[CONTRIBUTION FROM ABBOTT LABORATORIES]

Analgesics Derived from Tetrahydroacenaphthones[1]

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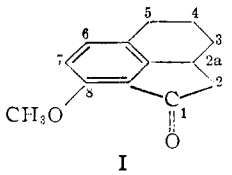
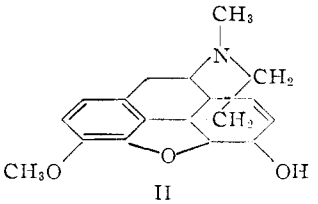
A series of Mannich derivatives of 8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1 (I) has been prepared from formaldehyde and the following amines: dimethylamine, piperidine (III), morpholine and pyrrolidine. One of the Mannich products (III) was reduced to the carbinol which in turn was acylated with propionic anhydride. The compound III when treated with phenylmagnesium bromide gave 1-phenyl-2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthylene as a result of carbinol dehydration.

As part of a systematic investigation of the analgesic properties of basic ketone derivatives, a series of Mannich products and derivatives of 8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1 (I) was prepared. The formal similarity between this ketone (I) and a portion of the codeine molecule (II) is apparent on comparison of the two structural formulas.

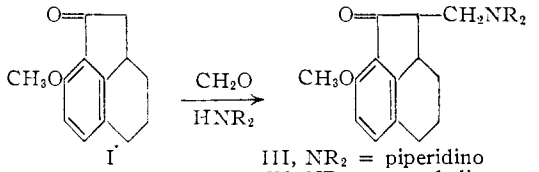


I



II

The parent ketone I was prepared by the method of Johnson and Glenn.[2] When treated with formaldehyde and certain secondary amines, I gave normal Mannich products III-VI, the physical constants of which are given in Table I.



III, NR_2 = piperidino
IV, NR_2 = morpholino
V, NR_2 = pyrrolidino
VI, NR_2 = dimethylamino

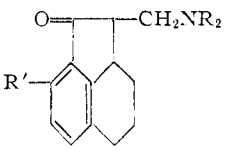
Two different procedures were used in the preparation of these compounds. When cyclic amines were used (procedure A), the best yields were obtained without solvent by stirring formalin, the ketone and the cyclic amine hydrochloride under nitrogen on a steam-bath. It was found advantageous to add a small amount of hydrochloric acid occasionally to keep the reaction acidic. This procedure is approximately the same as that given by Mosettig and May[3] for Mannich products of α-tetralone. When dimethylamine hydrochloride was used, the best yield was obtained by refluxing the amine hydrochloride, ketone, paraformaldehyde and a trace of hydrochloric acid in isoamyl alcohol (procedure B). Mannich products could not be isolated from the reactions with diethylamine, di-*n*-butylamine, 2-methylpiperidine or N-methylpiperazine.

Since 2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1 (III) possessed outstanding analgesic activity in dogs, the syntheses of several modifications of this structure were attempted. Interestingly enough, this compound could not be reduced catalytically with hydrogen; however, lithium aluminum hydride reduction gave the corresponding carbinol VIII which was acylated with propionic anhydride to the ester IX. Reaction of Compound III with phenylmagnesium bromide gave a colorless unstable carbinol hydrochloride which dehydrated on recrystallization to yellow 1-phenyl-2-piperidinomethyl-8-methoxytetrahydroacenaphthylene hydrochloride (X).

No attempt to change the length of the carbon

TABLE I

MANNICH PRODUCTS OF TETRAHYDROACENAPHTHONES



No.	Compound	Yield, %	Method	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	R′ = CH_3O NR_2 = piperidino	80	A	77–78 (90–91)	$C_{19}H_{25}NO_2$	76.22	76.40	8.42	8.36
III·HCl		33	B	160–161	$C_{19}H_{25}NO_2$·HCl	67.94	67.94	7.80	7.71
IV	R′ = CH_3O NR_2 = morpholino	59	A	135–135.5	$C_{18}H_{23}NO_3$	71.73	71.79	7.69	7.76
V	R′ = CH_3O NR_2 = pyrrolidino·HCl	29	A	158–160	$C_{18}H_{23}NO_2$·HCl	67.17	66.98	7.52	7.44
VI	R′ = CH_3O NR_2 = dimethylamino	44	B	87–88	$C_{16}H_{21}NO_2$	74.10	74.18	8.16	8.01
VII	R′ = H NR_2 = Piperidino HCl	47	B	164–165	$C_{18}H_{23}NO$·HCl	Calcd.: N, 4.58		Found: N, 4.57	

Also included in this Table is the piperidinomethyl derivative of tetrahydroacenaphthone-1 (VII).

