the spots turned to a green-blue tint. The palladium chloride reaction (8), despite its good sensitivity, showed the least color differentiation.

COMMENTS

The described procedures have revealed that the phenothiazine compounds examined in our experiments cannot be recognized completely by their color reactions or fluorescent properties. Only chromatography and electrophoresis made it possible to distinguish between substances giving the same color reactions or fluorescence but with a different radical on position 10 of the phenothiazine nucleus. This combination of chromatographic techniques with color reactions was of great help in many analyses in our laboratory concerned with the identification of phenothiazine drugs in toxicological investigations, in drug metabolism studies, in purification procedures, and in purity tests of commercial preparations.

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New 3-Thiophene Derivatives as Sedative Agents

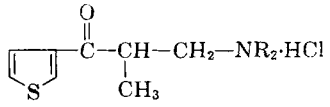
By HEINO A. LUTS† and W. LEWIS NOBLES

A group of compounds prepared from 3-propionylthiophene has been synthesized for pharmacological evaluation. Preliminary studies indicate that some of these agents combine sedative and stimulating properties in an unusual manner.

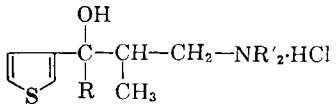
IN A SEARCH for compounds possessing possible analgetic activity, a program designed to produce certain Mannich bases and their derivatives from 3-propionylthiophene has been carried out. It has been noted that in many cases the 3-thienyl analog often has greater activity than the corresponding 2-thienyl compound (1–5). In fact, Campaigne (5) has suggested that, based on available data, it is impossible to predict the activity of the 3-thienyl isomer from a knowledge of the activity of the corresponding 2-isomer. Furthermore, Campaigne suggests that in any program in medicinal chemistry involving thiophene analogs, the 3-isomer should always be included since there is a high probability that it will be active and a good chance that it will be more active than the 2-isomer.

Previously, we (6) reported on the preparation of 2-substituted analogs of *d*-propoxyphene. In line with this and the above statements of Campaigne, it appeared quite logical to extend this work to the preparation of the corresponding 3-isomers.

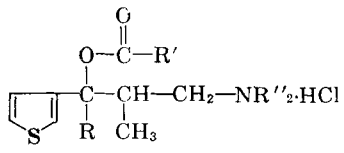
In our work, three general types of compounds were prepared. These are



Type I



Type II



Type III

The compound designated as Type I was prepared using the standard conditions normally employed in the Mannich reaction (7). Type II compounds were formed by the conventional Grignard reaction on the preceding Mannich base; also, the Mannich base was reduced to the

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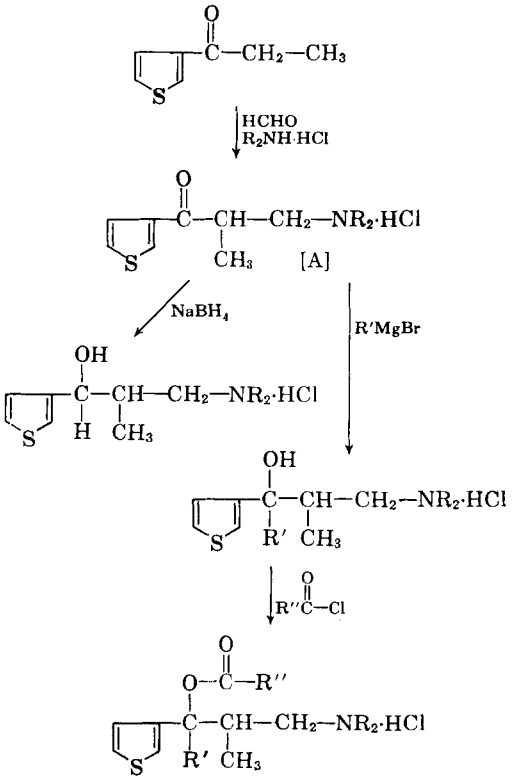
corresponding secondary alcohol by the use of sodium borohydride. A Type III compound was synthesized by means of refluxing the sodium salt of the alcohol with propionyl chloride in dioxane.

The general synthetic scheme utilized in the preparation of these agents follows

GENERAL SCHEME OF SYNTHESIS



Preliminary information (8) indicates that one of the compounds, 3-dimethylamino-2-methyl-1(3-thienyl)-1-phenylpropanol hydrochloride, combined sedative and stimulating properties in a most interesting manner.

