present in such a large excess that essentially all the basic oxygens of the ethers were involved in hydrogen bonds. Nagakura and Baba[1] approached the equilibrium from the opposite direction, and found that with an inert solvent (carbon tetrachloride) it was necessary to attain a concentration 0.15 M in dioxane before all the phenol molecules (4.5×10^{-4} M) were complexed with the ether. It is probable that one has, in the case of dioxane, two equilibria, which can be shifted depending upon the relative concentrations of reactants.

$$\text{Phenol} + \text{dioxane} \rightleftarrows \text{1:1 complex}$$

$$\text{1:1 complex} + \text{phenol} \rightleftarrows \text{2:1 complex}$$

What is most significant from these results is that when phenol is bound in a complex with an ether, it is prevented from participating in the alkylation reaction. This means that the hydroxyl group plays an important role in the alkylation. This role is most likely the solvation of the halogen atom of the alkyl halide.

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EAST LANSING, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

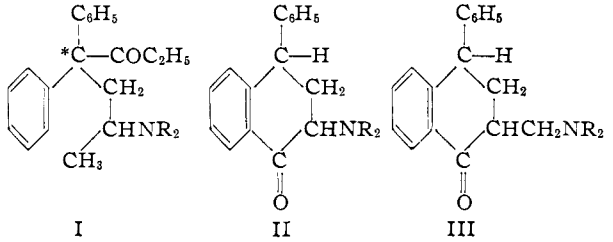
2-Substituted Amino- and Aminomethyl-4-phenyl-1-tetralones

BY STANLEY WAWZONEK AND JOHN KOZIKOWSKI[1,2]

RECEIVED OCTOBER 16, 1953

2-Dimethylamino-, 2-piperidino-, 2-morpholino-4-phenyl-1-tetralones and 2-dimethylaminomethyl-, 2-diethylaminomethyl- and 2-piperidinomethyl-4-phenyl-1-tetralone hydrochlorides have been prepared for testing as analgetics. The first group was made from 2-bromo-4-phenyl-1-tetralone while the second set was prepared by a Mannich reaction on 4-phenyl-1-tetralone with the appropriate amine hydrochloride.

Two series of compounds with the structural formulas II and III have been prepared in order to compare their pharmacological activity with that of the powerful analgetic, Methadon (I).



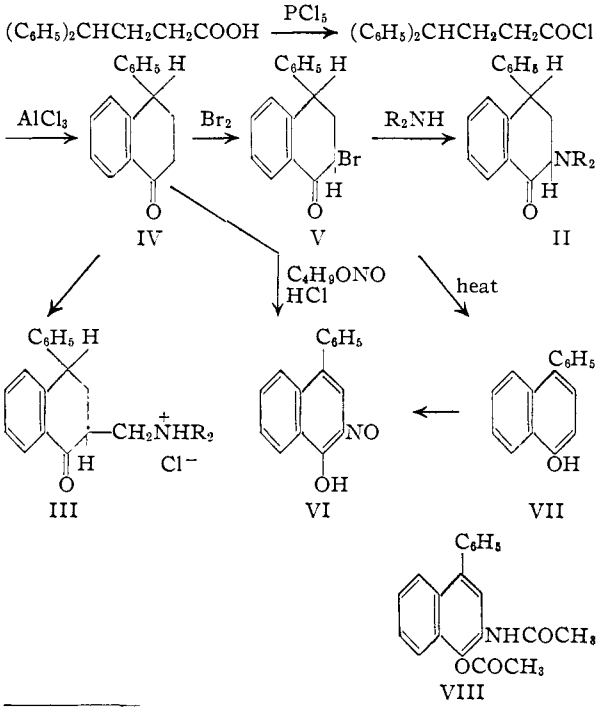
I II III

These compounds differ from Methadon in that that they do not have the quaternary carbon (C* in I) atom. One series has, however, three similar structural features; *viz.*, two phenyl groups and a dialkylaminoethyl grouping attached to carbon 4 in II. The ketonic group is not directly attached to carbon 4 but is separated by the vinyl group of the aromatic ring. The other series III has the dialkylamino group shifted from carbon 4 by an additional methylene group. These compounds were made in an effort to reduce toxic effects which the structure II might possess since it may be regarded as a substituted phenacylamine.

