[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

AMINES DERIVED FROM 3,3-DIPHENYL-2-BUTANONE AND 2,2-DIPHENYLCYCLOHEXANONE

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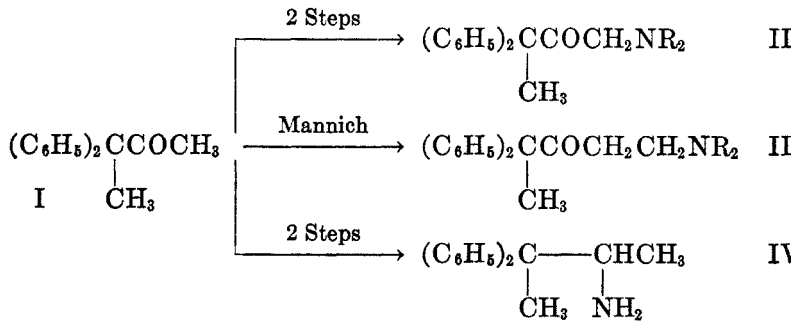
An important feature of the potent analgesic, methadon, seems to be the quaternary carbon atom to which are attached two phenyl groups, a carbonyl group, and a basic side chain. In order to determine whether arrangement of these essential groups in a different way around the quaternary carbon atom would still result in analgesic activity, the following derivatives of 3,3-diphenyl-2-butanone (I) (1) were prepared:



In Table I are listed the derivatives of types II and III which were prepared. In every case, however, the analgesic activity was of a low order.

A similar modification was employed in the preparation of analogous derivatives of 2,2-diphenylcyclohexanone (V) (2):

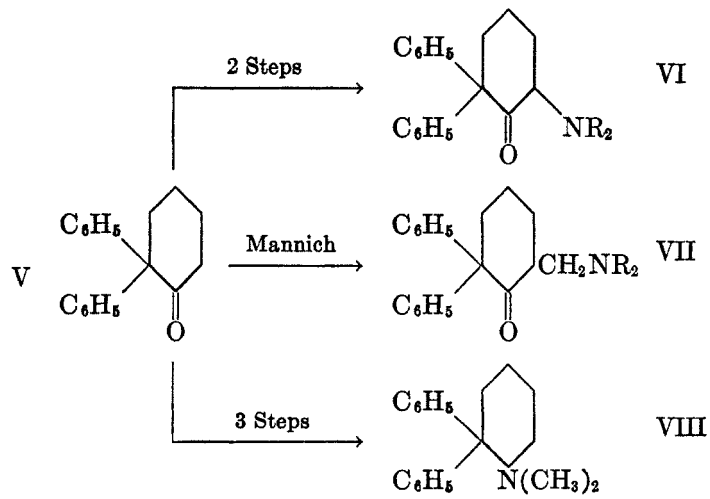


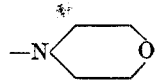
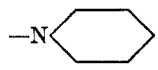
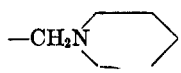
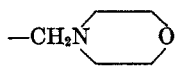
Table II lists the derivatives of types VI and VII which were prepared.[1] Here too, even though the basic residue is attached to the quaternary carbon atom through the cyclohexane ring, the analgesic activity in every case was of a low order. The cyclohexanone derivative VI ($-NR_2$ = piperidino) showed strong local anesthetic activity but proved to be too irritating for practical purposes.

The two amines IV and VIII were also prepared through the corresponding ketoximes. These likewise showed no interesting pharmacological properties.

TABLE I

1-DIALKYLAMINO-3,3-DIPHENYL-2-BUTANONES (II) AND 1-DIALKYLAMINO-4,4-DIPHENYL-3-PENTANONES (III)

$(C_6H_5)_2C(CH_3)COCH_2X$

X[a]	M.P.,[b] °C.	YIELD, %	FORMULA	ANALYSES, %					
				Calc'd			Found		
				C	H	N	C	H	N
$-N(CH_3)_2$	238–239	70[c]	$C_{18}H_{22}ClNO$	71.15	7.30	4.61	71.42	7.48	4.55
	219–221	75[c]	$C_{20}H_{24}ClNO_2$	69.45	6.99	4.05	69.67	6.88	3.81
	194–196	59[c]	$C_{21}H_{26}ClNO$	73.34	7.62	4.07	73.30	7.44	3.95
$-CH_2N(CH_3)_2$	170–171	33[d]	$C_{19}H_{24}ClNO$	71.83	7.61	4.41	71.56	7.56	4.41
$-CH_2N(C_2H_5)_2$	112–113	1[d]	$C_{21}H_{28}ClNO$	72.91	8.15	4.04	72.54	8.17	4.06
	188–189	36[d,e]	$C_{22}H_{28}ClNO$	73.85	7.88	3.91	73.68	7.70	4.01
	177–178	17[d]	$C_{21}H_{26}ClNO_2$	70.08	7.28	3.90	70.28	7.17	3.94

[a] All compounds reported as hydrochlorides. [b] Uncorrected. [c] Based on bromoketone. [d] Based on ketone. [e] Prepared in refluxing isoamyl alcohol.

