[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Amino Derivatives of 2,2-Diphenylcyclohexanone. I[1]

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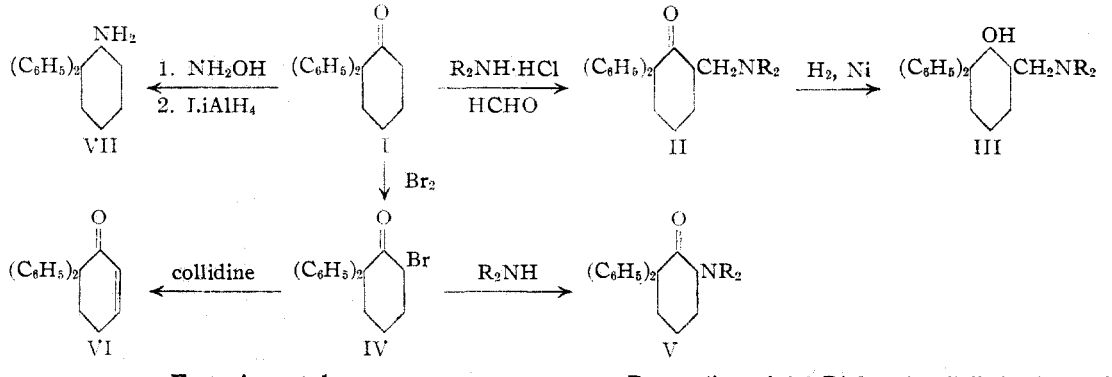
The purpose of this investigation was to synthesize compounds in which the keto group of the potent analgetic drug methadon is incorporated in a saturated ring. As examples of this type of structure we have prepared a number of amino substituted 2,2-diphenylcyclohexanone derivatives of types II and V. In addition, the amino alcohols III and the amine VII have been prepared for general pharmacodynamic screening tests.

Our starting material, 2,2-diphenylcyclohexanone (I), was prepared essentially according to the directions of Meerwein.[3] The β-amino ketones II were obtained smoothly by the Mannich reaction and could be hydrogenated uneventfully to the amino alcohols III. The α-amino ketones V were synthesized by treating the readily available bromo ketone IV with secondary amines. When 2,2-diphenyl-6-bromocyclohexanone (IV) was heated with collidine, hydrogen bromide was eliminated and 2,2-diphenylcyclohexen-5-one-1 (VI) was formed.

Reduction of 2,2-diphenylcyclohexanone oxime with lithium aluminum hydride furnished 2,2-diphenylcyclohexylamine (VII) in good yield. In view of the ease of this reduction, and of the hydrogenation of the β-amino ketones II to the amino alcohols III, we attempted to hydrogenate the α-amino ketones V to the corresponding amino alcohols. These experiments were unsuccessful, and we tried therefore to reduce the bromo ketone IV to a bromohydrin by the Ponndorff–Meerwein–Verley method. However, this step could not be accomplished, either.



Experimental

2,2-Diphenylcyclohexanone (I) was prepared by an adaptation of the procedure of Meerwein.[3] To an efficiently stirred mixture of 1395 g. of cyclopentanone and a solution of 980 g. of sodium cyanide in 3750 cc. of water was added over a period of 40 minutes a solution of 2000 g. of sodium bisulfite in 2700 cc. of water. The temperature was maintained below 30° by periodical addition of ice. The solution was filtered, the layers were separated, the aqueous layer was extracted with ether, and the latter evaporated. The crude cyanohydrin was refluxed with 7.5 l. of 37% hydrochloric acid for one hour, and the solution evaporated. The yield of 1-hydroxycyclopentanecarboxylic acid was 1306 g. (60%).