Both types of amines were synthesized from 4-phenyl-1-tetralone (IV) prepared from γ,γ-diphenylbutyric acid through the acid chloride.

Introduction of a substituted amino group on the ring was accomplished by bromination of the ketone and then treating the resulting 2-bromotetralone (V) with an excess of the secondary amines, dimethylamine, piperidine and morpholine.

Attempts to introduce a primary group by first forming the oximinoketone and then reducing could not be effected since butyl nitrite and hydrochloric acid gave solely 4-phenyl-2-nitroso-1-naphthol (VI). The structure of the latter compound was demonstrated by synthesis from the known 4-phenyl-1-naphthol (VII) prepared by cyclizing 4,4-diphenyl-3-butenoic acid.[3] This naphthol VII also could be obtained from the methiodide of 2-dimethylamino-4-phenyl-1-tetralone (II) and by the dehydrohalogenation of 2-bromo-4-phenyl-1-tetralone (V). Since the 4-phenyl-2-nitroso-1-naphthol (VI) melts with decomposition, the identity of the



(1) Abstracted in part from the Ph.D. thesis, August, 1953, of John Kozikowski.

(2) Ethyl Corporation Fellow, 1952–1953.

(3) W. S. Johnson and A. Goldman, THIS JOURNAL, **67**, 730 (1945).

two samples was established by obtaining the same reduction product, 4-phenyl-2-acetamido-1-naphthyl acetate (VIII), catalytically in acetic anhydride.

The Mannich reaction was used to prepare the 2-dimethylaminomethyl- (III) (R = CH_3), 2-diethylaminomethyl- (III) (R = C_2H_5) and 2-piperidinomethyl-4-phenyl-1-tetralone (III) (R_2 = $C_5H_{10}N$) hydrochlorides. In all these condensations bis-(1-keto-4-phenyl-2-naphthyl)-methane was obtained in varying amounts as a by-product.

Pharmacological results for the various compounds will be published elsewhere. Results for the hydrochlorides of 2-dimethylaminomethyl- (III) (R = CH_3) and the 2-diethylaminomethyltetralone (III) (R = C_2H_5) indicate analgetic activity at the toxic dose.[4]

Acknowledgment.—The authors wish to thank Dr. Edwin J. Fellows and Dr. Glenn E. Ullyot of Smith, Kline and French Laboratories for the pharmacological tests mentioned in this paper.

Experimental[5]

γ,γ-Diphenylbutyric Acid.—A mixture (144 g.) of diphenylvinylacetic acid and γ,γ-diphenylbutyrolactone[6] was dissolved in water (400 ml.) containing sodium hydroxide (24 g.) and the resulting solution hydrogenated in the presence of copper chromite catalyst at 1960 p.s.i. and 160° for 2 hours. Acidification of the solution gave an oily product which solidified on cooling. Crystallization from a mixture of benzene and petroleum ether (b.p. 60–100°) gave white crystals (123 g., 85%) melting at 103–106°. A sample mixed with one prepared from γ-phenylbutyrolactone[7] melted at the same point.

4-Phenyl-1-tetralone (IV).—γ,γ-Diphenylbutyric acid (191 g.) was added in small portions in the course of one hour to phosphorus pentachloride (181.5 g.) after initiation of the reaction by heating. Removal of the phosphorus oxychloride by codistillation with dry benzene (1300 ml.) under reduced pressure was followed by solution in dry thiophene-free benzene (1000 ml.) and addition of the resulting solution to a suspension of aluminum chloride (148 g.) in benzene (1.5 l.) at 10°. The resulting mixture was then kept at room temperature for 8 hours and decomposed with acid. Extraction of the benzene layer with alkali and removal of the solvent gave a residue which distilled at 130–150° (2–5 mm.); yield 163.5 g. (93%). The product solidified upon cooling and melted at 74–76°. Recrystallization from absolute ethanol gave colorless prisms melting at 75.5–76°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.48; H, 6.30. Found: C, 86.13; H, 6.14.

The 2,4-dinitrophenylhydrazone formed red-orange prisms from a mixture of ethyl acetate and ethyl alcohol melting at 221–223°.

Anal. Calcd. for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.69; H, 4.57; N, 13.80.

The semicarbazone formed a white amorphous solid from ethanol melting at 219–221°.

