Draw a base line joining the transmission maxima at 5.6 and 8.55 μ. Determine the appropriate absorbance values and calculate the 6.3/6.85 ratio from

$$\text{ratio} = \frac{(A_{6.3}{}^{p}) - (A_{6.3}{}^{bl})}{(A_{6.85}{}^{p}) - (A_{6.85}{}^{bl})}$$

where

$A_{6.3}{}^{p}$, $_{6.85}$ = absorbance of peak at 6.3 or 6.85 μ

$A_{6.3}{}^{bl}$, $_{6.85}$ = absorbance of base line at 6.3 or 6.85 μ

DISCUSSION

It is important in the sample treatment to ascertain that all water is driven out. There are water absorption bands in the region of interest, and the presence of water in the sample being scanned will give variable results for the absorbance ratio. On the other hand, care must be taken that the temperature does not rise high enough to cause ester formation, which would obviously result in a lowered salicylate salt content. There should be no problem if the procedure outlined above is followed. Other drying methods are available, but this was the method of choice in terms of convenience and simplicity.

Replicates of four spectra for each of 10 lots of ointment gave an average deviation of ± 0.006 in the absorbance ratio, which represents an error of approximately 0.2% in TEAS content. This precision is adequate for routine control of commercial samples.

The time required for the assay is about 30 minutes and includes drying and preparing the sample, running four spectra, and calculating results.

SUMMARY

A convenient, rapid, and accurate absorbance ratio method for the assay of triethanolamine salicylate in ointment base is proposed. The method is based on the spectrophotometric measurement of the infrared absorption of the salicylate ionized carboxyl and the system methylene groups. No measurement of amount of sample taken is necessary, and no standard needs to be run after the standard curve has been established.

REFERENCES

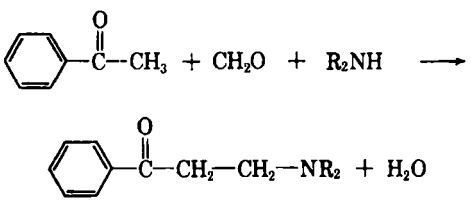
(1) Prochazka, V., and Richter, M., Czech. pat. 97,946 (Jan. 15, 1961); through *Chem. Abstr.*, **55**, 27796*i*(1961).
(2) Gaudin, O., U. S. pat. 2,596,674 (May 13, 1952); through *Chem. Abstr.*, **46**, 7714*h*(1952).
(3) Tamchyna, J., *Chem. Zvesti*, **10**, 553(1956); through *Chem. Abstr.*, **52**, 8693*d*(1958).

Mannich Bases and Alcohols from Hexamethylenimine

By W. LEWIS NOBLES and B. BLACKBURN THOMPSON*

The synthesis of a group of Mannich bases and secondary and tertiary γ-aminoalcohols derived from hexamethylenimine are described. These compounds are to be screened for possible pharmacological action.

THE MANNICH reaction has been extensively reviewed (1–4) and consists of the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride salt, an aldehyde, and a compound capable of supplying one or more replaceable hydrogen atoms. A typical condensation with acetophenone as the active hydrogen compound may be illustrated as



The mechanism of the Mannich reaction has been investigated by others (5–9). Hellmann and Opitz (5) and Cummings and Shelton (6) proposed that the reaction is initiated by a condensation between the amine and formaldehyde to yield an aminomethanol. The subsequent steps may be visualized as follows: attack of a proton on the oxygen atom of the aminomethanol, followed by expulsion of water, leads to the formation of a resonance-stabilized carbonium-immonium ion. This carbonium ion then reacts with the carbanion, which results from ionization of the active hydrogen-containing compound.

A large number of β-aminoketones (Mannich bases) have been prepared and tested as antispasmodics, local anesthetics, analgesics, and antibacterial agents (10–18). Secondary γ-aminoalcohols, prepared from Mannich bases by reduction with sodium borohydride (15, 19, 20), and tertiary γ-aminoalcohols, obtained by reacting Grignard reagents with Mannich bases (21), have been prepared and tested for similar pharmacological activity (15, 22, 23).