EXPERIMENTAL

Type I Compounds

3 - Dimethylamino - 2 - methyl - 1 - (3 - thienyl)-1-propanone Hydrochloride.—By the usual procedure for the preparation of a Mannich base from a ketone, 13.8 Gm. (0.1 mole) of 3-propionylthiophene, 3 Gm. of paraformaldehyde, and 8.1 Gm. (0.1 mole) of dimethylamine hydrochloride were refluxed in 25 ml. of ethanol. After refluxing for 29 hours, the solution was filtered while hot; it was then cooled. Subsequently, a mixture of 15 ml. of acetone and 85 ml. of dry ether was added. The solid obtained was removed by filtration and recrystallized to analytical purity from a solution of ethanol-ether to produce a yield of 9.1 Gm. (42%) of a compound, m.p. 158–160°.

Anal.—Calcd. for $C_{10}H_{16}ClNOS$: C, 51.40; H, 6.90; S, 13.72. Found: C, 51.37; H, 6.96; S, 13.86.

3-(3-Dimethylamino-2-methyl-propanoyl) thiophene.—This free base was obtained by making an aqueous solution of the above hydrochloride alkaline with ammonium hydroxide and ether extracting the resulting product. The ether extract was dried over Drierite and distilled in the range of 104–105°/0.3 mm.

Anal.—Calcd. for $C_{10}H_{15}NOS$: C, 60.85; H, 7.66; S, 16.02. Found: C, 60.73; H, 7.52; S, 16.13.

Type II Compounds

3 - Dimethylamino - 2 - methyl - 1 - (3 - thienyl)-1-propanol Hydrochloride.—Four hundred milligrams of sodium borohydride was added to 50 mg. of 50% methanol at 18–20°. Two and three-tenths grams (0.01 mole) of 3-(3-dimethylamino-2-methylpropanoyl) thiophene hydrochloride in 50% methanol was added dropwise at 20–22°. After the addition, the reaction mixture was warmed to 30°, maintained at this temperature for 30 minutes, and then heated to 50° for 15 minutes. Methanol was removed *in vacuo*. The residue was made basic with 6 *N* sodium hydroxide, extracted with ether, and dried over Drierite. Anhydrous hydrogen chloride was bubbled in. Recrystallization from an ethanol-ether mixture yielded 1.5 Gm. (60%) of a compound which melted in the range of 154–157°.

Anal.—Calcd. for $C_{10}H_{18}ClNOS$: C, 51.10; H, 7.72. Found: C, 51.33; H, 7.83; IR: OH, 303 μ.

3 - Dimethylamino - 2 - methyl - 1 - (3 - thienyl)-1-phenyl-propanol Hydrochloride.—Phenylmagnesium bromide was prepared from 3.16 Gm. (0.2 mole) of bromobenzene, 730 mg. (0.03 mole) of magnesium turnings, and anhydrous ether. The Grignard solution was stirred at room temperature during the dropwise addition of 2.95 Gm. (0.015 mole) of 3-(3-dimethylamino-2-methylpropanoyl) thiophene in 25 ml. of ether. The reaction mixture was stirred and refluxed for 1 hour; the mixture was then decomposed by the addition of 7 ml. of water. The ether layer was separated, the reaction mixture was extracted with two 25-ml. portions of ether, and the ether layers were combined and dried over Drierite. The hydrochloride was prepared in ether solution, using anhydrous hydrogen chloride. Recrystallization from an ethanol-ether mixture yielded 3.7 Gm. (81%) of a compound which melted in the range of 210–212°.

Anal.—Calcd. for $C_{16}H_{22}ClNOS$: C, 61.80; H, 7.13. Found: C, 61.79; H, 7.06.

3 - Dimethylamino - 2 - methyl - 1 - (3 - thienyl)-1- cyclohexyl - 1 - propanol Hydrochloride.—Cyclohexylmagnesium bromide was prepared from 3.2 Gm. (0.02 mole) of bromocyclohexane, 730 mg. (0.03 mole) of magnesium turnings, and anhydrous ether. The Grignard solution was stirred at room temperature during the dropwise addition of 2.95 Gm. (0.015 mole) of 3-(3-dimethylamino-2-methylpropanoyl)thiophene in 25 ml. of dry ether. The reaction mixture was stirred and refluxed for 1 hour and then decomposed by the addition of 7 ml. of water. The ether layer was separated, the reaction mixture was extracted with two 25-ml. portions of ether, and the ether layers were combined and dried over Drierite. The hydrochloride was prepared in ether solution, using anhydrous hydrogen chloride. A yield of 3.6 Gm. (76%) of the compound which melted in the range of 233–234° was obtained after recrystallization from an ethanol-ether mixture.

