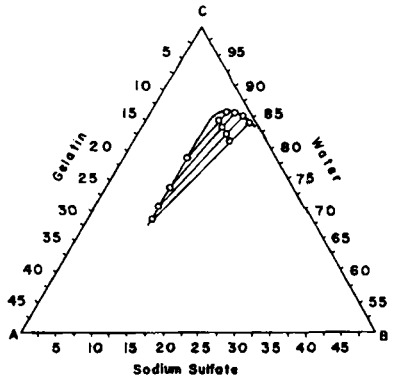

Fig. 4.—Phase diagram of gelatin, water, and sodium sulfate.

$p = \alpha + \delta n$, was determined as shown below by using the total known composition of each coacervated system and the calculated composition of the corresponding coacervate phase. $(p_C = \alpha + \delta n_C) - (p_T = \alpha + \delta n_T)$ can be rearranged to give

$$\frac{p_C - p_T}{n_C - n_T} = \delta$$

and therefore

$$\alpha = p_T - \delta n_T$$

$$p_E = \alpha + \delta n_E \qquad \text{(Eq. 7)}$$

The subscripts C, T, and E represent coacervate phase, total coacervate system, and equilibrium phase, respectively. By combining Eqs. 3 and 7

$$n_E = \frac{\Delta RI - \alpha_D}{\delta D + C} \qquad \text{(Eq. 8)}$$

The compositions of the equilibrium phases are presented in Table VI. The data in Table VI are plotted in Fig. 4.

SUMMARY AND CONCLUSIONS

1. The objective of this work was to develop a rapid method of determining the weight-in-weight concentration of a three-component solution using the experimentally determined specific gravity and refractive index of the solution.
2. Formulas were derived for calculating weight-in-weight concentrations without the need of tables.
3. The formulas are applicable to all three-component solutions in which there is no interaction of the ingredients.
4. In solutions in which there is interaction of the ingredients, such as aqueous solutions of ethanol, or methanol, or sodium sulfate, the weight-in-weight concentration can be determined by using a "diluting technique" which would minimize the effects of interaction.
5. The assay procedure is satisfactory for obtaining the data necessary for plotting three-component phase diagrams.

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Use of 3-Azabicyclo[3.2.2.]nonane in the Mannich Reaction III

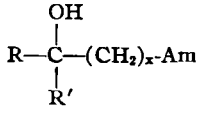
γ-Amino Tertiary Alcohols

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

Syntheses of a group of γ-amino tertiary alcohols by application of the Grignard reaction to the corresponding Mannich bases are described. These alcohols are to be screened for possible pharmacological activity.

IN OUR EARLIER publications (1, 2), a number of substituted β-amino ketones and γ-amino secondary alcohols employing 3-azabicyclo[3.2.2]-nonane as the amine moiety were synthesized for pharmacological screening. Denton and his associates (3) have previously established that certain structural modification of β-amino ketones had an effect on physiological activity. The authors wish to report upon the extension of our earlier studies to include the preparation of γ-amino tertiary alcohols.

The general structure of the γ-amino tertiary alcohols prepared by Denton and co-workers (4–10), as well as those presented here, are represented as



Of the tertiary amino carbinols which have been reported in the literature, many have shown

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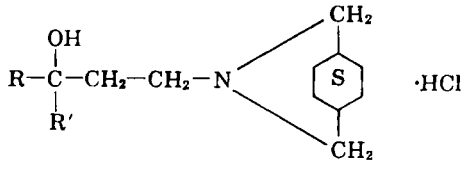
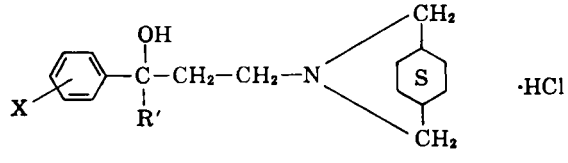
TABLE I.—γ-AMINO TERTIARY ALCOHOLS (HYDROCHLORIDE SALTS)



