.

[2] Many unsuccessful attempts have been made in this laboratory during the past eight years to reduce these α,β-diamino ketones to α,β-diamino secondary alcohols. α,β-Dimorpholinobenzylacetone could not be reduced using platinum oxide and 50 p.s.i. of hydrogen in absolute alcohol alone, or in an ethanol solution containing two molar equivalents of hydrogen chloride. Palladium on barium sulfate or on charcoal was not effective in reducing this compound, or α,β-ditetrahydroisoquinolinobenzylacetone, in absolute ethanol in the presence, or absence, of hydrogen chloride. α,β-Dimorpholinobenzylacetone was unchanged after shaking with hydrogen at 55° and 1500 p.s.i. in the presence of Raney nickel catalyst for four hours. This diamino ketone, as well as the related α,β-dimorpholinobenzylacetophenone, was unchanged by aluminum isopropoxide using the usual method to provide for the removal of acetone as it is formed during the reaction. Attempts to reduce these ketones with sodium and ethanol resulted in decomposition reactions.

chlorinated to yield 1-phenyl-1,2-dimorpholino-3-chlorobutane which reacted with morpholine to produce 1-phenyl-1,2,3-trimorpholinobutane. Another triamine, 1-phenyl-1,2-dimorpholino-3-aminobutane was obtained by reducing the oxime of α,β-dimorpholinobenzylacetone. The benzamide of this latter triamine was also prepared.

TABLE I

Physical and Analytical Data for Diamino Alcohols



$$\underset{\substack{|\\ N\\ \wedge}}{C_6H_5CH}\underset{\substack{|\\ N\\ \wedge}}{CH}\underset{\substack{|\\ OH}}{CH}R$$

	M.P., °C. YIELD, %				PERCENTAGE COMPOSITION					
					Carbon		Hydrogen		Nitrogen	
	No.			Formula	Calc'd	Found	Calc'd	Found	Calc'd	Found
4-Phenyl-2-butanol										
3,4-Dimorpholino	(IA)	173–175	99	$C_{18}H_{28}N_2O_3$	67.47	67.70	8.81	8.90	—	—
	(IB)	138–140				67.57		8.85		
3,4-Dipiperidino	(II)	90–93	84	$C_{20}H_{32}N_2O$	75.90	75.73	10.19	10.05	8.85	8.89
3,4-Bis-[dimethylamino]	(III)	50–52[a]	87	$C_{14}H_{24}N_2O$	71.14	71.15	10.24	9.95	11.86	11.90
3,4-Di-[p-methoxy-N-methylbenzylamino]	(IV)	oily product								
3-Morpholino-4-tetrahydroquinolino	(V)	130–131	81	$C_{23}H_{30}N_2O_2$	75.37	75.46	8.26	8.32	—	—
1,3-Diphenyl-1-propanol										
2,3-Dimorpholino	(VIA)	159–160	75	$C_{23}H_{30}N_2O_3$	72.22	72.25	7.91	7.62	7.33	7.28
	(VIB)	104–105								7.28
2-Morpholino-3-tetrahydroquinolino	(VIIA)	182–183	80	$C_{28}H_{32}N_2O_2$	78.47	78.77	7.53	7.74	—	—
	(VIIB)	163–164				78.39		7.23		

[a] B.p. 127–130° (0.20 mm.).

EXPERIMENTAL[3]

α,β-Bis-[dimethylamino]benzylacetone. A mixture of 153.0 g. (0.50 mole) of α,β-dibromobenzylacetone (8) and 800 ml. of dry ether was cooled to −12°. To this mixture was added, with rapid stirring, 100 g. (2.22 moles) of cold anhydrous dimethylamine. The reaction mixture was stirred for five hours while the temperature was held between −2 and −5°. The mixture was allowed to stand an additional 24 hours at 0°. The precipitated dimethylamine hydrobromide was removed and the filtrate washed with five 50-ml. portions of water. From the dried, concentrated solution was obtained a total of 53.2 g. (45.5% yield) of the desired

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

product, m.p. 97–99°. Recrystallization from 90% methanol gave a pale-yellow crystalline product, m.p. 98–99.5°.

Anal. Calc'd for $C_{14}H_{22}N_2O$: C, 71.75; H, 9.47; N, 11.96.

Found: C, 71.45; H, 9.49; N, 11.66.

Reduction of diamino ketones with lithium aluminum hydride. Three different procedures were used to reduce these various diamino ketones. The first of the following procedures was applied to the more soluble diamino ketones while the other two were used with the less soluble substances. See Table I. Procedures A and B are similar to those described by Nystrom and Brown (5) but more reaction time was required.

