phere of carbon dioxide, and the solution filtered. It was then extracted several times with ether and the ethereal extracts evaporated: yield, 0.5 g. of 2,4-dinitro-6-amino-*m*-xylene; m. p. 191°.

The water solution remaining after the ether extraction was neutralized and a slight excess of sodium hydroxide added, the brick-red precipitate formed was filtered off, washed and recrystallized from hot water: yield, 2.1 g. of brick red, needle-shaped crystals of 2-nitro-4,6-diamino-*m*-xylene; m. p. 213°. The diamine is soluble in alcohol, ether, dioxane, dilute acid and hot water but insoluble in cold water. *Anal.* Calcd.: N, 19.0. Found: N, 18.7.

The white crystalline dihydrochloride was prepared in the same way as the monoamine hydrochloride. *Anal.* Calcd.: Cl, 27.9. Found: Cl (Parr method), 27.6.

One and three-tenths grams of unreduced 2,4,6-trinitro-*m*-xylene was recovered from the filter residue.

Reduction by Catalytic Hydrogenation.—Six and three-hundredths grams of 2,4,6-trinitro-*m*-xylene was dissolved in 120 cc. of dioxane and 13.5 g. of Raney nickel with 0.125 g. of platinic chloride promoter. Hydrogen was introduced at 1 atm. absolute pressure. The hydrogenation proceeded very slowly at room temperature but at 60–70° went smoothly. The addition of $6H_2$ required forty-five minutes at which point the reaction became much slower, requiring two hundred and twenty minutes for the absorption of the next $3H_2$. The solution at this point was faint yellow in color, but darkened somewhat on filtering off the nickel and became very dark brown on standing overnight.

The reduction was repeated at 90° and 3 atm. absolute pressure. At this temperature the reaction was slightly exothermic and required only forty-five minutes for the addition of $9H_2$. After filtering off the nickel the dioxane solution was cooled, and saturated with dry hydrogen chloride. The violet precipitate of 2,4,6-triamino-*m*-xylene hydrochloride was filtered off, washed with dioxane, then dry ether and dried; yield, 99%. *Anal.* Calcd.: N, 18.8. Found: N, 18.3; Cl, 32.0 (indicating 2HCl).

The authors wish to acknowledge the assistance given by Mr. Julian Reasenberg in carrying out the hydrogenation experiment.

Summary

2,4,6-Trinitro-*m*-xylene was reduced with (1) ammonium sulfide giving better yields of 2,6-dinitro-4-amino-*m*-xylene than previously reported; (2) titanous chloride yielding the monoamino and diamino compounds; (3) hydrogen and Raney nickel giving 99% of the theoretical yield of 2,4,6-triamino-*m*-xylene.

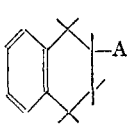
BROOKLYN, N. Y. RECEIVED FEBRUARY 25, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

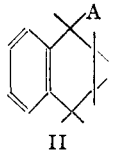
Substituted Tetrahydronaphthalenes. I. 1-Keto- and 1-Hydroxy-2-(*p*-dialkylaminobenzyl)-tetrahydronaphthalenes

BY R. L. SHRINER AND W. O. TEETERS

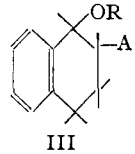
Tetrahydronaphthalene derivatives containing an hydroxyl and an amino group in the alicyclic portion represent a series of compounds containing one ring system and some of the functional groups present in morphine. A considerable number of basic tetrahydronaphthalene derivatives have been synthesized[1] and their pharmacological properties studied. About six different types of molecules, represented by formulas I–VI, have been prepared.



I

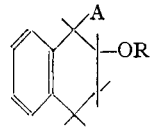


II

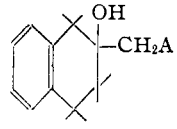


III

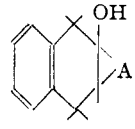
(1) (a) Bamberger and Müller, *Ber.*, **21B**, 1112 (1888); (b) Bamberger and Filehne, *ibid.*, **22B**, 777 (1889); (c) von Braun, Braunsdorf and Kirschbaum, *ibid.*, **55B**, 3648 (1922); (d) von Braun, Gruber and Kirschbaum, *ibid.*, **55B**, 3664 (1922); (e) von Braun and Weissbach, *ibid.*, **63B**, 3052 (1930); (f) Straus and Rohrbacher, *ibid.*, **54B**, 40 (1921); (g) Mosettig and Burger, THIS JOURNAL, **53**, 2295 (1931); (h) Gonzalez and Compoy, *Anales soc. espaň. fis. quim.*, **20**, 534 (1922).