Reduction of piperidine Mannich bases to yield the corresponding secondary alcohols or reaction with Grignard reagents to yield the appropriate tertiary alcohols gave agents of greater antispasmodic activity (10, 22). Mannich bases derived from propiophenone appear to have enhanced analgesic activity (16, 21) and are better local anesthetics (12, 13) and antifungal agents (16) than acetophenone derivatives. Certain β-aminoketones with complex amine moieties have shown an unexpected order of antibacterial activity (24).

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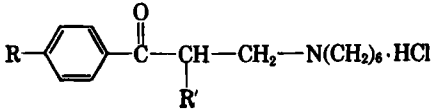
* Present address: School of Pharmacy, University of Georgia, Athens.

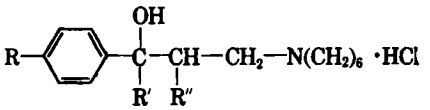
TABLE I.—MANNICH BASES



No.	R	R′	Formula	M.p., °C.[a]	Yield, %	Recryst. Solvent[b]	Microanalytical Data[c] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
1	H	H	$C_{15}H_{22}ClNO$	167.0–168.0[d]	45.0	A	67.27	67.01	8.28	8.18	...	...
2	H	CH_3	$C_{16}H_{24}ClNO$	183.5–184.5[e]	63.5	A	68.19	68.19	8.58	8.45	...	...
3	CH_3	H	$C_{16}H_{24}ClNO$	151.0–152.5[f]	35.0	A	68.19	68.34	8.58	8.58	4.97	4.98

[a] Melting points are uncorrected. [b] Recrystallization solvents are as follows: A, ethanol–acetone (1:4 by volume); B, 2-propanol–petroleum ether (60–110° boiling range) mixture (1:4 by volume); C, 2-propanol. [c] Microanalyses were performed by Weiler and Strauss, Oxford, England; A. Bernhardt, Mülheim (Ruhr), West Germany; and H. Galbraith, Knoxville, Tenn. [d] Reported to melt at 165–166°C. (26). [e] Kost *et al.* (26) reported m.p. 198–200°C. [f] Literature melting point was 171–173°C. (26).

TABLE II.—γ-AMINOALCOHOLS



No.	R	R′	R″	Formula	M.p., °C.[a]	Yield, %	Recryst. Solvent[b]	Microanalytical Data[c] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
1	H	H	H	$C_{15}H_{24}ClNO$	115.5–117.5	82.2	B	66.77	66.63	8.97	8.86	5.19	5.32
2	H	H	CH_3	$C_{16}H_{26}ClNO$	231.5–232.5	87.5	B	67.70	67.92	9.23	9.23	4.94	4.88
3	CH_3	H	H	$C_{16}H_{26}ClNO$	118.5–120.5	29.0	B	67.70	67.51	9.23	9.40	4.94	4.76
4	H	CH_3	H	$C_{16}H_{26}ClNO$	188.0–190.0	6.2	B	67.70	67.49	9.23	9.31	4.94	5.06
5	H	CH_3	CH_3	$C_{17}H_{28}ClNO$	187.5–189.0	45.5	A	68.55	68.43	9.47	9.42	4.70	4.51
6	CH_3	CH_3	H	$C_{17}H_{28}ClNO$	209.5–210.0	7.9	C	68.55	68.51	9.47	9.49	4.70	4.55
7	H	C_2H_5	H	$C_{17}H_{28}ClNO$	167.5–168.5	7.5	B	68.55	68.39	9.47	9.44	4.70	4.77
8	H	C_2H_5	CH_3	$C_{18}H_{30}ClNO$	197.0–198.5	50.1	C	69.31	69.21	9.70	9.76	4.49	4.46
9	CH_3	C_2H_5	H	$C_{18}H_{30}ClNO$	197.0–197.5	7.5	B	69.31	69.20	9.70	9.53	4.49	4.66
10	H	C_6H_5	H	$C_{21}H_{28}ClNO$	229.0–231.0	8.2	B	72.91	72.84	8.16	8.02	4.05	4.21
11	H	C_6H_5	CH_3	$C_{22}H_{30}ClNO$	208.5–211.0	39.2	C	73.41	73.52	8.40	8.50	3.89	3.86
12	CH_3	C_6H_5	H	$C_{22}H_{30}ClNO$	223.0–225.0	10.1	C	73.41	73.18	8.40	8.56	3.89	3.95