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EXPERIMENTAL

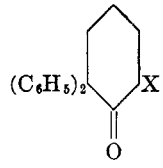
3,3-Diphenyl-2-butanone (I) was prepared according to the procedure outlined by Meerwein (1). Since experimental details are lacking in this case, the following procedure is

[1] Burger, Bennet, Turnbull, and Dinwiddie (Abstracts of Papers, A.C.S. Meeting, Philadelphia, April, 1950, p. 13K) have recently indicated the preparation of cyclohexanone derivatives of the identical type.

given. Fifty-six grams of 1,1-dimethyl-2,2-diphenylethylene glycol (1) was added with stirring to 300 cc. of concentrated sulfuric acid cooled in an ice-bath, keeping the temperature below 5°. After standing at room temperature for two hours the red solution was poured into ice-water and diluted to a volume of three liters. After refrigeration overnight, the yellow solidified product was filtered, taken up in ether, washed with bicarbonate solution,

TABLE II

6-DIALKYLAMINO- (VI) AND 6-DIALKYLAMINOMETHYL-2,2-DIPHENYLCYLOHEXANONES (VII):



X[a]	M.P.,[b] °C.	YIELD, %	FORMULA	ANALYSES, %					
				Calc'd			Found		
				C	H	N	C	H	N
—$N(C_2H_5)_2$[e]	186–187	1[c]	$C_{23}H_{32}ClNO_2$[f]	70.86	8.27	3.59	71.43	7.61	3.69
—N⟨⟩	200–201	68[c]	$C_{24}H_{32}ClNO_2$[f]	71.70	8.02	3.48	71.48	8.21	3.51
—N⟨⟩[h]	187–191	81[c]	$C_{23}H_{30}ClNO_2$[f]	71.20	7.79	3.61	71.10	7.56	3.89
—N⟨O⟩	238–239	78[c]	$C_{22}H_{26}ClNO_2$	71.04	7.04	3.76	71.14	6.87	3.76
—$CH_2N(CH_3)_2$[e,g]	165–166	27[d]	$C_{22}H_{30}ClNO_2$[f]	70.29	8.04	3.72	69.45	8.05	3.87
—$CH_2N(C_2H_5)_2$	158–159	31[d]	$C_{24}H_{34}ClNO_2$[f]	71.29	8.48	3.46	70.98	8.56	3.53
—CH_2N⟨⟩	229–230	30[d]	$C_{24}H_{30}ClNO$	75.07	7.87	3.64	75.07	7.91	3.70
—CH_2N⟨O⟩	173–174	8[d]	$C_{23}H_{28}ClNO_2$	71.57	7.31	3.63	71.78	7.37	3.66

[a,b,c,d] See corresponding footnotes for Table I. [e] Not obtained analytically pure. [f] Contains one molecule of methanol of crystallization. [g] Free base: needles from Skellysolve B, m.p. 106–107°. *Anal.* Calc'd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.09; H, 8.07; N, 4.59. [h] Free base: flat prisms from Skellysolve B, m.p. 111–113°. *Anal.* Calc'd for $C_{22}H_{25}NO$: C, 82.71; H, 7.87; N, 4.38. Found: C, 82.98; H, 7.76; N, 4.36.

and dried. After removal of the ether, the residue was distilled *in vacuo*. There was obtained 38 g. (73% yield) of ketone I, b.p. 101–103°/0.3 mm., m.p. 40–41°.

2,2-Diphenylcyclohexanone (V) was also prepared according to the method of Meerwein (2). Cyclopentanone was treated with anhydrous hydrogen cyanide and the resulting cyanohydrin hydrolyzed in an 85% over-all yield to 1-hydroxycyclopentanecarboxylic acid. Direct esterification with methanol gave the corresponding methyl ester in an 80% yield. Treatment of this hydroxy ester with excess phenylmagnesium bromide gave the corre-

sponding glycol in yields varying from 94 to 98% in three runs (Meerwein reported a 60% yield). However, the quantitative yield reported by Meerwein for the pinacol rearrangement of this glycol could be duplicated only when the sulfuric acid was diluted with ether according to the following procedure.

A solution of 77 g. of the glycol in 350 cc. of ether was added dropwise with stirring to 380 cc. of concentrated sulfuric acid, keeping the temperature below 5°. After standing for two hours at room temperature the solution was poured into ice and diluted to a volume of four liters. The product was filtered, washed well with water and pentane, and dried. There was obtained 71.5 g. (99% yield) of ketone V, m.p. 93–96°. One recrystallization from Skellysolve B gave large prisms, m.p. 97–99°.