(1) Presented before the Medicinal Division of the American Chemical Society, Chicago, Ill., September, 1953.

(2) W. S. Johnson and H. J. Glenn, THIS JOURNAL, **71**, 1087 (1949).

(3) E. Mosettig and E. L. May, *J. Org. Chem.*, **5**, 528 (1940).

chain in the 2-position of compound I was successful. Bromination of 8-methoxytetrahydroacenaphthone-1 gave an unstable bromo compound which when treated with piperidine gave a tar possibly due to dehydrohalogenation between the α-bromo atom and the very active 2a-hydrogen. Attempted alkylation of I with diethylaminoethyl chloride using various alkaline alkylating reagents such as sodamide always gave unstable O-alkylation products.

All of the compounds reported here were tested for analgesia by Dr. R. K. Richards, Kenneth Kueter, and their associates of these laboratories using a modified Wolff, Hardy and Goodell procedure in dogs. Compounds III, VI and VII possessed appreciable analgesic activity in dogs, III especially so. However, when tried clinically in humans, III was shown to possess only moderate activity.

Experimental[4,5,6]

8-Methoxy-2a,3,4,5-tetrahydroacenaphthone-1 (I).—This compound, m.p. 98–99°, was prepared by the method of Johnson and Glenn[2] in the approximate yields secured by them.

The oxime of 8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1, prepared in 96% yield from I in alcohol–pyridine solution, was recrystallized first from acetic acid–water (needles) and then from ethylene dichloride (colorless blades), m.p. 240–241.5° dec.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 72.01; H, 7.09.

8-Methoxy-2-piperidinomethyl-2a,3,4,5-tetrahydroacenaphthone-1 (III).—The preparation of this compound is given in detail to illustrate preparative methods A and B.

Method A.—A mixture of 4.04 g. (0.02 mole) of 8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1, 2.51 g. (0.0205 mole) of piperidine hydrochloride, 2.0 cc. of formalin solution and one drop of concentrated hydrochloric acid was heated on a steam-bath under a slow stream of nitrogen until the system liquefied. Mechanical stirring was started and the mixture was stirred and heated under nitrogen for a period of two hours during which time one drop of concentrated hydrochloric acid was added every 15 minutes and an additional 2.0 cc. of formalin solution was added after one hour. After cooling, 25 cc. of 5% hydrochloric acid was added with stirring and the resulting solution was extracted three times with ether to remove neutral contaminates. The aqueous acid solution was made strongly basic with 10% sodium hydroxide solution and the precipitated base was taken up in three ether extractions. After drying the ethereal extracts over anhydrous magnesium sulfate, the solvent was removed under diminished pressure and the resulting oil was dried at room temperature for several hours at 2 mm. pressure to constant weight during which time crystallization occurred. The yield of crude basic ketone was 4.84 g. (80.8%), m.p. 68–74°. Recrystallization from Skelly B gave fine pale yellow needles, m.p. 77–78°.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.40; H, 8.36.

From one run, an isomorphic form which melted at 90–91° was isolated. This had the correct analysis for the free base and gave the same hydrochloride.

The hydrochloride of 8-methoxy-2-piperidinomethyl-2a,3,4,5-tetrahydroacenaphthone-1 was formed when an ether solution of the free base was treated with ethereal hydrogen chloride. The salt melted at 160–161° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{19}H_{25}NO_2 \cdot HCl$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.94; H, 7.71; N, 4.26.

Occasionally when this salt was recrystallized from methanol–ether, it crystallized with one molecule of methanol of crystallization, m.p. 134.5–136°.

Anal. Calcd. for $C_{19}H_{25}NO_2 \cdot HCl \cdot CH_3OH$: C, 65.29; H, 8.22; N, 3.81. Found: C, 65.79; H, 7.88; N, 3.88.

Method B.—A solution of 4.04 g. (0.02 mole) of 8-methoxy-2a,3,4,5-tetrahydroacenaphthone-1, 2.5 g. (0.2005 mole) of piperidine hydrochloride, 0.90 g. (0.03 mole) of paraformaldehyde and 4 drops of concentrated hydrochloric acid in 30 cc. of isoamyl alcohol was refluxed vigorously for a period of 15 minutes. An additional 0.90 g. (0.03 mole) of paraformaldehyde was then added in small portions over a period of 30 minutes of continual refluxing. After cooling, the alcohol solution was made alkaline by shaking with a few cubic centimeters of 10% sodium hydroxide solution. The basic material was removed from the alcohol solution by thorough extraction with 10% hydrochloric acid. The acid solution was made alkaline with 10% sodium hydroxide solution and the free base was taken up in ether. After drying the ether solution over anhydrous magnesium sulfate and filtering, the hydrochloride was precipitated in the form of an oil with ethereal hydrogen chloride. This slowly crystallized to give 3.10 g. of crude hydrochloride which was recrystallized from methanol–ether to give 2.20 g. (32.8%) of colorless material, m.p. 160–161°.

