

band, as may be seen in spectrum A of the same figure.

TERTIARY AMINE SALTS

The tertiary amine salts are by far the most common class of amines used pharmacologically. It has been possible to draw conclusions concerning correlations from many tertiary amine spectra. Table III lists the amine salts used in this study along with their characteristic absorption bands. A tertiary amine salt has the simplest NH^+ absorption spectrum since it contains only one hydrogen. The distinguishing feature of NH^+ spectra is a broad and intense peak located in the range of 2770-2380 cm^{-1} . The exact location of the absorption peak depends on whether the molecule contains water of hydration. Water of hydration affects the bonding between NH^+ and X^- so that the band shifts to higher frequency when hydrated. The band is assigned to an NH^+ stretching vibration. The range of this band may seem large, but the shape of the band and its intensity leave little doubt in assigning it to NH^+ in an unknown material. The peak is of such characteristic shape and intensity that it could not be confused with the primary or secondary amine salts. Figure 1 illustrates the shape and location of the various NH_3^+ , NH_2^+ , NH^+ absorption bands. Their unique characters can be seen at once.

It might be appropriate to mention at this point that, on the basis of this study, the authors agree with Nakanishi (7) that for identification purposes

the solid state spectra are most reliable when reference spectra are available. The absorption bands of these amine salts would be greatly altered by solvent effects in solution spectra, so that those peaks that owe their unique shape and position to their degree of hydrogen bonding and crystal lattice would be changed beyond recognition. It is recommended that similar compounds be run in the solid state as Nujol mulls in preference to potassium bromide disks to avoid ion exchange with the potassium bromide matrix and to avoid alteration of the crystal lattice by pressure exerted during formation of the disk.

SUMMARY

The spectra of 80 pharmaceutical amines of varying structure and class have been analyzed. Spectra-structure correlations have been made on the absorption bands of NH_3^+ , NH_2^+ , and NH^+ groups which enable one to make a rapid identification of the class of amine present.

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Mannich Reaction at the 4-Methyl Group in Schistosomicidal Agents, Lucanthone and Oxalucanthone

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The schistosomicidal agents lucanthone (I) and oxalucanthone (II), when subjected to reaction with formaldehyde and diethylamine in the presence of concentrated hydrochloric acid, condensation took place to give 1-(2-diethylaminoethyl-amino)-4-diethylaminoethylthiathanthone (III) and 1-(2-diethylaminoethylamino)-4-diethylaminoethyl-6-chloroxanthone (IV), respectively. Without the addition of acid, the reaction failed to occur.

THE BIOLOGICAL activity of the schistosomicidal (1) and antitumor agents (2) lucanthone, chemically 1-(2-diethylaminoethylamino)-4-methylthiathanthone (I) and its analog, oxalucanthone or 1-(2-diethylaminoethylamino)-4-methyl-6-chloroxanthone, lies in the *p*-toluidine moiety common in both molecules which constitutes a methyl group at a *para* position to an amino side chain at the 1-position. Changes involving either or both groups will bring about a loss in chemotherapeutic activity (3).

These facts suggested the authors' studies of the chemical nature of the 4-methyl group.

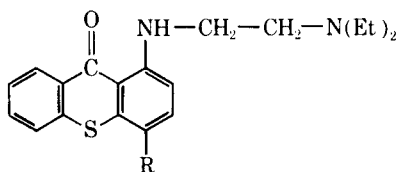
Received July 21, 1965, from the National Research Centre, Dokky, Cairo, Egypt, United Arab Republic.
Accepted for publication October 8, 1965.

In a previous communication, the authors reported that the methyl group at the 4-position in both molecules of I and II can be chlorinated when treated with gaseous chlorine in the presence of an acid binding material to build up the monochlorinated derivatives (4).

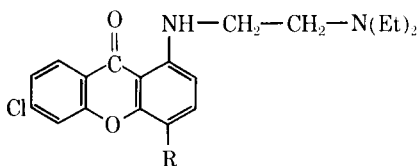
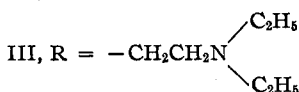
In the present work, the behavior of this group toward reaction with formaldehyde and diethylamine known as Mannich reaction was investigated.

