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2,882,273

THERAPEUTIC AGENTS

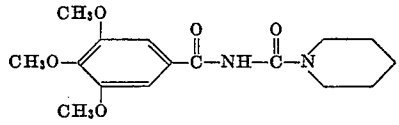
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No Drawing. Application February 7, 1958 Serial No. 713,789

3 Claims. (Cl. 260—294)

The present invention relates to certain heterocyclic compounds of therapeutic value, e.g., as nonhypnotic sedatives and clinical tranquillizers, and more particularly to N-1-piperidine-carbonyl-3,4,5-trimethoxybenzamides and its nontoxic metal salts.

There is provided by the present invention a member selected from the group consisting of a compound having the formula



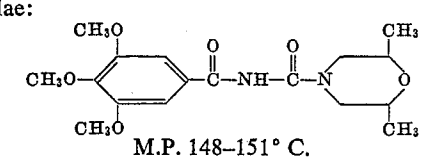
and nontoxic metal salts of said compound.

Examples of nontoxic metal salts include salts with alkali metals, e.g. sodium, potassium, with alkaline earth metals, e.g. calcium, and with such other nontoxic metals as magnesium, aluminum and iron. These metal salts are prepared by treatment of the compound with one equivalent of a strong base, e.g. sodium hydroxide, sodium hydride, aluminum ethoxide.

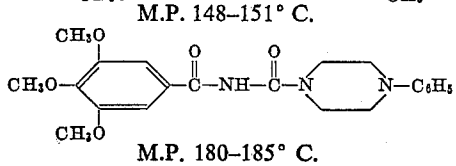
The compounds of this invention are useful as pharmaceuticals and as pharmaceutical intermediates. More specifically, compounds of this invention are nonhypnotic sedatives and clinical tranquillizers of use in anxiety states, neuroses, emotional disturbances, insomnia, hypertension and the like. The compounds of the present invention also possess other valuable therapeutic properties as local anesthetics, analgesics and as potentiators of drugs active on the central nervous system.

These compounds produce remission in cases of severe psychoneurotic depression and severe psychotic depression and potentiate the analgesic action of morphine and codeine both in duration and degree when the compound is given by oral administration, e.g. in a daily dose of 400 to 2400 mgms. Compounds of the present invention repress the secretion of gastric acid in man and animals and markedly reduce gastric motility. Thus, use may be made by intraperitoneal injection in the Shay rat of an aqueous solution of about 5% concentration by weight in a dosage of about one-half the LD_{50}.

One of the most surprising features of the present invention is the finding of potent physiological activity for these compounds in view of the absence of such activity in the closely related compounds having the following formulae:

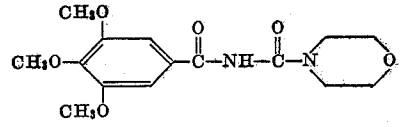


M.P. 148–151° C.



M.P. 180–185° C.

and



M.P. 155–158° C.

The following examples are given to illustrate the scope of this invention without limiting it thereto.

EXAMPLE 1

(a) *1-piperidinecarboxamide*

Urea (60.1 g., 1.0 mole) was heated to 140° C. and piperidine (85.2 g., 1.0 mole) was added dropwise as rapidly as refluxing would permit with the temperature maintained at 140–150° C. About 45 minutes was required for the addition; reaction was rapid with vigorous evolution of ammonia. The mixture was heated an additional 30 minutes at 150° C. and then poured at once into a beaker where it crystallized rapidly as a quantitative yield of 1-piperidinecarboxamide, M.P. 89–96° C. Recrystallization in methyl isobutyl ketone raises the melting point to 95–99° C.

(b) *N-1-piperidinecarbonyl-3,4,5-trimethoxybenzamide*

1-pyridinecarboxamide (25.6 g., 0.2 mole) was added in three portions to a stirred suspension of sodium hydride (4.8 g., 0.2 mole) in 200 ml. benzene at room temperature. On heating to reflux for two hours, hydrogen was evolved and a thick paste-like mixture was obtained. Methyl 3,4,5-trimethoxybenzoate (45.2 g., 0.2 mole) and the mixture was stirred under reflux for four hours; pyridine (1 ml.) was added as a catalyst. The reaction mixture was filtered to remove some suspended solid and the filtrate was distilled in vacuo to remove solvent. Water was then added and the mixture was again concentrated by distillation in vacuo, leaving a strongly alkaline solution of the sodium salt of the product which was acidified with 6 N HCl to precipitate the product, N - 1 - piperidinecarbonyl - 3,4,5 - trimethoxybenzamide, as a gum. After decanting the water and washing the gum twice with water, the addition of about 50 ml. of 20% NaOH precipitated the crystalline sodium salt of the product, 63 g., M.P. 84–88° C. after two recrystallizations from ethyl acetate.

Analysis.—Calc'd. for $C_{16}H_{21}N_2O_5Na$: C, 55.9; H, 6.17. Found: C, 55.9; H, 6.44.

EXAMPLE 2

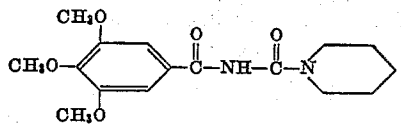
Sodium hydride (1.3 g.) was suspended in 250 ml. benzene and converted to sodium methoxide by the addition of 6 ml. methanol in three portions at 15 minute intervals; the mixture was then stirred with heating until all the sodium hydride had reacted. After adding 6.4 g. (0.05 mole) 1-piperidine-carboxamide and 11 g. (0.05 mole) methyl 3,4,5-trimethoxybenzoate the mixture was stirred under reflux for two hours, cooled, filtered to remove some turbidity and the solvent was removed by distillation in vacuo both before and after the addition of water. The resulting aqueous solution of the sodium salt of N-(1-piperidinecarbonyl)-3,4,5-trimethoxybenzamide was acidified with 6 N HCl to precipitate N - (1 - piperidinecarbonyl) - 3,4,5 - trimethoxybenzamide as a gum which was isolated by decantation, washed with three portions of water and converted by the addition of 25 mls. 20% sodium hydroxide to the crystalline sodium salt. This salt was collected, azeotropically dried in toluene and recrystallized from ethyl acetate, 3.9 g., M.P. 85–89° C. The melting point became 145–165° C. after drying 8 hours at 65° C. in vacuo over P_2O_5.

The aqueous phase from which the acid form of the product, i.e. N-(1-piperidinecarbonyl)-3,4,5-trimethoxybenzamide, had precipitated as a gum was allowed to stand and then gave the acid form of the product as a crystalline solid, 3.4 g., M.P. 136–139° C. after four recrystallizations from isopropyl alcohol and drying in vacuo at 65° C. over P_2O_5.

Analysis.—Calc'd. for $C_{16}H_{22}N_2O_5$: C, 59.7; H, 6.90. Found: C, 59.57; H, 6.96.

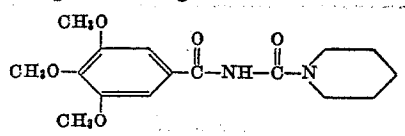
I claim:

1. A member selected from the group consisting of a compound having the formula



and nontoxic metal salts of said compound.

2. The compound having the formula



3. A nontoxic metal salt of the compound of claim 2.

No references cited.