1-Hydroxy-2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthene VIII.—A solution of 6.00 g. (0.020 mole) of 8-methoxy-2-piperidinomethyl-2a,3,4,5-tetrahydroacenaphthone-1 in 100 cc. of dry ether was added dropwise over a period of 30 minutes to a solution of 0.40 g. (0.0105 mole) of lithium aluminum hydride in 50 cc. of dry ether under a slow stream of dry nitrogen. This caused gentle refluxing. The addition funnel was rinsed with a further 50 cc. of dry ether. The mixture was stirred four hours under nitrogen at room temperature and then permitted to stand 16 hours at room temperature without stirring. The complex was decomposed by the cautious dropwise addition of 10 cc. of water with stirring under nitrogen, and the mixture was filtered. The lithium salts were washed well with ether. The combined ether solution was washed with water and then extracted well with 10% hydrochloric acid. The acid solution was made basic with 20% sodium hydroxide solution, the precipitated oil was taken up in ether, and the ether solution was washed with water and saturated brine and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed under vacuum without external heating and the residual light yellow viscous oil was dried to constant weight at 1 mm. pressure at room temperature. The yield was 5.50 g. (91%).

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03. Found: C, 75.53; H, 9.25.

1-Propionoxy-2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthene (IX).—A solution of 3.02 g. (0.01 mole) of 1-hydroxy-2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthene in 30 cc. of pyridine and 10 cc. of propionic anhydride was refluxed three hours. The solvents were distilled at water-pump pressure on a steam-bath to give a residual oil. After cooling, this was dissolved in 20% hydrochloric acid and the solution was extracted with ether to remove neutral contaminates. The acidic solution was then made basic with 20% sodium hydroxide solution and the precipitated oil was taken up in ether. The ether solution was clarified with Norit, dried over potassium carbonate, filtered and the solvent was removed under vacuum without external heating. The residual oil was then filtered through a sintered glass funnel and dried to constant weight at a pressure of 0.5 mm. at room temperature. The yield was 2.03 g. (57%) of a clear yellow viscous oil.

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found: C, 74.07; H, 8.63; N, 4.03.

1-Phenyl-2-piperidinomethyl-8-methoxy-2a,3,4,5-tetrahydroacenaphthylene Hydrochloride (X).—To a solution of phenylmagnesium bromide prepared from 0.30 g. (0.0125 mole) of magnesium and 1.65 g. (0.0105 mole) of bromobenzene in 20 cc. of dry ether was added dropwise with stirring at room temperature over a period of 15 minutes a solution of 2.99 g. (0.01 mole) of 8-methoxy-2-piperidinomethyl-2a,3,4,5-tetrahydroacenaphthone-1 in 15 cc. of dry ether. The yellow complex which formed at once was stirred an additional 30 minutes at room temperature and then refluxed one hour. After cooling, complex decomposition

(4) All melting points are uncorrected.

(5) H. J. Glenn and B. W. Horrom, U. S. Patent 2,589,934 (Mar. 18, 1952).

(6) All microanalyses by Mr. E. F. Shelberg and staff.

was effected by the dropwise addition with stirring of 25 cc. of saturated ammonium chloride solution. The ether layer was washed with water and dried over anhydrous magnesium sulfate. The addition of ethereal hydrogen chloride precipitated 3.50 g. of crude colorless hydrochloride. This was dissolved in methanol and dry ether was added just to faint turbidity. On cooling, 0.18 g. of solid separated which could not be identified. The further addition of several portions of ether, each followed by periods of cooling brought about the crystallization of 2.02 g. (51%) of the dehydrated product in the form of yellow round clumps, m.p. 172–174°.

Anal. Calcd. for $C_{25}H_{29}NO\cdot HCl$: C, 75.83; H, 7.64. Found: C, 75.41; H, 7.57.

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY][1]

The Oxidation of Di-*t*-butylpyrogallol by Oxygen in Alkaline Solution. II. Absorption Spectra of the Products

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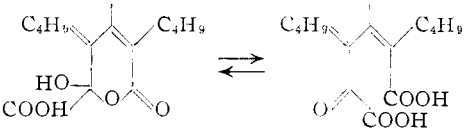
Ultraviolet and infrared absorption spectra are presented for four crystalline products of oxidation of di-*t*-butylpyrogallol by oxygen in alkaline solution and for six related products. The spectra are discussed in relation to the structures assigned to these compounds on the basis of chemical and spectroscopic data. The principal types of structures involved are substituted α-pyrones, cyclopentenedione and cyclopentanediones.