DISCUSSION

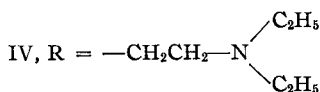
The Mannich reaction is a condensation between an amine (primary or secondary) or its salt with formaldehyde and a compound containing an active hydrogen which is replaced by a substituted amino-methyl group. The acidic component in the Man-



I, R = CH₃



II, R = CH₃



nich reaction can be an activated methyl group (5). The methyl group, in a heterocyclic system, as quinaldine (6) and picoline (7), can undergo aminomethylation by this reaction. While in 4-hydroxyquinaldine both the 3-position adjacent to the -OH group and the methyl group at the 2-position are subject to attack, substitution takes place at either site depending upon the pH of the medium (8).

When compounds I and II were subjected to the Mannich reaction using formaldehyde and diethylamine as the condensation partners in a nonacidic medium, *i.e.*, without addition of acid, the reaction failed to occur, but upon the addition of concentrated hydrochloric acid, it went to completion to give III and IV, respectively.

To detect the absence of the methyl group in compounds III and IV, both were subjected to *p*-dimethylaminobenzaldehyde condensation in the presence of fused zinc chloride, and no reaction occurred while I and II underwent the reaction under similar conditions (4).

EXPERIMENTAL

Lucanthone (I) and oxalucanthone (II) were prepared according to the procedures described by Mauss (9).

1-(2-Diethylaminoethylamino)-4-diethylaminoethylthioxanthone (III).—A 3.4-Gm. quantity of I (0.01 mole) was dissolved in 20 ml. of absolute ethyl alcohol, 2.10 ml. of diethylamine (in excess) was added while shaking, and finally 1.87 ml. of 40% formaldehyde solution was added dropwise. This was followed by the addition of 2 ml. of concentrated HCl, and the mixture was refluxed for 4 hr. on a steam bath. Then the reaction mixture was con-

centrated to a syrupy product. When kept in deep-freeze overnight, it solidified. The mass was recrystallized from ethyl alcohol. It melted at 262° and was soluble in water.

The free base was liberated through the addition of sodium carbonate to the hydrochloride solution which was filtered and recrystallized from ethyl alcohol as reddish-orange crystals, m.p. 124°. Yield 3.5 Gm., 82%.

Anal.—Calcd. for C₂₆H₂₈N₃OS: C, 70.54; H, 8.28. Found: C, 70.38; H, 7.92.

1-(2-Diethylaminoethylamino)-4-diethylaminoethyl-6-chloroxanthone (IV).—A 1.79-Gm. quantity of II (0.005 mole) was dissolved in 15 ml. of absolute ethyl alcohol, 2 ml. of diethylamine (excess) was added, followed by 2 ml. of 40% formaldehyde solution; finally 2 ml. of concentrated HCl was added. The whole mixture was refluxed for 4 hr. on a steam bath. Then the solution was concentrated to a viscous residue which solidified upon standing in the deep-freeze overnight. The product was then recrystallized from ethyl alcohol, m.p. 213°, and was soluble in water. The water solution was made alkaline through the addition of sodium carbonate. The free base liberated was extracted with ether twice, and the ether extract was dried over sodium sulfate. The ether was distilled, and the residual material was recrystallized from methyl alcohol. It had m.p. 94°. Yield 1.4 Gm., 63%.

Anal.—Calcd. for C₂₆H₂₄ClN₃O₂: C, 67.62; H, 7.72; N, 9.46. Found: C, 66.99; H, 6.96; N, 8.87.

Attempts for Carrying the Reaction in Nonacidic Medium.—The same procedure described for reaction with I and II was followed for both compounds, but without external addition of the concentrated hydrochloric acid. No reaction occurred and they were recovered unchanged (no depression in melting point).

Attempts for the Condensation of III and IV with *p*-Dimethylaminobenzaldehyde.—III and IV were brought to condensation with *p*-dimethylaminobenzaldehyde in the presence of fused zinc chloride. No reaction occurred and they were recovered (no depression of melting point), while I and II underwent the condensation reaction (4).

CONCLUSION

In an acidic medium, the methyl group at the 4-position in lucanthone and oxalucanthone can undergo the Mannich reaction, while in a nonacidic one, the reaction failed to occur.

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