same amount of Diaphene and soap was similarly treated, no significant change in absorbance or color took place.

On exposing a similar solution at pH 8 in a 1.00-cm. silica cell to short ultraviolet light (using a short-wave ultraviolet lamp, model SL 2537, with a short-wave ultraviolet filter, Model SL 2537[4]) a considerable decrease in absorbance took place in a period of 40 minutes after which a gradual change occurred through a total period of three hours. When a pH 3 solution was exposed to the short ultraviolet light, no significant change in absorbance took place in the same period of time.

A long-wave ultraviolet lamp, model SL 3660, with a long-wave ultraviolet filter, model SL 3660[4], was used to determine the effect of long ultraviolet light on Diaphene solutions of pH 8 and pH 3. Absorbances were determined in the same manner (using 90% methanol at pH 8 and pH 3, respectively, in the solvent cell). It was found that long ultraviolet light had more or less the same effect as sunlight on both solutions of Diaphene. No apparent color change took place in either solution after exposure to short or long ultraviolet light, as observed in the 1.0-cm. silica cell. It could be recommended that Diaphene containing preparations that are alkaline should be protected from sunlight as well as ultraviolet light.

DISCUSSION

The spectrophotometric method proposed by Childs and Parks (5) for assaying hexachlorophene in the presence of soap when used for Diaphene gave results that were lower than expected. When liquid soap bases were employed in constructing the standard curve, results were found to be more accurate.

The proposed method eliminates the necessity of the establishment of a standard graph. The method also does not necessitate the presence of the same soap sample free from Diaphene. The proposed spectrophotometric assay for Diaphene was used for assaying liquid soaps and hand creams with accuracy.

[4] Mineralight, marketed by Fisher Scientific Co.

SUMMARY

A rapid, convenient, and accurate differential method for the assay of Diaphene in liquid soaps and hand creams has been proposed. The method is based on the differential spectrophotometric assay for hexachlorophene in liquid soaps developed by Childs and Parks (5).

This proposed method does not necessitate the establishment of a standard graph as was necessary in the Childs and Parks procedure. The method also does not require the same soap base free from Diaphene.

The optical density of Diaphene in solutions at pH 8 is reduced by sunlight and ultraviolet light.

REFERENCES

(1) Gottlieb, S., and Marsh, P. B., *Ind. Eng. Chem., Anal. Ed.*, **18**, 16(1946).
(2) Ettinger, M. B., Ruchoft, C. C., and Liska, R. J., *Anal. Chem.*, **23**, 1783(1951).
(3) Johnson, C. A., and Savidge, R. A., *J. Pharm. Pharmacol.*, **10**, 171(1958).
(4) Larson, H. L., *J. Am. Chemists' Soc.*, **28**, 301(1951).
(5) Childs, R. F., and Parks, L. M., THIS JOURNAL, **45**, 313(1956).
(6) Lord, J. W., McAdam, J. A., and Jones, E. B., *Soap, Perfumery Cosmetics*, **26**, 783(1953).
(7) Clements, J. E., and Newburger, S. H., *J. Assoc. Offic. Agr. Chemists*, **37**, 190(1954).
(8) Matuszak, J. B., Bope, F. W., and Harris, L. E., *Drug Std.*, **28**, 68(1960).
(9) Van Der Pol, H. J., *Pharm. Weekblad*, **20**, 881(1958).
(10) Suffis, R., and Dean, D. E., *Proc. Sci. Sect. Toilet Goods Assoc.*, **30**, 13(1958).
(11) Private communication, Dr. H. C. Stecker, Stecker Chemicals, Inc., Ridgeway, N. J.

Use of 3-Azabicyclo[3.2.2]nonane in the Mannich Reaction II. Secondary γ-Amino Alcohols

By C. DEWITT BLANTON, Jr., and W. LEWIS NOBLES

The syntheses of a group of secondary γ-amino alcohols by reduction of the corresponding Mannich base with sodium borohydride are described. These alcohols are to be screened for possible pharmacodynamic activity.

IN THE FIRST paper of this series (1), a number of substituted β-amino ketones were synthesized for pharmacological evaluation employing the Mannich reaction and 3-azabicyclo[3.2.2]-nonane as the amine moiety. Previously, Denton (2) and his associates had similarly prepared certain amino ketones and converted them to the corresponding secondary and tertiary alcohols. In many cases, the conversion to the alcohol had a significant effect on the physiological activity. Therefore, it was considered that the transformation of the ketones previously reported by us (1), might possibly have a similar effect. In

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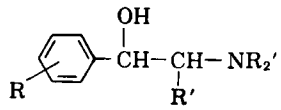
addition, the γ-amino alcohols are generally more stable than the corresponding ketones.