No.[a]	R	R′	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Methyl	Phenyl	41.5	234–234.5	$C_{18}H_{22}ClNO$	69.79	69.53	9.05	8.98	4.52	...
2	Phenyl	Benzyl	70.0	247–248	$C_{24}H_{27}ClNO$	74.71	74.47	8.31	8.20	3.63	3.75
3	Phenyl	Phenyl[d]	52.1	247–248	$C_{23}H_{25}ClNO$	73.38	73.61	8.17	8.47	3.72	3.79
4	Ethyl	Phenyl	64.8	225–227	$C_{19}H_{24}ClNO$	70.48	70.52	9.27	9.05	4.33	4.50
5	Phenyl	*p*-Methylphenyl	46.2	270–271	$C_{24}H_{27}ClNO$	74.71	74.69	8.31	7.91	3.63	3.55
6	Phenyl	*p*-Methoxyphenyl	40.0	244–245	$C_{24}H_{27}ClNO_2$	71.71	71.82	8.02	7.87	3.48	3.58
7	Phenyl	1-Naphthyl[d]	16.4	253–255	$C_{27}H_{27}ClNO$	75.97	76.10	7.62	7.56	3.28	3.32
8	Phenyl	*p*-Ethoxyphenyl	60.6	240–242	$C_{25}H_{29}ClNO_2$	72.18	72.03	8.24	8.03	3.37	3.55
9	Benzyl	*p*-Methoxyphenyl	39.0	231–232.5	$C_{25}H_{29}ClNO_2$	72.18	72.33	8.24	8.19	3.37	3.44
10	Benzyl	1-Naphthyl[d]	22.4	257–258	$C_{28}H_{29}ClNO$	76.28	76.57	7.83	7.60	3.18	3.17
11	Benzyl	*p*-Ethoxyphenyl	48.7	227–228	$C_{26}H_{29}ClNO_2$	72.62	73.39	8.44	8.67	3.26	3.22
12	Benzyl	2-Naphthyl	52.1	256–259	$C_{28}H_{28}ClNO$	77.12	77.24	7.86	7.78	3.21	3.30
13	Phenyl	*p*-Butoxyphenyl	28.8	214–215	$C_{27}H_{32}ClNO$	73.03	73.24	8.63	8.68	3.15	3.22
14	Benzyl	*p*-Methylphenyl	66.6	228–230	$C_{25}H_{28}ClNO$	75.03	74.90	8.57	8.66	3.50	3.42
15	Phenyl	Cyclohexyl	39.8	250–252	$C_{23}H_{30}ClNO$	73.08	72.65	9.60	9.12	3.71	4.11

[a] All γ-amino tertiary alcohols in this table were recrystallized from an ethanol-acetone or ethanol-ether solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for 0.25 mole of water.

TABLE II.—γ-AMINO TERTIARY ALCOHOLS (HYDROCHLORIDE SALTS)



No.[a]	X	R	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	*p*-Fluoro	Phenyl[d]	36.2	270.5–271.5	$C_{23}H_{23}ClFNO$	70.05	70.02	7.49	7.43	3.55	3.62
2	*p*-Fluoro	Benzyl	70.6	233 –235	$C_{24}H_{21}ClFNO$	71.36	71.44	7.74	8.16	3.47	3.61
3	*p*-Chloro	Phenyl[e]	63.1	281 –283	$C_{23}H_{23}Cl_2NO$	66.03	65.94	7.25	7.08	3.35	3.37
4	*p*-Chloro	Benzyl	60.1	255 –260	$C_{24}H_{21}Cl_2NO$	68.57	68.29	7.38	7.56	3.33	3.31
5	*p*-Bromo	Phenyl	58.7	275 –277	$C_{23}H_{23}BrClNO$	61.26	61.02	6.44	6.22	3.11	3.05
6	*p*-Bromo	Benzyl	62.4	258 –260	$C_{24}H_{21}BrClNO$	62.01	62.08	6.72	6.66	3.01	2.88
7	*p*-Iodo	Phenyl	39.4	272 –277 dec.	$C_{23}H_{23}ClINO$	55.48	55.62	5.88	5.90	2.81	2.64
8	*p*-Iodo	Benzyl	36.6	244 –244.5	$C_{24}H_{21}ClINO$	56.31	56.56	6.10	5.93	2.74	2.69

[a] All γ-amino tertiary alcohols in this table were recrystallized from an ethanol-acetone or ethanol-ether solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for one-fourth mole of water. [e] Calculated for two-thirds mole of water.

greater antispasmodic activity than the ketones from which they were derived (9–11). Some are suitable for the treatment of Parkinsonism and also for the treatment of similar tremors brought about as side-effects by certain tranquilizing drugs (12, 13). Numerous amino carbinols have been synthesized and reported (14–20) to exhibit pharmacological activity—such as antispasmodics, analgesics, antihistaminics, and local anesthetics. Some of the amino carbinols were not of interest, but they have been reported as useful intermediates for preparation of active agents. Extension of the present work to include such derived products will be presented in subsequent publications.