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.21; H, 6.11; N, 14.98. Found: C, 73.12; H, 6.16; N, 14.87.

2-Bromo-4-phenyl-1-tetralone (V).—To a solution of 4-phenyl-1-tetralone (IV) (163.5 g.) in dry carbon tetrachloride (1 l.) was added very slowly with stirring a solution of bromine (118.5 g.) in carbon tetrachloride (500 ml.) and the resulting solution stirred for one hour. Removal of the solvent under reduced pressure (20–30 mm.) gave a dark viscous residue which became crystalline upon trituration with *n*-butyl ether; yield 181 g. (82%). Crystallization from *n*-butyl ether gave a white waxy solid melting at 95–96.2°.

Anal. Calcd. for $C_{16}H_{13}BrO$: C, 63.80; H, 4.35. Found: C, 63.88; H, 4.19.

4-Phenyl-1-naphthol (VII).—2-Bromo-4-phenyl-1-tetralone (V) (10 g.) when heated for one hour at 210–230° liberated hydrogen bromide and gave a tarry residue. This product was dissolved in ether, washed with sodium bicarbonate solution and then distilled under reduced pressure (2–5 mm.). The resulting oil solidified when treated with petroleum ether (b.p. 40–75°). Recrystallization from a mixture of benzene and petroleum ether (b.p. 40–75°) gave 4-phenyl-1-naphthol (VII) (2.4 g., 32.7%), m.p. 138–139°. This sample did not depress the melting point of an authentic sample.[3]

2-Dimethylamino-4-phenyl-1-tetralone (II).—2-Bromo-4-phenyl-1-tetralone (V) (15 g.) at −50° was treated with anhydrous dimethylamine (25 g.) at −50°. The resulting mixture was allowed to come slowly to room temperature with stirring over a period of 12–18 hours. After the removal of excess dimethylamine under reduced pressure, the solid residue was extracted using a Soxhlet extractor under nitrogen with dry peroxide-free ether (150 ml.). In all the handlings of the compound air was excluded as much as possible to prevent the formation of a dark green product. The resulting ether solution when evaporated under reduced pressure and nitrogen gave yellow prisms mixed with a red brown oil. Washing with absolute ethanol followed by acetone gave a crystalline product giving a negative Beilstein test and melting at 103–133°; yield 10.5 g. (79.3%).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.09; H, 7.22; N, 5.28.

The dimethylamine hydrobromide remaining in the extractor thimble melted at 133° and weighed 6.2 g.

The hydrobromide of the aminotetralone, prepared by passing hydrogen bromide gas into an ether solution (200 ml.) of the amine (5.0 g.), was soluble in acetonitrile and could be precipitated by ether as reddish-orange prisms (2.7 g., 41%) melting at 205–208° dec.

Anal. Calcd. for $C_{18}H_{20}BrNO$: C, 62.43; H, 5.83; N, 4.04. Found: C, 62.01; H, 5.93; N, 4.43.

The methiodide formed by refluxing the amine (4.0 g.) with excess methyl iodide (25 ml.) for 12 hours was recrystallized from ethyl acetate, m.p. 172–174° dec.; yield 3.0 g. (49%). Further recrystallization from a mixture of acetonitrile and ether and then from acetone gave white platelets melting at the same point.

Anal. Calcd. for $C_{19}H_{22}INO$: C, 56.03; H, 5.45; N, 3.44. Found: C, 56.13; H, 5.83; N, 3.17.

The methiodide (1 g.) when heated with 5% sodium hydroxide (20 ml.) gave a strong amine smell. Removal of the solvent followed by heating at 210–220° for one hour gave a residue which was acidified and extracted with benzene. Removal of the solvent gave a very small amount of 4-phenyl-1-naphthol.

2-Morpholino-4-phenyl-1-tetralone.—This compound was prepared in a similar manner to that used for the dimethylaminotetralone with the exception that the bromoketone (V) (10 g.) was dissolved in ether (50 ml.) and mixed with morpholine (15 g.) at room temperature. Similar precautions were taken to exclude air in order to prevent the formation of green products. The yellow platelets (8.0 g., 78%) formed melted at 140–147° dec.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.05; H, 6.86; N, 4.42.