An examination of the ring system utilized in these studies will indicate a relationship to the complex heterocyclic systems which occur in certain natural products, such as cocaine and atropine. Thus, in every instance, caged structures are present in the molecule. Furthermore, it may be noted that the ring systems in cocaine may be regarded as a condensed piperidine-pyrollidine nucleus whereas the present amine component, 3-azabicyclo[3.2.2]nonane may be considered to be a cyclohexane ring condensed with a hexamethyleneimine moiety. Similarly, this system may be compared with many derivatives of the solanaceous alkaloids which also possess the condensed piperidine-pyrollidine nucleus.

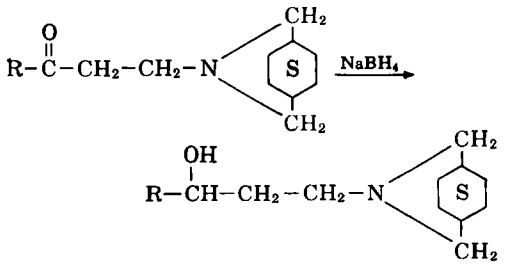
Lutz and co-workers (3) have reported the preparation and screening of 184 amino alcohols against avian malaria. The general structure of the secondary alcohols is represented as



These compounds included examples of 50 variations in the benzene nucleus and over 60 variations in the N,N-dialkyl groups on the nitrogen. Although most of these amino alcohols proved to be inactive, special mention should be made of the α-dichlorophenyl-β-dioctylaminoethanols which proved to be equal to or better than quinine in tests against avian malaria.

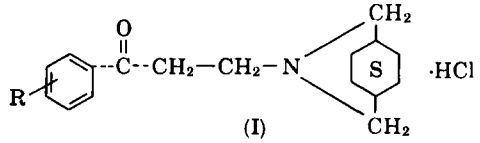
Denton and his associates (4) reported the preparation of a secondary alcohol, 3-(1-piperidyl)-1,2-diphenyl-1-propanol hydrochloride, and noted that it ranked higher in antispasmodic activity than did the seven tertiary alcohols with which it was compared. 3-Dimethylaminophenyl-1-propanol hydrochloride was prepared by Denton and co-workers (5) and was found to rank low in antispasmodic activity when compared with 15 tertiary alcohols.

We have prepared a series of secondary alcohols from the substituted β-amino ketones previously reported (1) according to the reaction

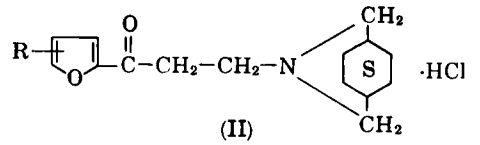


Our results are reported in Tables I and II.

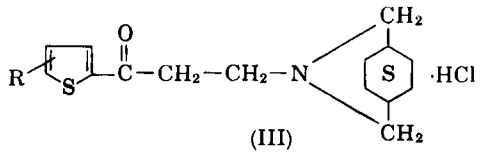
During the course of this work, compounds having the general structure of types I and III were converted to alcohols without difficulty. Under these conditions, treatment of compounds of type II did not give the expected secondary alcohol.



(I)



(II)



(III)

It is possible as Elderfield (6) reports that the furan ring is more easily reduced than the benzene ring to give the tetrahydrofurfuryl alcohol together with smaller amounts of the products of reductive ring opening: pentanediols-1,2, and -1,5, and pentanol-1.

PHARMACOLOGICAL RESULTS

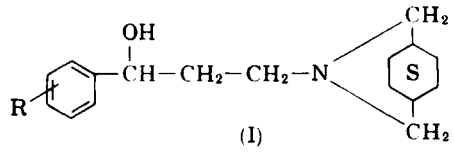
Preliminary screening data (7) indicate a weak central nervous system activity for compound 16 (Table I). This activity was characterized by hypotonia, salivation, and fore-limb clonus. Compounds 1 and 2 of Table I and compound 1 of Table II failed to produce any overt activity when administered orally in doses of 300 mg./Kg. As other results become available, it is anticipated that they will be reported as an integral part of this overall study.

EXPERIMENTAL

The preparation of the γ-amino secondary alcohols was patterned after the method of Chaikin and Brown (8) as employed by Rogers and Nobles (9). These secondary alcohols were all prepared by one of the following two procedures. Basically, as will be evident from an inspection of the actual procedures, these methods differ only in regard to the manner in which the final product is isolated.