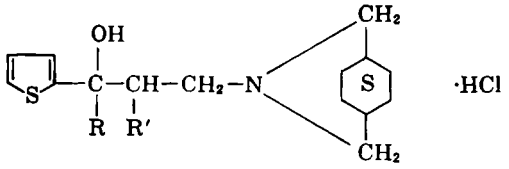
PHARMACOLOGICAL RESULTS

Only partial results from the preliminary biological screening are available.[1] Results of tests for activity as antispasmodics, analgesics, and local anesthetics are not available and will be the subject of future publications. None of the γ-amino tertiary alcohols submitted for screening have exhibited the antimicrobial activity or toxic properties observed for the corresponding Mannich bases.[2] Compound 2 (Table II) was considered in preliminary studies as a good enzyme inhibitor of cholesterol biosynthesis. Further tests revealed no significant ability to lower total plasma or liver cholesterol content. Compound 5 (Table II) was characterized as having marginal ability for enzyme inhibition of cholesterol biosynthesis. Interesting pharmacodynamic and/or chemotherapeutic properties were not reported in the limited amount of data available.

[1] The pharmacological results reported in this section were supplied by Dr. Paul N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa.

[2] Unpublished data.

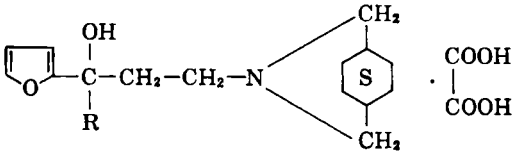
TABLE III.—γ-AMINO TERTIARY ALCOHOLS



No.[a]	R	R′	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Phenyl	Hydrogen	36.2	230–232 dec.	$C_{21}H_{23}ClNOS$	66.73	66.60	7.47	7.52	3.71	3.91
2	Benzyl	Hydrogen	82.3	227–228.5	$C_{22}H_{25}ClNOS$	67.41	68.17	7.71	7.89	3.57	3.41
3	*p*-Methylphenyl	Hydrogen	22.4	246–247	$C_{22}H_{25}ClNOS$	67.41	66.94	7.71	7.55	3.57	3.34
4	Phenyl	Methyl	10.4	244–245	$C_{22}H_{25}ClNOS$	67.41	67.34	7.71	7.57	3.57	3.28
5	Benzyl	Methyl	34.9	225–226	$C_{23}H_{27}ClNOS$	68.04	68.55	7.99	8.06	3.45	3.44

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

TABLE IV.—γ-AMINO TERTIARY ALCOHOLS



No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Phenyl[d]	44.0	125–127	$C_{22}H_{29}NO_6$	65.79	65.91	7.03	7.09	3.35	3.38
2	Benzyl[e]	63.7	93– 95	$C_{24}H_{31}NO_6$	63.74	63.30	7.40	7.12	3.10	3.13

[a] All γ-amino tertiary alcohols in this table were recrystallized from an ethanol-acetone or ethanol-ether solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for 1.25 moles of water. [e] Calculated for 1.25 moles of water.

EXPERIMENTAL

The preparation of γ-amino tertiary alcohols involves the reaction of a β-amino ketone with a Grignard reagent. Six different reagents were utilized in the preparation of this series of compounds: methylmagnesium bromide, ethylmagnesium bromide, phenylmagnesium bromide, benzylmagnesium chloride, *p*-methylphenylmagnesium bromide, and cyclohexylmagnesium bromide. Only the first three were obtained commercially. Higher yields were generally obtained when the reagent was prepared immediately before use. The procedure of Gilman and Catlin (21) was followed for the preparation of the Grignard reagents.