4-Phenyl-2-piperidino-1-tetralone.—This compound was prepared according to the directions given for the morpholino compound in a 67% yield and melted at 94–114°.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.35; H, 7.43; N, 4.28.

The wide melting point range observed with the aminotetralones is probably due to the presence of a mixture of diastereoisomers.

2-Nitroso-4-phenyl-1-naphthol (VI).—A mixture of 4-phenyl-1-naphthol (VII) (30 g.)[6] and fused zinc chloride (25 g.) in ethanol (30 ml.) was heated to boiling and treated with sodium nitrite (12.5 g.) dissolved in a minimum amount of water. The resulting mixture was heated at 100° for 3 hours and the zinc salt filtered after cooling. Decomposition of the salt with hydrochloric acid gave 2-nitroso-4-phenyl-1-naphthol (VI) which was purified by digestion

(4) "Medicinal Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 436.

(5) Melting points are not corrected.

(6) W. S. Johnson, J. W. Petersen and W. P. Schneider, THIS JOURNAL, **69**, 74 (1947).

(7) J. F. Eijkman, *Chem. Weekblad*, **1**, 421 (1904).

with 5% alcoholic potassium hydroxide (400 ml.) for 1-hour. The potassium salt formed was filtered and converted into the free naphthol with acid. Crystallization from ethanol gave golden yellow crystals (16.5 g., 49%) melting at 183–183.5° dec.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.04; H, 4.51; N, 5.29.

A solution of 4-phenyl-1-tetralone (IV) (3.0 g.) in ethanol (50 ml.) at 0° was treated successively with concentrated hydrochloric acid (1 ml.) and butyl nitrite (1.88 g.) in ethanol (25 ml.). The resulting solution was kept at 0° for one hour and then refluxed for 1.5 hours. Cooling of the resulting solution gave 2-nitroso-4-phenyl-1-naphthol (VI) (2.25 g.) (67%) melting at 182–3° dec.

2-Acetamido-4-phenyl-1-naphthyl Acetate (VIII).—2-Nitroso-4-phenyl-1-naphthol (VII) (2.5 g.) in acetic anhydride (150 ml.) was treated in the presence of platinum oxide (0.1 g.) with hydrogen at 40 p.s.i. at room temperature for five minutes. Removal of the solvent under reduced pressure gave 2-acetamido-4-phenyl-1-naphthyl acetate (VIII) (2.7 g.). One recrystallization from 75% acetic acid and one from benzene gave a white solid melting at 214°.

Anal. Calcd. for $C_{20}H_{17}O_3N$: C, 75.22; H, 5.37; N, 4.39. Found: C, 74.95; H, 5.30; N, 4.50.

2-Substituted aminomethyl-4-phenyl-1-tetralones (III).—4-Phenyl-1-tetralone (IV) (0.05 mole), paraformaldehyde (1.65 g.) and the amine hydrochloride (0.05 mole) were refluxed in absolute ethanol (20 ml.) under nitrogen for 5 hours and then poured into dilute hydrochloric acid. Extraction with ether gave a mixture of the unchanged tetralone and bis-(4-phenyl-1-keto-2-naphthyl)-methane. The latter after three crystallizations from ethyl acetate and one from a mixture of benzene and ethyl acetate melted at 213–215°. The amount isolated was 2 g. each for the dimethylamine and piperidine runs and 0.2 g. in the diethylamine preparation.

Anal. Calcd. for $C_{33}H_{28}O_2$: C, 86.84; H, 6.14. Found: C, 87.08; H, 6.30.

The hydrochloric acid solution was neutralized with sodium carbonate and extracted with ether. The ether extracted was dried and the amine hydrochloride formed with hydrogen chloride gas. The yields and physical properties for the various hydrochlorides are given in Table I.