IV



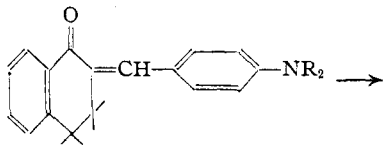
V



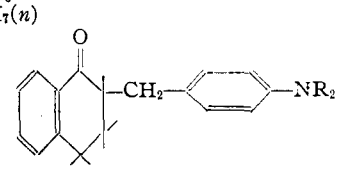
VI

Where A is amino, alkylamino, dialkylamino, piperidino; R is hydrogen, alkyl.

The pharmacological data reported are quite interesting since the compounds may exhibit local anesthetic, mydriatic, hypnotic or pressor action. However, none of them had the analgesic action of morphine. In the present work tetrahydronaphthalene derivatives corresponding to formulas VII and VIII were prepared. The condensation of α-tetralone with *p*-dimethyl-, *p*-diethyl- and *p*-di-*n*-propylaminobenzaldehyde produced the *p*-dialkylaminobenzal derivatives (VII) which were reduced catalytically with hydrogen and platinum to the corresponding benzyl compounds (VIII). The reduction stopped at this stage even though the benzyl ketones (VIII)

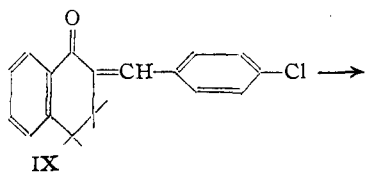


VII (a) R = CH_3
VII (b) R = C_2H_5
VII (c) R = $C_3H_7(n)$

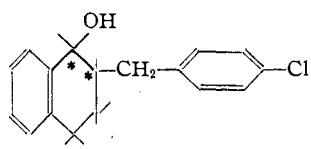


VIII (a) R = CH_3
VIII (b) R = C_2H_5
VIII (c) R = $C_3H_7(n)$

were isolated, purified and then treated with fresh platinum catalyst. This was somewhat surprising since in a preliminary study of the reduction of unsaturated ketones it was found that the *p*-chlorobenzal derivative of α-tetralone (IX)



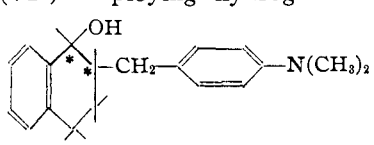
IX



X (α and β)

was reduced smoothly to the saturated carbinol (X) by means of platinum and hydrogen. This carbinol has two asymmetric carbon atoms (*) and hence may exist in two diastereoisomeric forms, both of which were obtained.

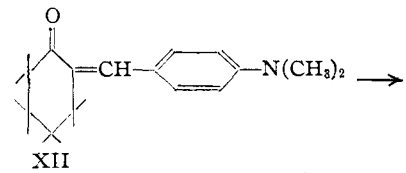
One amino alcohol (XI) was finally obtained by direct reduction of the corresponding unsaturated ketone (VII) employing hydrogen and Raney



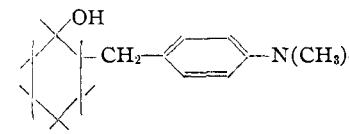
XI (α and β)

nickel as the catalyst. The two possible diastereoisomeric forms (*dl-cis* and *dl-trans*) were separated. Since there is no proof of the configuration, the two isomers were merely denoted as the α- and β-forms. Both forms yielded crystalline hydrochlorides and these water-soluble salts were used for the pharmacological tests.

In order to determine the effect of the tetrahydronaphthalene nucleus, two compounds were synthesized both of which contained the same side chain but in one the benzene nucleus was lacking while in the other the alicyclic ring was opened. The first compound was 2-(*p*-dimethylaminobenzyl)-cyclohexanol (XIII), obtained by the catalytic reduction of the unsaturated ketone (XII) which had been previously prepared by the

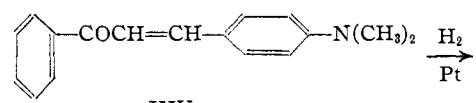


XII

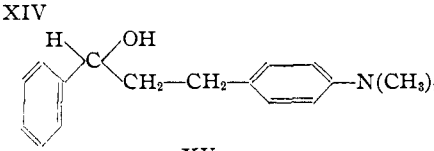


XIII

condensation of cyclohexanone with *p*-dimethylaminobenzaldehyde.[2] The other compound prepared for comparison purposes was 1-phenyl-3-(*p*-dimethylaminophenyl)-1-propanol (XV) which was obtained by the catalytic reduction of *p*-dimethylaminobenzalacetophenone (XIV).