3,3-Diphenyl-2-butanone oxime was prepared in the usual manner from ketone I in 87% yield, m.p. 149–151° (long flat prisms from methanol).

Anal. Calc'd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16.
Found: C, 80.70; H, 7.26.

1,1-Diphenyl-2-aminobutane (IV). Preliminary attempts to reduce the above oxime in ethanolic hydrogen chloride solution with 20% palladium-charcoal catalyst at low pressure failed. Hydrogenation was finally accomplished in ethanolic ammonia with Raney nickel catalyst (5 g. for 10 g. of oxime) activated with chloroplatinic acid, at 75° and 1000 pounds hydrogen pressure for eight hours. The product, obtained in only 40% yield, was isolated as the *hydrochloride*, m.p. 224–225° (from isopropanol).

Anal. Calc'd for $C_{16}H_{20}ClN$: C, 73.42; H, 7.78; N, 5.35.
Found: C, 72.95; H, 7.92; N, 5.36.

2,2-Diphenylcyclohexanone oxime could not be prepared in good yield by the usual dilute alkali procedure. However, refluxing 8.6 g. of ketone V with 8.6 g. of hydroxylamine hydrochloride in a solution of 43 cc. of pyridine in 43 cc. of dry ethanol gave, after removal of solvents and recrystallization from 95% ethanol, 7 g. (77% yield) of the oxime (long needles), m.p. 203–204°.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.23.

2,2-Diphenylcyclohexylamine. A solution of 7.4 g. of the above oxime in 100 cc. of dry methanol was treated with 5 cc. of liquid ammonia. Three grams of Raney nickel and 0.03 g. of chloroplatinic acid hexahydrate was added and the mixture was hydrogenated at 75° and 1400 pounds pressure for one hour. The product, isolated as the *hydrochloride*, weighed 6 g. (75% yield), m.p. 267–268° (from isopropanol-ether).

Anal. Calc'd for $C_{18}H_{22}ClN$: N, 4.86. Found: N, 4.94.

A sample was converted to the free *base*: colorless platelets from Skellysolve B, m.p. 91–92°.

Anal. Calc'd for $C_{18}H_{21}N$: C, 86.00; H, 8.42; N, 5.57.
Found: C, 86.17; H, 8.47; N, 5.40.

N,N-Dimethyl-2,2-diphenylcyclohexylamine (VIII). A solution of 1.4 g. of 2,2-diphenylcyclohexylamine (free base) in 7 cc. of 90% formic acid was refluxed with 0.33 g. of paraformaldehyde for four hours. Removal of the solvent *in vacuo* and isolation of the product as the *hydrochloride* gave 1.3 g., m.p. 231–235°. Recrystallization from ethanol-ether gave m.p. 235–236°.

Anal. Calc'd for $C_{20}H_{26}ClN$: C, 76.04; H, 8.29; N, 4.43.
Found: C, 75.86; H, 8.59; N, 4.16.

1-Bromo-3,3-diphenyl-2-butanone. To a solution of 22.4 g. (0.1 mole) of ketone I in 250 cc. of dry ether at 25° was added, dropwise with stirring over a period of 2½ hours, a solution of 16 g. of bromine in 125 cc. of chloroform. The temperature rose to 30° during the addition. The mixture was stirred for another hour and poured into ice-water. After washing to neutrality, the ether and chloroform were distilled and the residue was distilled *in vacuo*. There was obtained 26 g. (86% yield) of colorless product, b.p. 164–165°/0.8 mm., n_D^{25} 1.5980. This bromoketone could not be crystallized.

Anal. Calc'd for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99.
Found: C, 65.47; H, 5.36.

As indicated by the analytical results this bromo compound is not pure. However, it was used successfully without further purification.

6-Bromo-2,2-diphenylcyclohexanone. The bromination of cyclohexanone V was carried out in essentially the same manner as indicated above for the bromination of butanone I. From 20 g. of ketone V in 250 cc. of dry ether and 25 cc. of chloroform, treated with 12.8 g. of bromine in 100 cc. of chloroform, was obtained 26 g. (98% yield) of product, m.p. 112–115°. Recrystallization from Skellysolve B for analysis gave colorless, slender needles, m.p. 114–115°.

Anal. Calc'd for $C_{18}H_{17}BrO$: C, 65.69; H, 5.21.
Found: C, 65.89; H, 4.95.