TABLE I

2-SUBSTITUTED-AMINOMETHYL-4-PHENYL-1-TETRALONE HYDROCHLORIDES

$C_{16}H_{13}OCH_2NR_2 \cdot HCl$		R = CH_3[a]	R = C_2H_5[b]	R_2 = C_5H_{10}[a]
M.p., °C.		182–185 dec.	144–147 dec.	177[f] dec.
Yield, %		15[c]	42[d]	28[e]
Formula		$C_{19}H_{22}ONCl$	$C_{21}H_{26}ONCl$	$C_{22}H_{26}ONCl$
Analyses, %				
Carbon	Calcd.	72.26	73.36	74.26
	Found	72.24	73.43	74.32
Hydrogen	Calcd.	6.97	7.57	7.31
	Found	7.25	7.58	7.43

[a] Three recrystallizations from acetone–absolute ethanol. [b] Four recrystallizations from absolute ethanol. [c] Ketone covered, 3.4 g. [d] Ketone recovered, 4.0 g. [e] Ketone recovered, 4.0 g. [f] Solid formed upon decomposition disappeared at 232°.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

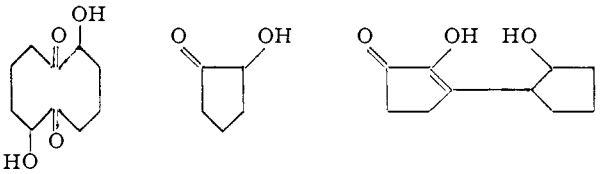
The Acyloin Reaction in the Closing of the Five-membered Ring[1]

BY MARTIN CORDON, JACK D. KNIGHT AND DONALD J. CRAM[2]

RECEIVED SEPTEMBER 4, 1953

The constitution of the major product of the acyloin reaction with dimethyl glutarate has been demonstrated to be either 3-(2'-hydroxycyclopentyl)-2-hydroxy-2-cyclopentenone (IIIA) or a tautomer. A number of reactions of the substance are described. Although analogous product could not be isolated from the acyloin reaction as applied to dimethyl pimelate, a condensation reaction between two molecules of 2-hydroxy-1-cycloheptanone occurred in the presence of base to give what is probably 2-(2'-hydroxycycloheptylidine)-7-hydroxycycloheptanone, or a tautomer.

As part of our study of the *trans*-annular electronic interactions in large rings[3] we desired to prepare as an intermediate 1,6-cyclodecandiol-2,7-dione (I). The low yield of 2-hydroxycyclopentanone (II) obtained from dimethyl glutarate under heterogeneous and high dilution conditions[4,5] coupled with the occasional isolation of dimeric cyclic acyloin[6] led to the hope that I could be obtained through the heterogeneous acyloin reaction with dimethyl glutarate under low dilution conditions. Although the isolation of neither I nor II was realized, a substance III whose properties are consistent with structure IIIA was isolated in about 40% yield from the reaction mixture.



I II IIIA

Compound III possesses the formula $C_{10}H_{14}O_3$, has weakly acidic properties, gives a deep purple color with ferric chloride, decolorizes bromine in carbon tetrachloride, and possesses infrared (see experimental) and ultraviolet absorption spectra (see Fig. 1) consistent with an α,β-unsaturated ketonic function. Furthermore, III consumes two moles of periodic acid, gives a negative acyloin test,[7] and forms derivatives that characterize the compound both as a diol (bis-*p*-nitrobenzoate and bis-*p*-toluenesulfonate) and a diketone (bis-oxime and bis-phenylhydrazone).

The chemical reactions that led to the structure of III are summarized in the formulations. Compound III absorbed hydrogen in the presence of palladium–on–charcoal to give IV if the reaction was interrupted after one mole of hydrogen was

(1) This work was supported in part by the Office of Naval Research.

(2) Requests for reprints should be addressed to this author.

(3) (a) D. J. Cram and H. Steinberg, THIS JOURNAL, **73**, 5691 (1951); (b) H. Steinberg and D. J. Cram, *ibid.*, **74**, 5388 (1952); (c) D. J. Cram and N. L. Allinger, *ibid.*, **76**, 726 (1954).

(4) (a) J. C. Sheehan, R. C. O'Neill and M. H. White, *ibid.*, **72**, 3376 (1950); (b) J. D. Knight and D. J. Cram, *ibid.*, **73**, 4136 (1951).

(5) Good yields of five-membered ring product have been obtained with a homogeneous acyloin reaction (sodium and liquid ammonia) by J. C. Sheehan, R. C. Coderre, L. A. Cohen and R. C. O'Neill, *ibid.*, **74**, 6155 (1952).

(6) (a) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 1822 (1947); (b) J. C. Sheehan and R. C. O'Neill, THIS JOURNAL, **72**, 4614 (1950).

(7) W. Rigby, *J. Chem. Soc.*, 794 (1951).