XIV



XV

Pharmacological Tests.—Through the courtesy of the Lilly Research Laboratories the physiological action of the above compounds was determined. The benzal ketones (VII) and the benzyl ketones (VIII) did not produce stable hydrochlorides. They were tested as dry powders for surface anesthesia on the rabbit's eye and were found to produce such severe irritation that no definite action could be observed. A suspension of each of these ketones in mineral oil was given orally to mice and found to have no analgesic value. No toxic effects were noted in cats in doses as high as one gram per kilogram of body weight.

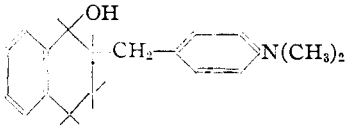
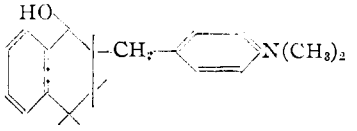
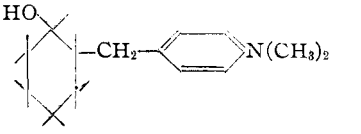
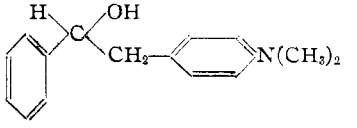
The hydrochlorides of the amino alcohols XI (α), XI (β), XIII and XV did not exhibit the characteristic analgesic effects of morphine in mice or guinea pigs. No vomiting was produced and they had no relaxing effect on the isolated small intestine of the rabbit. They did, however,

(2) Pfeiffer, *Ann.*, **441**, 228 (1925).

cause local anesthesia and the data obtained on 1% aqueous solutions of the hydrochlorides of these amino alcohols are shown in Table I.

TABLE I

PHARMACOLOGICAL DATA

Compound	Toxicity (mg./g. in mice)	Anesthesia (minutes) Guinea pig skin	Rabbit's eye
XI (α) 	110	35	None
XI (β) 	150	35	46
XIII 	160	73	45
XV 	80	35	25
Procaine	50	24	None
Cocaine	17	41	20

These data in Table I show several interesting relationships between structure and physiological action. It will be noted that the α-form of XI caused no anesthesia when applied to the rabbit's eye whereas the isomeric β-form did cause topical anesthesia. This represents another example of variation in pharmacological action with stereochemical configuration. In the present instance the β-form of XI was an oil and more soluble than the solid α-isomer. The difference in pharmacological action may be due to differences in either the degree or mode of oriented adsorption of the two compounds by the nerve fibers.

A second interesting point is the fact that whereas XIII is the least toxic and XV the most toxic, the tetrahydronaphthalenes XI (α and β) are intermediate in their toxicity.

In the third place, the alicyclic carbinol (XIII) is approximately twice as effective in producing both injection and topical anesthesia as the aryl carbinol (XV). All of the compounds were rather irritating and hence further modifications in structure will be necessary before they are of practical value.

Experimental

1-Keto-2-(*p*-dimethylaminobenzal)-tetrahydronaphthalene (VIIa).—A solution of 14.9 g. (0.1 mole) of *p*-dimethylaminobenzaldehyde in 80 cc. of ethanol was added to a well-stirred solution of 3.85 g. of sodium hydroxide in 105 cc. of water. To this suspension was added 14.6 g. of α-tetralone. The resulting solution was refluxed with stirring for three hours, during which time the condensation product separated. The mixture was cooled, the unsaturated ketone filtered and recrystallized from 95% ethanol. An 82% yield of yellow crystals melting[3] at 155.5–156.5° was obtained.

Anal. Calcd. for $C_{19}H_{19}ON$: N, 5.05. Found: N, 5.09.

The oxime was prepared as a derivative by refluxing equivalent amounts of the ketone and hydroxylamine in alcoholic sodium hydroxide solution. Yellow crystals melting at 207.5–208° were obtained.

Anal. Calcd. for $C_{19}H_{20}ON_2$: N, 9.59. Found: N, 9.64.