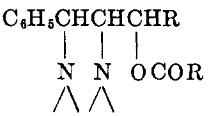
Procedure A. To a solution of 0.05 mole of lithium aluminum hydride in 250 ml. of dry ether was added slowly (five hours) with stirring a solution of 0.1 mole of the diamino ketone dissolved or suspended in 300 ml. of dry ether. The excess lithium aluminum hydride was hydrolyzed by the dropwise addition of water. The supernatant ether layer was separated, washed with water and dried over calcium sulfate.

The ether solutions were evaporated to give the crude products. In this way the diamino alcohol (II), recrystallized from methanol and water, was obtained from α,β-dipiperidinobenzylacetone (9). The diamino alcohol (III), which was readily purified by vacuum distillation, was prepared from α,β-bis-[dimethylamino]benzylacetone. The diamino alcohol (IV) was obtained from α,β-di-[*p*-methoxy-N-methylbenzylamino]benzylacetone (10), only as a crude oil which could neither be distilled nor induced to crystallize.

Procedure B. The slightly soluble diamino ketones (0.10 mole) were placed in the cup of a Soxhlet extraction apparatus and refluxed with 500 ml. of dry ether containing 0.10 mole of lithium aluminum hydride until all of the material had dissolved (16 to 30 hours). The products were isolated as in procedure A and purified by recrystallization from aqueous

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR DERIVATIVES OF THE DIAMINO ALCOHOLS



$$\begin{array}{l}C_6H_5CHCHCHR\\ \qquad\;\, |\quad\, |\quad\; |\\ \qquad\;\, N\quad N\quad OCOR\\ \qquad /\backslash\;\, /\backslash\end{array}$$

	M.P., °C.	YIELD, %	FORMULA	PERCENTAGE COMPOSITION					
				Carbon		Hydrogen		Nitrogen	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
BENZOATES OF:									
(IA)	167–169	80	$C_{26}H_{32}N_2O_4$	70.73	70.61	7.60	7.53	6.60	6.60
(IB)	148–150	75							6.48
(II)	119–120	60	$C_{27}H_{36}N_2O_2$	77.11	77.47	8.63	8.38	6.66	6.92
(III)	91–92	80	$C_{21}H_{28}N_2O_2$	74.08	73.80	8.29	8.15	8.23	8.15
(IV)	98–100	5	$C_{35}H_{40}N_2O_4$	—	—	—	—	5.07	5.12
(VIB)	153–155	50	$C_{30}H_{34}N_2O_4$	74.05	73.98	7.04	7.23	5.76	5.71
ACETATES OF:									
(IA)	142–143	81	$C_{20}H_{30}N_2O_4$	66.22	66.48	8.34	8.55	7.73	7.68
(IB)	101–102	60			66.16		8.17	—	—
(II)	75–76	90	$C_{22}H_{34}N_2O_2$	—	—	—	—	7.81	8.04
(III)	65–66	95	$C_{16}H_{26}N_2O_2$	69.03	68.83	9.42	9.11	10.07	10.10
(V)	158–160	80	$C_{25}H_{32}N_2O_3$	73.50	73.58	7.90	8.09	—	—
(VIB)	177–178	90	$C_{25}H_{32}N_2O_4$	70.73	70.58	7.60	7.82	6.60	6.54
(VIIA)	188–189	98	$C_{30}H_{34}N_2O_3$	76.56	76.24	7.28	7.15	—	—

ethanol. In this way the two racemic mixtures (VIA) and (VIB) were obtained from the high-melting isomer (m.p. 175°) of α,β-dimorpholinobenzylacetophenone (11). The diamino alcohol (V) was prepared from α-morpholino-β-tetrahydroquinolinobenzylacetone (12). The two racemic mixtures (VIIA) and (VIIB) resulted from the reduction of α-morpholino-β-tetrahydroquinolinobenzylacetophenone (13).

Procedure C. A solution of 0.1 mole of the diamino ketone in 500 ml. of dry benzene was mixed slowly with 300 ml. of dry ether containing 0.10 mole of lithium aluminum hydride and the mixture refluxed for five hours. Using this procedure the two racemates (IA) and (IB) were obtained by the reduction of α,β-dimorpholinobenzylacetone (4). The reaction mixture was worked up as decsribed in the above procedures. The racemates were obtained by fractional recrystallization from aqueous ethanol.