[a] Melting points are corrected. [b] Recrystallization solvents are as follows: A, ethanol–acetone (1:4 by volume); B, 2-propanol–petroleum ether (60–110° boiling range) mixture (1:4 by volume); C, 2-propanol. [c] Microanalyses were performed by Weiler and Strauss, Oxford, England; A. Bernhardt, Mülheim (Ruhr), West Germany; and H. Galbraith, Knoxville, Tenn.

Luts and Nobles (25) reported anti-inflammatory activity, anticonvulsant activity, and analgesic activity in members of a series of β-aminoketones and secondary and tertiary γ-aminoalcohols derived from heptamethylenimine. β-Aminoketones derived from hexamethylenimine were reported to possess CNS tranquilizing ability (26) and local anesthetic activity (26, 27). Most of the β-aminoketones were also observed to exhibit febrile activity (26, 27) and vasodilator activity (27). Extension of the series of hexamethylenimine derivatives to include the secondary and tertiary γ-aminoalcohols seemed desirable. The preparation and chemical properties of β-aminoketones and secondary and tertiary γ-aminoalcohols derived from hexamethylenimine are described in this manuscript. The results of the pharmacological evaluation will be published at a later date.

EXPERIMENTAL

Mannich Bases (β-Aminoketones).—The procedure of Mannich and Lammering (12), as applied by Nobles *et al.* (14, 15), was employed for the preparation of the Mannich bases. Pertinent data are provided in Table I.

Secondary γ-Aminoalcohols (Table II, No. 1–3).—The preceding Mannich bases were reduced with sodium borohydride in aqueous methanol according to the procedure of Chaikin and Brown (19), as employed by Nobles (20) and by Rogers and Nobles (15). The data for these compounds are listed in Table II.

Tertiary γ-Aminoalcohols (Table II, No. 4–12).—The procedure of Pohland and Sullivan (21) was employed for the preparation of these compounds. Relevant physical and chemical properties are given in Table II.

DISCUSSION OF RESULTS

Hexamethylenimine (azepane), a homolog of piperidine, was converted to the hydrochloride salt and condensed with acetophenone, propiophenone, or *p*-methylacetophenone and paraformaldehyde in ethanol according to the procedure of Mannich and Lammering (12). *sym*-Trioxane, an acetal, failed to function as a source of formaldehyde in the reaction. Evidently acetals are unable to depolymerize in the relatively dry ethanol employed in the reaction, while hemiacetals, such as paraformaldehyde, are readily converted to free aldehyde. Pertinent data are given in Table I.

The Mannich bases were reduced with sodium borohydride according to the procedure of Chaikin and Brown (19), as applied by Nobles (20) and by Rogers and Nobles (15). The products of the reduction, secondary γ-aminoalcohols, were isolated from dry ether as the hydrochlorides. Physical and chemical properties are listed in Table II.

In a similar manner the procedure of Pohland and Sullivan (21) was employed for the preparation of tertiary γ-aminoalcohols. Methyl-, ethyl-, and phenylmagnesium bromide were reacted with Mannich bases of acetophenone, propiophenone, and *p*-methylacetophenone; the resultant aminoalcohols were isolated as the hydrochlorides. Pertinent data are provided in Table II.

In the isolation of all the secondary and tertiary γ-aminoalcohols it was desirable to chill the dry ethereal solution before treatment with anhydrous hydrogen chloride. Oil formation, and possibly side reactions, appear to be retarded by this measure. Prolonged treatment of the solution with anhydrous hydrogen chloride gave some evidence of decomposition.