1-Keto-2-(*p*-diethylaminobenzal)-tetrahydronaphthalene (VIIb).—A 58% yield of this unsaturated ketone melting at 95–95.5° was obtained from *p*-diethylaminobenzaldehyde and α-tetralone by following exactly the procedure above.

Anal. Calcd. for $C_{21}H_{23}ON$: N, 4.59. Found: N, 4.73.

1-Keto-2-(*p*-di-*n*-propylaminobenzal)-tetrahydronaphthalene (VIIc).—The same procedure gave a 70% yield of this product provided the mixture was allowed to stand for several days so that crystallization was complete. It melted at 123–123.5°.

Anal. Calcd. for $C_{23}H_{27}ON$: N, 4.20. Found: N, 4.42.

2-*p*-Dimethylaminobenzal-1-cyclohexanone (XII).—The preparation of this compound has been reported previously by Pfeiffer and co-workers.[2] However, neither their method of synthesis nor the above general method of preparation was satisfactory for the present work. The most consistent results were obtained by using the following method. In a suitable flask 4 g. of potassium hydroxide was dissolved in 90 cc. of water and 20 g. of cyclohexanone and 10 g. of *p*-dimethylaminobenzaldehyde added. The mixture was refluxed for twenty-four hours, and the excess cyclohexanone removed by steam distillation. The solid product was filtered and extracted with hot 70% alcohol from which the condensation product recrystallized and melted at 127.0–127.5°. The yield was 8.5 g. of pure product (55.5% of the theoretical).

When the general method described for VIIa was followed the product was the 2,6-bis-(*p*-dimethylaminobenzal)-1-cyclohexanone melting at 248–249°, which checked the value reported by Pfeiffer.[2]

***p*-Dimethylaminobenzalacetophenone (XIV).**—A 92% yield of this ketone was obtained, melting at 113–114.5°, by following the directions of Rupe.[4]

Reduction of the Benzal Compounds to the Benzyl Compounds.—When a suspension of 0.025 mole of each of

(3) All melting points are corrected.

(4) Rupe, Collin and Schnuderer, *Helv. Chim. Acta*, **14**, 1340 (1931).

the unsaturated ketones VII (a), (b), and (c) in 150 cc. of warm alcohol was shaken with hydrogen in the presence of 0.1 g. of platinum oxide catalyst, hydrogen was gradually absorbed. The reduction stopped when one mole of hydrogen had been taken up. Most of the alcohol was removed by evaporation and the reduced product was recrystallized from that solvent. The yields in each case were above 90% of the theoretical. The reduced compounds are characterized in Table II in which the Roman numerals refer to the structures shown in the preceding general discussion.

TABLE II

1-KETO-2-(*p*-DIALKYLAMINOBENZYL)-TETRAHYDRONAPHTHALENES

No.	R	Molecular formula	M. p., °C.	Analyses, %N Calcd.	Found
VIII (a)	CH_3	$C_{19}H_{21}ON$	112–112.5	5.02	5.07
VIII (b)	C_2H_5	$C_{21}H_{25}ON$	57.5–58	4.56	4.68
VIII (c)	$C_3H_{11}(n)$	$C_{23}H_{29}ON$	65.5–66	4.18	4.24
VIII (a)	Oxime, CH_3	$C_{19}H_{22}ON_2$	166.5–167.5	9.52	9.60

1 - Hydroxy - 2 - (*p* - dimethylaminobenzyl) - tetrahydronaphthalene (XI α and β).—A sample of 7 g. of the unsaturated ketone (VIIa) was suspended in 200 cc. of warm alcohol and 0.5 g. of Raney nickel catalyst was added. The reduction was carried out at three atmospheres pressure and room temperature, and two moles of hydrogen was slowly absorbed over a period of ten hours. The solvent was evaporated and a red oil separated which finally solidified. The diastereoisomers of the secondary alcohol (XI) were separated by fractional crystallization from ligroin. The α-form crystallized in beautiful pink needles which melted at 100–100.5°.

Anal. Calcd. for $C_{19}H_{23}ON$: N, 4.98. Found: N, 4.95.

The β-form was an amber-colored viscous oil when distilled, and had the following boiling point: 195–198° at 2 mm. (bath 230°).

Anal. Calcd. for $C_{19}H_{23}ON$: N, 4.98. Found: N, 4.97.