Preparation of 1-dialkylamino-3,3-diphenyl-2-butanones (II). *Piperidino derivative.* A solution of 6.6 g. of 1-bromo-3,3-diphenyl-2-butanone in 60 cc. of dry ether was treated with 3.72 g. of piperidine. The precipitation of piperidine hydrobromide began almost at once and the mixture warmed perceptibly. After standing overnight at room temperature, the piperidine hydrobromide was filtered and washed with ether. The combined washings and filtrate were shaken with 60 cc. of 2 *N* sodium hydroxide and washed with four 60-cc. portions of water. The ether was then extracted with two 60-cc. portions of 10% hydrochloric acid. The combined acid extracts were made alkaline with excess sodium hydroxide. The precipitated oil was taken up in ether, washed, and dried over magnesium sulfate. Treatment of the filtered ether solution with ethereal hydrogen chloride precipitated 4.4 g. (59% yield) of *1-piperidino-3,3-diphenyl-2-butanone hydrochloride*, m.p. 194–196°. Recrystallization from isopropanol-ether did not raise the melting point. The dimethylamino and morpholino derivatives (Table I) were prepared in a similar manner.

Preparation of 6-dialkylamino-2,2-diphenylcyclohexanones (VI). *Morpholino derivative.* The bromine atom in the cyclohexanone derivative proved to be less reactive than that in the bromobutanone. Reactions with the secondary amines were carried out in refluxing toluene. A solution of 8.6 g. of 6-bromo-2,2-diphenylcyclohexanone in 30 cc. of dry toluene was refluxed and stirred with 6.5 g. of morpholine for five hours. The morpholine hydrobromide was filtered and the filtrate was worked up as described in the immediately preceding procedure. There was obtained 7.6 g. (78% yield) of product which on recrystallization from isopropanol gave 5.1 g. of fine needles, m.p. 238–239°. Further details on this compound and on other members of the same series are given in Table II. As can be seen, the yield of the diethylamino derivative was very low. The dimethylamino derivative could not be prepared even when the reaction was carried out under pressure in a closed system. The first three compounds in Table II were recrystallized from a methanol-ether mixture and contained one molecule of methanol of crystallization.

Preparation of 1-dialkylamino-4,4-diphenyl-3-pentanones (III). *Dimethylamino derivative.* A solution of 8.96 g. (0.04 mole) of 3,3-diphenyl-2-butanone (I) in 40 cc. of dry ethanol was refluxed for 12 hours with 16.4 g. of dimethylamine hydrochloride, 3.0 g. of paraformaldehyde, and 0.2 cc. of concentrated hydrochloric acid. The reaction mixture was treated with dilute hydrochloric acid and ether and separated. The acidic extract was made basic with 20% sodium hydroxide and the oil which separated was taken up in ether and washed with water to neutrality. Drying of the ether solution (magnesium sulfate) and treatment with ethereal hydrogen chloride gave 4.2 g. (33% yield) of colorless crystalline powder, m.p. 170–171° (rapid heating). Recrystallization from methanol-ether resulted in no change, although the rate of heating of the bath affected the melting point appreciably. Further details, as well as data on other compounds of this series, are given in Table I. The piperidino derivative could not be prepared in this manner, but a higher-boiling solvent, isoamyl alcohol, was necessary. The procedure used in this case was essentially that described below for the cyclohexanone derivatives.

Preparation of 6-dialkylaminomethyl-2,2-diphenylcyclohexanones (VII). *Dimethylamino derivative.* A mixture of 5 g. (0.02 mole) of 2,2-diphenylcyclohexanone, 2.4 g. of dimethylamine hydrochloride, 1.6 g. of paraformaldehyde, and 30 cc. of isoamyl alcohol was refluxed for ten minutes. Then a further 1.6 g. of paraformaldehyde was added in small portions over a

period of 30 minutes with continued refluxing. After addition was complete, 0.2 cc. of concentrated hydrochloric acid was added and refluxing was continued for another five minutes. The cooled solution was extracted with three 50-cc. portions of water. The combined aqueous extracts were made alkaline with 20% sodium hydroxide and the precipitated basic oil was converted to the *hydrochloride* in the usual manner. There was obtained 1.9 g. (27% yeild) of product, m.p. 161–166°, which on recrystallization from methanol-ether gave fine colorless needles, m.p. 165–166°, containing one molecule of methanol of crystallization. The last two compounds in Table II were recrystallized from isopropanol which did not appear in the product. The rate of heating of these Mannich compounds affected their melting points appreciably. The reported melting points were taken with rapid heating.

SUMMARY

A number of amines derived from 3,3-diphenyl-2-butanone and from 2,2-diphenylcyclohexanone have been prepared as possible analgesics related to methadon.

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REFERENCES

(1) MEERWEIN, *Ann.*, **396**, 259 (1913).
(2) MEERWEIN, *Ann.*, **376**, 156, 231 (1910).