The general method of Pohland and Sullivan (19, 22) for the preparation of γ-amino tertiary alcohols was employed as described by Rogers and Nobles (23). The parent β-amino ketones used for the preparation of the γ-amino tertiary alcohols reported at this time were presented in paper I (1) of this series; three exceptions are the ketones used for preparation compounds 7 and 8 (Table II), 1 and 2 (Table IV), and 13 (Table I). For compound 3 (Table I), it was first necessary to prepare *p*-butoxyacetophenone. This was accomplished by the procedure of Allen and Gates (24). The preparation and characterization of *p*-butoxyacetophenone have been reported by Profft (25) and Bockstahler (26). For the preparation of compounds 7 and 8 (Table II), it was necessary to prepare *p*-iodoacetophenone. This was accomplished by the procedure of Adams and Noller (27).

β - [3 - (3 - Azabicyclo[3.2.2.]nonyl)] - 4 - (n - butoxy)propiophenone.—From the alkoxy ketone, the β-amino ketone (Mannich base) was prepared in a 69.6% yield by the procedure described earlier (1). A melting point of 193–195° was recorded.

Anal.—Calcd. for $C_{21}H_{32}ClNO_2$: C, 68.92; H, 8.86; N, 3.87. Found: C, 68.82; H, 8.76; N, 3.87.

β - [3 - (3 - Azabicyclo[3.2.2.]nonyl] - 1 - (furyl) - 1-propanone.—This β-amino ketone used for the preparation of tertiary alcohols 1 and 2 (Table IV) was prepared in a 59.7% yield by the procedure previously outlined (1). The compound melted with decomposition at 211–213°.

Anal.—Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.58; H, 7.75; N, 5.07.

β - [3 - (3 - Azabicyclo[3.2.2.]nonyl] - 4 - iodopropiophenone.—This β-amino ketone used for the preparation of tertiary alcohols 7 and 8 (Table II) was prepared in a 38.2% yield by the procedure previously outlined (1). The compound melted with decomposition at 228–230°.

Anal.—Calcd. for $C_{17}H_{23}ClINO$: C, 48.63; H, 5.48; N, 3.34. Found: C, 48.34; H, 5.53; N, 3.53.

Tertiary alcohols of the three types described in paper I (1) are listed in Tables I–IV.

For the isolation of the γ-amino tertiary alcohols of the furan derivatives (Type II), the product of the Grignard reaction had to be treated with oxalic acid instead of hydrogen chloride. When attempts to isolate the product as the hydrochloride were made, only resinous and tarry products were observed. It appears that under such acid conditions the furan derivatives are readily decomposed. This is not an

unexpected characteristic for furans. The procedure for the isolation of the neutral oxalates was patterned after that of Adamson (16).

SUMMARY

A total of 31 γ-amino tertiary alcohols which are to be screened for possible pharmacodynamic or chemotherapeutic activity is presented. It is anticipated that further modifications of these structures and detailed pharmacological reports will be presented in later publications.

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Antibiotic Therapy of Experimental Leptospiral Infection in Chick Embryos II

Comparison of the Action of Demethylchlortetracycline and Three Other Tetracyclines With and Without Ascorbic Acid on *Leptospira icterohaemorrhagiae*

By S. F. QUAN*, M. I. GOLDENBERG, and C. W. ABBOTT

Saline and antibiotic solutions, with and without ascorbic acid, were injected into 7-day-old chick embryos inoculated with *Leptospira icterohaemorrhagiae* 1 day after infection. All inoculations were made into the yolk sac. The treated embryos were observed for prolongation of life and for survival rates over a period of 12 to 14 days. Demethylchlortetracycline was about twice as active as tetracycline and oxytetracycline and about 10 times as active as chlortetracycline. Ascorbic acid alone did not influence the course of the infection and did not affect their therapeutic activity when given with antibiotics.

DEMETHYLCHLORTETRACYCLINE (DMCT), a recently introduced commercial antibiotic, is reported to have advantages over the older tetracycline antibiotics with respect to chemical stability, antibacterial activity, and efficiency of maintaining an effective serum level (1–4).

The chemical structure of DMCT is identical to that of chlortetracycline with the absence of a methyl group in the 6 position of the tetracycline molecule. While DMCT has not been reported to have been tested in the chemotherapy of leptospirosis, chlortetracycline (CT), oxytetracycline (OT), and tetracycline (TC) have been effective against experimental leptospiral infections in chick embryos, hamsters, guinea pigs, dogs, and cattle (5–10). Furthermore, Howarth (11) was successful in clearing swine carriers of *Leptospira pomona* with CT and OT, while Stoenner and his associates (12) eliminated *L. ballum* from a naturally infected colony of mice using CT.

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