The ester, obtained from the acid and methanol in the presence of concentrated sulfuric acid in a yield of 77%, reacted with a twofold excess of phenylmagnesium bromide to give yields of 80 to 91% of diphenyl-(1-hydroxy-1-cyclopentyl)-carbinol. We were unable to get good yields of 2,2-diphenylcyclohexanone from the pinacol rearrangement with sulfuric acid as described by Meerwein, but found[4] that refluxing 50 g. of the pinacol in 350 cc. of glacial acetic acid containing 0.3 g. of iodine for thirty minutes, cooling, and pouring onto ice led to a yield of 98% of a product melting at 96.5–99°. Recrystallization from ethanol gave 39.5 g. (85%) of colorless prisms, m. p. 98.5–99.5°.

Preparation of 2,2-Diphenyl-6-dialkylaminomethylcyclohexanones (II).—These compounds were prepared by dissolving 0.12 mole of the secondary amine hydrochloride and 0.1 mole of 2,2-diphenylcyclohexanone in isoamyl alcohol, heating to reflux, adding a fivefold excess of paraformaldehyde portionwise over a ten-minute period, and refluxing for fifteen minutes further. After cooling, the *p*H was adjusted to below 3, if necessary, by addition of methanolic hydrogen chloride, ether was added to precipitate the salts, which were filtered and dissolved in water. The aqueous solution was made alkaline with sodium carbonate, the amine extracted with ether, the dried extract evaporated, and the product recrystallized from isoöctane. Characteristics of the products are listed in Table I. Since it was difficult to recrystallize the hydrochlorides to a constant melting point, and one of the salts was observed to decompose somewhat on standing, analyses are reported generally for the free bases.

Preparation of 2,2-Diphenyl-6-dialkylaminomethylcyclohexanols (III).—The hydrochlorides of the 2,2-diphenyl-6-dialkylaminomethylcyclohexanones (II) were hydrogenated in ethanol solution at atmospheric pressure with Adams platinum catalyst, the time varying from two to six hours. The resulting hydrochlorides were dissolved in water, the free amino alcohols precipitated by adding

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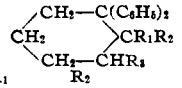
(3) Meerwein and Unkel, *Ann.*, **376**, 156 (1910); Meerwein, *ibid.*, **396**, 231 (1913).

(4) *Cf.* Bachmann, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 73.

TABLE I

DERIVATIVES OF 2,2-DIPHENYLCYCLOHEXANONE[a]



No.	R_1	R_2	R_3[c]	Solv. of recrystn.	Yield, %	M. p., °C. (cor.)	Molecular composition: Formula	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]
II	=O		$CH_2N(CH_3)_2$[d]	Isoöctane	30	108.5–109.5	$C_{21}H_{25}NO$	82.04	82.18	8.20	8.18
III	H	OH	$CH_2N(CH_3)_2$	Isoöctane	90	108.5–109.5[e]	$C_{21}H_{27}NO$	81.51	81.35	8.80	8.80
II	=O		$CH_2NC_4H_8O\cdot HCl$[f]	Ethanol	22	163	$C_{23}H_{28}ClNO_2$	71.58	71.78	7.31	7.54
III	H	OH	$CH_2NC_4H_8O$	Benzene–isoöctane	100	151.5–152	$C_{23}H_{29}NO_2$	78.59	78.68	8.32	8.16
II	=O		$CH_2NC_5H_{10}$	Isoöctane	29	108.5	$C_{24}H_{29}NO$	82.95	82.92	8.41	8.47
III	H	OH	$CH_2NC_5H_{10}$	Isoöctane	70	115.5–116	$C_{24}H_{31}NO$	82.47	82.49	8.94	8.75
IV	=O		Br	Benzene–ligroin	95	117–117.5[g]	$C_{18}H_{17}BrO$	65.66	65.69	5.21	5.39
V	=O		NC_4H_8O[h]	Ligroin	90	127.5–128	$C_{22}H_{25}NO_2$	78.77	78.98	7.51	7.71
V	=O		NC_5H_{10}[i]	Ligroin	55	124.5–125[j]	$C_{23}H_{27}NO$	82.84	83.12	8.16	7.63
	=NOH		H	Ethanol	97	208.5[k]	$C_{18}H_{19}NO$	81.47	81.75	7.22	7 27
VII	H	NH_2	H	Isoöctane	80	92–92.5	$C_{18}H_{21}N$	N, 5.57	5.54		
	H	NHAc	H	Benzene–ligroin	72	164	$C_{20}H_{23}NO$	N, 4.78	4.94		