Approximately 2 g. of the α-form and 2.5–3.0 g. of the β-form were obtained by this method of separation.

Each of the above free bases was dissolved in absolute ether and dry hydrogen chloride passed into the solution. The hydrochloride of the α-form was recrystallized from absolute alcohol. It formed colorless crystals which melted, with decomposition, at 175–176°.

Anal. Calcd. for $C_{19}H_{24}ONCl$: N, 4.41; Cl, 11.18. Found: N, 4.58; Cl, 11.25.

The hydrochloride of the β-form was an extremely hygroscopic white solid which could not be purified further.

2-(*p*-Dimethylaminobenzyl)-cyclohexanol (XIII).—The *p*-dimethylaminobenzal derivative of cyclohexanone was reduced in a 95% alcohol solution with platinum oxide as the catalyst. The calculated two moles of hydrogen was absorbed over a five-hour period. The solvent was removed and the amino alcohol distilled. The boiling point was 156–158° at 3 mm. (bath 200–205°).

Anal. Calcd. for $C_{15}H_{23}ON$: N, 5.96. Found: N, 6.12.

The hydrochloride of this amino alcohol was prepared by dissolving the free base in absolute ether and passing in dry hydrogen chloride. The crude hydrochloride was dissolved in absolute alcohol, and an equal volume of absolute ether added. The solution was placed in an ice box for twenty-four hours and beautiful colorless crystals of the hydrochloride separated. They melted, with decomposition, at 194–195.5°. No indication of the presence of diastereoisomers was observed.

Anal. Calcd. for $C_{15}H_{24}ONCl$: Cl, 13.17; N, 5.19. Found: Cl, 13.23; N, 5.22.

1-Phenyl-3-(*p*-dimethylaminophenyl)-1-propanol (XV).—A sample of 6.5 g. of *p*-dimethylaminobenzalacetophenone was dissolved in 100 cc. of warm 95% alcohol, 0.1 g. of platinum oxide added and the solution shaken with hydrogen at 3 atmospheres pressure. At the end of two hours, two moles of hydrogen had been absorbed. The mixture was filtered and the filtrate fractionated. The amino alcohol distilled at 182–188° at 3 mm.

Anal. Calcd. for $C_{17}H_{21}ON$: N, 5.48. Found: N, 5.50.

The hydrochloride of this amino alcohol was an oil which could not be solidified. A solution of the base in the calculated amount of hydrochloric acid was prepared and used for the pharmacological tests.

1 - Hydroxy - 2 - (*p* - chlorobenzyl) - tetrahydronaphthalene (X α and β).—A sample of 6.7 g. of 1-keto-2-(*p*-chlorobenzal)-tetrahydronaphthalene (prepared from *p*-chlorobenzaldehyde and α-tetralone) was dissolved in 100 cc. of 95% alcohol, 0.1 g. of platinum oxide catalyst added and the mixture shaken with hydrogen at 3 atmospheres pressure. Two moles of hydrogen was absorbed in five hours. The alcohol was removed by evaporation and the residue dissolved in 300 cc. of ligroin. The first fraction collected upon slow evaporation of the solvent weighed 3 g. and melted at 119–122°. The melting point of this α-form became constant at 124–124.5° after two more recrystallizations.

Anal. Calcd. for $C_{17}H_{17}OCl$: Cl, 13.03. Found: Cl, 13.07.

The second and third fractions, which weighed 3 g., were combined and fractionally crystallized from ligroin. After repeated crystallization the pure β-form which melted at 91–92° was obtained.

Anal. Calcd. for $C_{17}H_{17}OCl$: Cl, 13.03. Found: Cl, 13.17.

Summary

Condensation of α-tetralone with *p*-dialkylaminobenzaldehydes yielded a series of 1-keto-2-(*p* - dialkylaminobenzal) - tetrahydronaphthalenes which were reduced catalytically to the corresponding benzyl compounds. Two diastereoisomeric forms of 1-hydroxy-2-(*p*-dimethylaminobenzyl)-tetrahydronaphthalene were obtained by the catalytic reduction of 1-keto-2-(*p*-dimethylaminobenzal)tetrahydronaphthalene. The pharmacological action of these compounds has been compared with that of 2-(*p*-dimethylaminobenzyl)-cyclohexanol and that of 1-phenyl-3-(*p*-dimethylaminophenyl)-1-propanol.

URBANA, ILLINOIS RECEIVED FEBRUARY 1, 1938