The yields of Mannich bases, secondary, and tertiary γ-aminoalcohols are uniformly low for *p*-methylacetophenone and consistently high for propiophenone. In general, acetophenone derivatives were obtained in intermediate yields. These data may reflect solubilities in the recrystallization solvents more closely than they reflect reaction yields since members of the propiophenone series were all rapidly precipitated on recrystallization, while members of the *p*-methylacetophenone series were obtained in crystalline form only after refrigeration for several days at sub-zero temperatures.

The order of addition of Grignard reagent and Mannich base has been reported to be important in obtaining high yields of the tertiary γ-aminoalcohols (28). No definite conclusions could be drawn from the present studies. Preliminary data, while not conclusive, indicated that the best order of addition depends more on the nature of the reactants than on any inherent advantage of the order of addition *per se*. Further studies are planned.

REFERENCES

(1) Blicke, F. F., in "Organic Reactions," Vol. 1, John Wiley and Sons Inc., New York, N. Y., 1942, pp. 303–341.
(2) Karbe, H., *Arch. Pharm.*, **283**, 38(1950).
(3) Reichert, B., "Die Mannich Reaktion," Springer-Verlag, Berlin, Germany, 1959.
(4) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(5) Hellmann, H., and Opitz, G., *Angew. Chem.*, **68**, 265 (1959); *Chem. Ber.*, **89**, 81(1956); **90**, 8, 15(1957); *Ann.*, **604**, 214(1957); **605**, 141(1957).
(6) Cummings, T. F., and Shelton, J. R., *J. Org. Chem.*, **25**, 419(1960).
(7) Bodendorf, K., and Koralewski, G., *Arch. Pharm.*, **271**, 101(1933).
(8) Liebermann, S. V., and Wagner, E. C., *J. Org. Chem.*, **14**, 1001(1949).
(9) Alexander, E. R., and Underhill, E. J., *J. Am. Chem. Soc.*, **71**, 4014(1949).
(10) Denton, J. J., *et al.*, *ibid.*, **71**, 2048(1949); **72**, 3792(1950).
(11) Burckhalter, J. H., and Johnson, S. H., *ibid.*, **73**, 4835 (1951).
(12) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(13) Levvy, G. A., and Nisbet, H. B., *J. Chem. Soc.*, **1938**, 1053.
(14) Blanton, C. D., Jr., and Nobles, W. L., THIS JOURNAL, **51**, 878(1962).
(15) Rogers, F. C., and Nobles, W. L., *ibid.*, **51**, 273(1962).
(16) Nobles, W. L., and Burckhalter, J. H., *ibid.*, **47**, 77 (1958).
(17) Britton, S. B., *et al.*, *ibid.*, **44**, 717(1958); **43**, 644 (1954).
(18) Caldwell, H. C., and Nobles, W. L., *ibid.*, **44**, 273 (1955).
(19) Chaikin, S. W., and Brown, W. G., *J. Am. Chem. Soc.*, **71**, 122(1949).
(20) Nobles, W. L., Dissertation, University of Kansas, Lawrence, 1952.
(21) Pohland, A., and Sullivan, J. R., *J. Am. Chem. Soc.*, **75**, 4458(1953); **77**, 3400(1955).
(22) Denton, J. J., *et al.*, *ibid.*, **71**, 2050, 2053, 2054 (1949); **72**, 3279, 3795(1950).
(23) Blanton, C. D., Jr., and Nobles, W. L., THIS JOURNAL, **52**, 46(1953).
(24) Nobles, W. L., unpublished data, patent application submitted.
(25) Luts, H. A., and Nobles, W. L., THIS JOURNAL, in press.
(26) Kost, A. N., *et al.*, *Vestn. Mosk. Univ., Ser. II*, **15** (No. 3), 66(1960); through *Chem. Abstr.*, **54**, 24791(1960).
(27) Kudrin, A. N., *et al.*, *Farmakol. i Toksikol.*, **25**, 437 (1962); through *Chem. Abstr.*, **58**, 1830(1963).
(28) Blanton, C. D., Jr., Dissertation, University of Mississippi, University, 1962.