[a] All compounds appear as colorless crystals unless otherwise noted. [b] Most of the microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. [c] NC_4H_8O = morpholino-; NC_5H_{10} = piperidino-. [d] Hydrochloride, from methanol–acetone, m. p. 165.5°. [e] Mixture m. p. with 2,2-diphenyl-6-dimethylaminomethylcyclohexanone, 85–89°. [f] Free base, from isoöctane, m. p. 100–101°. [g] Pale gray crystals. [h] Hydrochloride, from ethanol, m. p. 239°. [i] Hydrochloride, from ethanol, m. p. 198°. [j] Buff crystals. [k] Hydrochloride, from ethanol, m. p. 266–269°.

sodium carbonate solution, extracted into ether, dried and worked up by recrystallization from isoöctane.

2,2-Diphenyl-6-bromocyclohexanone (IV).—Into a solution of 2.5 g. (0.01 mole) of 2,2-diphenylcyclohexanone in 25 cc. of carbon tetrachloride was dropped a solution of 1.6 g. (0.01 mole) of bromine in 8 cc. of carbon tetrachloride, decolorization occurring rapidly. The solution was washed, the solvent evaporated, and the product was recrystallized.

Preparation of 2,2-Diphenyl-6-dialkylaminocyclohexanones (V).—A dry toluene solution of 0.22 mole of the secondary amine and 0.1 mole of the bromo ketone IV was refluxed for 20 hours. The precipitated amine hydrobromide was filtered, and the solution washed with water until neutral. It was then extracted with four portions of 10% hydrochloric acid, the combined extracts were made alkaline with sodium carbonate solution and the crude product was extracted into ether. The residue from the dried ether extract was recrystallized.

2,2-Diphenylcyclohexanone Oxime.—A solution of 10 g. of 2,2-diphenylcyclohexanone and 10 g. of hydroxylamine hydrochloride in 100 cc. of pyridine was refluxed for two hours, poured into water, and the crystalline oxime was recrystallized.

2,2-Diphenylcyclohexylamine (VII).—A solution of 2 g. of 2,2-diphenylcyclohexanone oxime in 100 cc. of dry isopropyl ether and 30 cc. of ethyl ether was dropped into a well stirred suspension of 1 g. of lithium aluminum hydride in 50 cc. of the same solvent mixture over a period of 20 minutes. The mixture was then refluxed (55°) for an additional five hours and allowed to stand for forty hours. The complex was decomposed with water and then with 50 cc. of 10% hydrochloric acid, the ether layer was washed with 10% hydrochloric acid, and the combined acid portions were made strongly alkaline. The alkaline solution was extracted with ether, the extract dried over potassium carbonate, the ether was evaporated and the solid residue recrystallized. The **N-acetyl derivative** was prepared with acetic anhydride in pyridine.

2,2-Diphenylcyclohexen-5-one-1 (VI).—A solution of 13.2 g. of 2,2-diphenyl-6-bromocyclohexanone in 30 cc. of collidine was refluxed for about 20 hours until the calculated quantity of collidine hydrobromide had formed. The black mixture was poured into 500 cc. of dilute acetic acid and extracted with benzene. The tarry residue was treated with benzene and isoöctane, and 3 g. (30%) of colorless needles was isolated. They melted at 94.5–96° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.07; H, 6.49.

A dibromide, prepared in carbon tetrachloride solution, appeared as colorless crystals (from benzene), m. p. 175–176°.

Anal. Calcd. for $C_{18}H_{16}Br_2O$: C, 52.97; H, 3.95. Found: C, 53.12; H, 3.95.

Summary

A number of amino derivatives of 2,2-diphenylcyclohexanone and 2,2-diphenylcyclohexanol have been prepared for pharmacological screening tests.

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