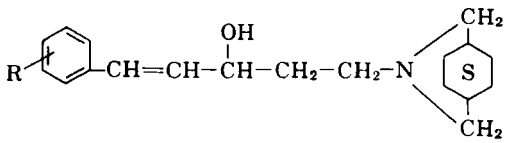
Procedure A.—The γ-amino secondary alcohols were prepared by the general procedure of suspending 0.05 mole of the β-amino ketone hydrochloride in 100 ml. of distilled water and making the solution basic to litmus with 10% sodium hydroxide solution. The free Mannich base was then collected. If this was a solid, it could be filtered off. If the free base was a liquid, it could be collected by extraction with ether. The Mannich base was dissolved in 100 ml. of methanol. This alcoholic solution was placed in a 300-ml. three-neck flask fitted with a dropping

TABLE I.—SECONDARY γ-AMINO ALCOHOLS

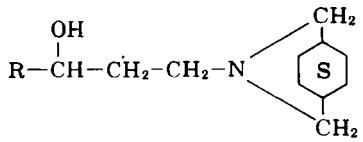


(I)

No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Hydrogen	...	241–242	$C_{17}H_{25}NO.HCl$	69.08	68.66	8.87	9.14	4.74	4.96
2	*p*-Nitro	80	113–114	$C_{17}H_{24}N_2O_3$	67.10	67.11	7.89	8.02	9.21	9.39
3	*p*-Methoxy	79	93–94	$C_{18}H_{27}NO_2$	74.74	74.84	9.34	9.47	4.84	5.24
4	*p*-Ethoxy	84	88–89	$C_{19}H_{29}NO_2$	75.25	74.96	9.51	9.55	4.64	4.59
5	*p*-Chloro	93	104–105	$C_{17}H_{24}ClNO$	69.51	69.66	8.18	8.17	4.77	4.79
6	*p*-Methyl	85	98–99	$C_{18}H_{27}NO$	79.07	79.23	9.95	10.22	5.12	5.13
7	*p*-Fluoro	49	49–50	$C_{17}H_{24}FNO$	73.61	73.55	8.72	8.93	5.05	5.25
8	*p*-Phenyl	82	117–120	$C_{23}H_{29}NO$	82.34	81.71	8.71	8.63	4.17	4.34
9	*p*-Bromo	89	108–109	$C_{17}H_{24}BrNO$	60.36	60.88	7.15	7.15	4.14	4.15
10	*m*-Nitro	68	213–214	$C_{17}H_{24}N_2O_3.HCl$	59.90	59.94	7.39	7.56	8.22	8.31
11	*p*-Ethyl	92	85–86	$C_{19}H_{29}NO$	79.39	79.51	10.17	10.52	4.87	5.03
12	*o*-Hydroxy	34	164–165	$C_{17}H_{25}NO_2.HCl$	65.49	65.35	8.35	8.09	4.49	4.65
13	*p*-Hydroxy[d]	76	72–75	$C_{17}H_{25}NO_2$	69.62	69.98	9.22	9.24	4.78	5.08
14	*m*-Bromo	59	233–234	$C_{17}H_{24}BrNO.HCl$	54.47	54.69	6.68	6.77	3.74	3.83
15	*m*-Hydroxy	88	137–138	$C_{17}H_{25}NO_2$	74.18	74.32	9.09	9.84	5.09	5.11



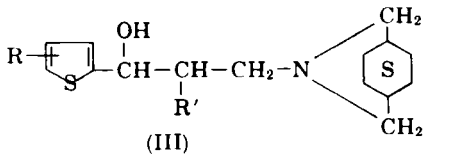
16	Hydrogen	72	78–79	$C_{19}H_{27}NO$	79.95	80.09	9.53	9.33	4.91	4.79
17	*p*-Methoxy	83	84–85	$C_{20}H_{29}NO_2$	76.19	75.97	9.21	9.19	4.44	4.15
18	*p*-Chloro[e]	22	178–180	$C_{19}H_{26}ClNO.HCl$	61.71	61.78	7.77	7.69	3.79	3.57



19	1-Naphthyl	43	213–214	$C_{21}H_{27}NO.HCl$	72.92	73.05	8.16	8.10	4.05	4.25
20	2-Naphthyl	59	217–218	$C_{21}H_{27}NO.HCl$	72.92	73.14	8.15	8.13	4.05	4.03

[a] All secondary γ-amino alcohols were recrystallized from an ethanol-water or ethanol-acetone solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are by Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for one mole of water. [e] Calculated for three-fourths mole of water.