Derivatives of the diamino alcohols. The benzoates were prepared by reaction of the diamino alcohols with benzoyl chloride in pyridine solution. The acetates were prepared by reaction with acetic anhydride. Both types of derivatives were recrystallized from aqueous ethanol. See Table II.

1-Phenyl-1,2-dimorpholino-3-chlorobutane. Cooled solutions of 3.35 g. (0.0105 mole) of (IA) in 15 ml. of chloroform and 2.5 g. (0.021 mole) of thionyl chloride in 5 ml. of chlorofrom were mixed and refluxed for 30 minutes. The excess thionyl chloride and chloroform were removed under reduced pressure and the crude product suspended in a mixture of 0.9 gm. of sodium hydroxide, 25 ml. of water, and 150 ml. of ether. The ether layer was separated, washed with water, and dried. Evaporation of the solvent gave a red-colored residue which, after several recrystallizations from benzene and petroleum ether mixtures, gave a colorless product, m.p. 156–157°, wt. 1.10 g. (31% yield).

Anal. Calc'd for $C_{18}H_{27}ClN_2O_2$: C, 63.79; H, 8.03; N, 8.27.

Found: C, 63.89; H, 8.26; N, 8.08.

1-Phenyl-1,2,3-trimorpholinobutane. A 1.88-g. (0.005 mole) sample of the crude dihydrochloride of 1-phenyl-1,2-dimorpholino-3-chlorobutane was mixed with 1.30 g. (0.015 mole) of morpholine in 15 ml. of absolute ethanol. The reaction mixture was warmed for ten minutes on the steam-bath and allowed to stand at room temperature for one day. The solvent was removed under reduced pressure and the residue washed with water. The insoluble portion remaining was recrystallized twice from 95% ethanol to give 1.20 g. (61% yield) of a colorless product, m.p. 178–179°; when mixed with (IA), m.p. 151–160°.

Anal. Calc'd for $C_{22}H_{35}N_3O_3$: N, 10.79. Found: N, 11.08, 10.53.

α,β-Dimorpholinobenzylacetone oxime. A mixture of 9.55 g. (0.03 mole) of α,β-dimorpholinobenzylacetone (4), 4.20 g. (0.06 mole) of hydroxylamine hydrochloride, and 5.95 g. (0.06 mole) of potassium acetate in 100 ml. of 95% ethanol was warmed gently with stirring for 30 minutes and then allowed to stand at room temperature for two days. The precipitated material was removed, washed with water, and dried to give 5.40 g. of a colorless product, m. p. 164–166°. Evaporation of the residual reaction mixture gave 2.50 g. of product, m.p. 161–164°. These two crops were combined and recrystallized from 95% ethanol to give 6.30 g. (63% yield) of colorless crystals, m.p. 167–168°.

Anal. Calc'd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.61.

Found: C, 65.15; H, 8.42; N, 12.75.

1-Phenyl-1,2-dimorpholino-3-aminobutane. The above oxime was not changed by an attempted catalytic hydrogenation using palladium on charcoal and 50 p.s.i. Only the starting oxime was recovered from an attempted reduction using lithium aluminum hydride according to *Procedure B* as described above.

A 2.20-g. sample of the oxime was dissolved in 50 ml. of boiling absolute ethanol and 2.60 g. of sodium was added slowly to this solution, as small pieces, in 30 minutes. The reaction mixture was cooled to room temperature and 10 ml. of water added to destroy the sodium ethoxide. The solution was made acidic with 6 *N* hydrochloric acid and the solvents removed under a vacuum. The residue was treated with dilute sodium hydroxide. From the oily precipitate was obtained 0.45 g. (21%) of a colorless product, m.p. 139–140°, recrystallized from benzene and petroleum ether mixtures.

Anal. Calc'd for $C_{18}H_{29}N_3O_2$: N, 13.16. Found: N, 12.99.

Benzoylation of this product with benzoyl chloride in benzene solution using ordinary isolation techniques gave a 74% yield of a colorless product, m.p. 179–181°, recrystallized from absolute ethanol and from benzene and petroleum ether mixtures.

Anal. Calc'd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92.
Found: C, 71.13; H, 7.55; N, 10.03.

SUMMARY

α,β-Diamino ketones are readily reduced to the corresponding secondary alcohols by lithium aluminum hydride. One of these diamino alcohols was chlorinated to produce an α,β-diamino chloro compound, which was converted to the triamino product by reaction with an amine. A triamino compound was also produced by a sodium-alcohol reduction of an α,β-diamino ketone oxime. The acetyl and benzoyl derivatives of several of these products were prepared.

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