In an earlier paper[2] spectroscopic evidence was referred to in arriving at the probable structures of four crystalline compounds isolated as products of oxidation of di-*t*-butylpyrogallol in alkaline solution. Both the ultraviolet and infrared absorption spectra of these products and some of their derivatives are presented here for purposes of characterization and for discussion in relation to the structures assigned to them. The compounds are referred to here by the same Roman numerals as were used before.[2] Since proof of the proposed structures cannot now be made by reliable interpretation of the available absorption spectra, the discussion is limited to examination of the compatibility of the spectra with the assigned structures.

The ultraviolet absorption spectra were obtained on a Cary Model 11 Recording Spectrophotometer and the infrared spectra were recorded on a Beckman Model IR-3 Spectrophotometer with sodium chloride optics.

Compound IV.—Although the ultraviolet spectrum of compound IV (Fig. 1), a dibasic acid, resembles in general appearance that of simple carboxylic acids,[3] the molar absorption coefficient is of a higher order of magnitude. At 220 mμ, ϵ is about 10,000, suggesting[4] either diene conjugation or unsaturation α,β to either a keto or carboxyl group, the wave length of maximum absorption being depressed by substituent groups. The infrared spectrum of compound IV as a solid suspended in mineral oil (Fig. 6a) shows the bands in the 3.8μ region most characteristic of carboxylic acids[5] and shows a rather sharp band at 3320 cm.$^{-1}$ which is strong evidence for presence of an OH group not part of a carboxyl group.[5] Of the carbonyl band peaks at 1707 and 1734 cm.$^{-1}$, the former is due to the carboxyl group[5] and the latter is approximately that expected for a δ-lactone carbonyl group. Although apparently no examples of carbonyl frequencies of δ-lactones with α,β-unsaturation are available for comparison, a frequency of about 1720 cm.$^{-1}$ is predicted, on the assumption that the effect of conjugation is about the same as observed for aliphatic esters and γ-lactones.[6-8] The position of the remaining peak in the double bond region at 1629 cm.$^{-1}$ is typical of a carbon–carbon double bond conjugated to a carbonyl group.[6] Thus all of these most reliably interpreted features of the infrared spectrum of compound IV are in agreement with the assignment of the lactol structure IVa to the solid state with equilibrium in solution between the lactol structure and the keto–dibasic acid structure IV



IVa IV

In view of the similar environment of methyl groups in all *t*-butyl groups, one expects to find certain frequencies characteristic of *t*-butyl groups. An examination of the infrared spectra of a number of hydrocarbons containing *t*-butyl groups[9,10] showed that bands near 1470, 1395, 1365, 1260, 1200 and 920 cm.$^{-1}$ appear in the spectra of *t*-butyl compounds, those near 1365 and 1470 cm.$^{-1}$ being

(1) United States Department of Agriculture, Agricultural Research Administration, Bureau of Agricultural and Industrial Chemistry, Albany, California.

(2) T. W. Campbell, THIS JOURNAL, **73**, 4190 (1951); compare H. Schulze and W. Flaig, *Ann.*, **575**, 231 (1952).

(3) I. I. Rusoff, J. R. Platt, H. B. Klevens and G. O. Burr, THIS JOURNAL, **67**, 673 (1945).

(4) See *e.g.*, E. A. Braude, *Ann. Rept. Chem. Soc.*, 105 (1945).

(5) M. St. C. Flett, *J. Chem. Soc.*, 962 (1951).

(6) R. S. Rasmussen, *Fortschr. Chem. org. Naturstoffe*, **5**, 331 (1948).

(7) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

(8) J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(9) American Petroleum Institute Research Project 44, Carnegie Inst. of Technology, Catalog of Infrared Spectral Data: Serial No. 442, 2,2-Dimethylpropane, Shell Development Co., Emeryville, Calif.; serial no. 471, *t*-butylbenzene, U. S. Naval Research Lab., Washington, D. C.; serial no. 559, *t*-butylcyclohexane, Nat. Bur. Std., Radiometry Section, Washington, D. C.; serial no. 579, 2,2,5-trimethylhexane, U. S. Naval Research Lab., Washington, D. C.; serial no. 586, 3,3-dimethyl-1-butene, U. S. Naval Research Lab., Washington, D. C.; serial no. 808, 2,2-dimethylbutane, The Texas Co., Beacon, New York; serial no. 959, 3-*t*-butylthiophene, Socony Vacuum Laboratories, Paulsboro, New Jersey.

(10) N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950).