TABLE II.—SECONDARY γ-AMINO ALCOHOLS



(III)

No.[a]	R	R′	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Hydrogen	Hydrogen	42	221–222	$C_{15}H_{23}NOS.HCl$	59.70	59.63	7.96	7.98	4.65	4.44
2	Hydrogen	Methyl	69	232–233	$C_{16}H_{25}NOS.HCl$	60.83	60.53	8.30	8.40	4.43	4.32
3	5-Bromo	Methyl	34	240–242	$C_{16}H_{24}BrNOS.HCl$	48.67	48.98	6.34	6.36	3.55	3.46

[a] All secondary γ-amino alcohols were recrystallized from an ethanol-water or ethanol-acetone solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul Craig of Smith Kline & French Laboratories, Philadelphia, Pa.

funnel, thermometer, reflux condenser, and magnetic stirrer. To this was added 0.1 mole of sodium borohydride dissolved in 50 ml. of methanol. The addition was conducted at such a rate as to maintain the temperature between 20–40°. After the evolution of hydrogen had subsided somewhat, the methanol was removed under water-pump vacuum. The residue was suspended in 100 ml. of distilled water and extracted with three 100-ml. portions of ether. The ether was then removed under diminished pressure and the solid material recrystallized to analytical purity from an ethanol-water solution.

Procedure B.—This method was utilized only when the secondary alcohol obtained upon removal of the ether was an oil. The liquid alcohols obtained by Procedure A were dissolved in 100 ml. of anhydrous ether. This ether solution was treated with anhydrous hydrogen chloride and the ether decanted from the sticky mass which adhered to the sides of the flask. A few milliliters of acetone was added and shortly a white solid appeared. This solid material was recrystallized to analytical purity from an ethanol-acetone solution.

Compound number 19 from Table I was prepared from the corresponding ketonic Mannich base. This Mannich base was prepared from 1-acetonaphthone in a 31% yield according to procedures previously indicated (1). After recrystallization to analytical purity from an ethanol-acetone solution, a m.p. of 219–221° was observed.

Anal.—Calcd. for $C_{21}H_{25}NO \cdot HCl$: C, 73.34; H, 7.62; N, 4.07. Found: C, 73.53; H, 7.59; N, 4.06.

REFERENCES

(1) Blanton, C. D., and Nobles, W. L., THIS JOURNAL, **51**, 878(1962).
(2) Denton, J. J., Turner, R. J., Neier, W. B., Lawson, V. A., and Schedl, H. P, *J. Am. Chem. Soc.*, **71**, 2048(1949).
(3) Lutz, R. H., *et al.*, *J. Org. Chem.*, **12**, 617(1947).
(4) Denton, J. J., Neier, W. B., and Lawson, V. A., *J. Am. Chem. Soc.*, **71**, 2050(1949).
(5) Denton, J. J., Neier, W. B., and Lawson, V. A., *ibid.*, **71**, 2053(1949).
(6) Elderfield, R. C., "Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1950, p. 161.
(7) Made available through the courtesy of Dr. Paul Craig of Smith Kline & French Laboratories.
(8) Chaikin, S. W., and Brown, W. G., *J. Am. Chem. Soc.*, **71**, 122(1949).
(9) Rogers, F. C., and Nobles, W. L., THIS JOURNAL, **51**, 273(1962).

Kinetics of Rapid Aggregation in Suspensions

Comparison of Experiments with the Smoluchowski Theory

By W. I. HIGUCHI, R. OKADA, G. A. STELTER, and A. P. LEMBERGER

Rates of aggregation of initially monodispersed 1.83-μ polystyrene latex particles in various electrolyte solutions at different electrolyte concentrations have been studied. The experiments involved the determination of the distribution of singlets, doublets, and triplets as a function of time with the Coulter Counter. In order to permit a comparison of the data with theory, theoretical calculations of the "bimolecular" rate constants were carried out for both the diffusion-controlled mechanism and the surface-controlled mechanism. These rate constants were employed to construct theoretical curves which were used to evaluate the data. Maximum rates observed approached the Smoluchowski rate to within about a factor of two. With the purified samples the rates were found to be relatively independent of electrolyte concentration and type. Rates observed with the unpurified samples in salt solutions were substantially lower than those for the purified suspension even at high salt concentrations.

MOST STUDIES (1–4) of aggregation in solid-liquid or liquid-liquid dispersed systems have involved methods based on observation of the sedimentation behavior. While in many instances the desired information may be or may best be obtained by these techniques, it is generally difficult to quantitate aggregation, *per se*, from such experiments.

With the introduction of a novel instrument, the Coulter Counter,[1] it has become possible to conveniently study aggregation without the complicating effects of sedimentation. Recently (5) the reversible aggregation in oil-in-water emulsions was studied with the aid of this instrument. Considerable insight into the problem was gained from this investigation.

In the present communication, results of a study of the kinetics of rapid aggregation of initially monodispersed polystyrene latex suspension particles are reported. The purposes of this work were to evaluate the validity of the existing theories as they apply to rapid aggrega-

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Presented to the Scientific Section, A.PH.A., Las Vegas meeting, March 1962.

[1] Coulter Industrial Sales Co., Chicago, Ill.