Anal.—Calcd. for $C_{16}H_{28}ClNOS$: C, 60.57; H, 8.80; N, 4.39. Found: C, 60.46; H, 8.72; N, 4.10. U.V. max. 233 mμ (5110); 238 mμ shed (5900); 245 mμ shed (3020).

3 - Dimethylamino - 2 - methyl - 1 - (3 - thienyl)-1-benzyl-1-propanol Hydrochloride.—Benzylmagnesium bromide was prepared from 3.4 Gm. (0.02 mole) of benzyl bromide, 730 mg. (0.03 mole) of magnesium turnings, and anhydrous ether. The Grignard solution was stirred at room temperature during the dropwise addit on of 2.9 Gm. (0.015 mole) of 3-(3-dimethylamino-2-methylpropanoyl) thiophene in 25 ml. of dry ether. The reaction mixture was stirred and refluxed for 1 hour; it was then decom posed by the addition of 7 ml. of water. The ether layer was separated, the reaction mixture was extracted with two 25-ml. portions of ether, and the ether layers were combined and dried over Drierite. The hydrochloride was prepared as indicated above. After recrystallization from an ethanol-ether mixture, a yield of 3.8 Gm. (78%) of a compound which melted at 207° was obtained.

Anal.—Calcd. for $C_{17}H_{24}ClNOS$: C, 62.46; H, 7.40; N, 4.29. Found: C, 62.12; H, 7.19; N, 4.38.

3 - Dimethylamino - 1 - propyl - 1 - (3 - thienyl)-2-methyl-1-propanol Methiodide.—Three hundred and ninety-four milligrams (0.002 mole) of 3-(3-dimethylamino-2-methylpropanoyl) thiophene was treated with an equal molar quantity of propylmagnesium bromide in 15 ml. of dry ether; this mixture was refluxed for 2 hours and then decomposed with the addition of water. The ether .ayer was separated and extracted with two 10-ml. portions of ether. The ether layers were combined, dried over Drierite, and then evaporated to dryness. The residue was dissolved in 10 ml. of acetone. The quaternary salt of the free base was formed by the addition of 1 ml. of methyl iodide; 5 ml. of ether was added to precipitate the salt. A yield of 5.2 Gm. (68%) of the methiodide, m.p. 120–127°, was thus obtained.

Anal.—Calcd. for $C_{14}H_{26}INOS$: C, 43.87; H, 6.84. Found: C, 43.38; H, 6.56.

Type III Compound

4 - Dimethylamino - 1 - phenyl - 2 - (3 - thienyl)-3-methyl-2-propanoyloxybutane Hydrochloride.—To 20 ml. of dry dioxane, 46 mg. (0.002 mole) of sodium metal was added, and the mixture was stirred and heated at reflux temperature until sodium sand resulted. Five hundred and eighty milligrams (0.002 mole) of 3-dimethylamino-2-methyl-1-(3-thienyl)-1-benzyl-1-propanol was added slowly and refluxed for 6 hours. The solution was cooled, and 186 mg. (0.0022 mole) of propionyl chloride was added. After refluxing for 6 hours, the mixture was cooled, water was added, and the mixture was made basic to litmus with sodium carbonate. The solution was extracted three times with 20-ml. portions of ether; the combined extracts were dried over anhydrous potassium carbonate, and the compound was converted in the usual manner to the hydrochloride. A yield of 297 mg. (39.4%) of a compound, m.p. 217°, was thus obtained.

Anal.—Calcd. for $C_{20}H_{28}ClNO_2S$: C, 62.89; H, 7.39; N, 3.67. Found: C, 62.61; H, 7.33; N, 3.73.

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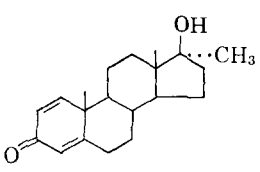
Quantitative Fluorometric Determination of Methandrostenolone

By F. TISHLER, P. B. SHETH, M. B. GIAIMO, and W. J. MADER

A fluorometric procedure is described for the determination of methandrostenolone (17α-methyl-17β-hydroxyandrosta-1,4-dien-3-one). The method is based on the flluorogen formed when the steroid is heated with hydrochloric acid at 100°. In order to determine the selectivity of this reaction, a number of related steroids has been studied.

METHANDROSTENOLONE[1] is a new tissue-building compound prepared in these laboratories. Its structural formula is illustrated:



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[1] Ciba's trade name for methandrostenolone is Dianabol.