Preparation of Alkoxyquinoline Derivatives and Their Evaluation as Potential Central Nervous System Stimulants

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Abstract □ A variety of substituted amides of 6,7-dimethoxy-2-hydroxyquinoline-3-carboxylic acid were synthesized. Three of these compounds, tested as potential central nervous system stimulants, showed no marked biological activity.

Keyphrases □ Alkoxyquinoline derivatives—potential CNS stimulants, synthesis □ Stimulants—CNS, alkoxyquinoline derivatives, synthesis

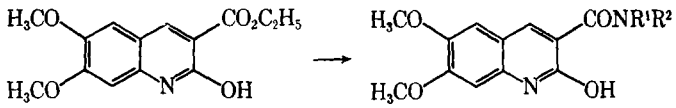
The analeptic activity of aromatic heterocyclic tetrazoles (1), such as nikethamide, ethamivan, and their *N*-ethylamides (2, 3) is well known. In addition, the *N*,*N*-diethylamides of numerous ring systems (such as pyrazole, thiazole, isoxazole, and the imidazolopyrimidines) as well as some xanthines and pyridines show analeptic activity (2, 4). Some CNS-sympathomimetic drugs such as the benzyl-, morpholinyl-, and piperidyl-*N*-ethylamide derivatives (2, 3) are also employed as psychomotor stimulants to elevate the mood or to improve the sense of well being of patients suffering from certain psychiatric depressions. The biological effects of the aforementioned drugs could be explained by the incorporation of a nitrogen atom in the ring systems (5), possibly providing resistance to enzymatic inactivation by steric protection of the amino groups (6), as in the case of phenmetrazine or methylphenidate. Similarly, *N*-alkyl groups, which are substituted with more bulky groups than methyl, diminished activity; the absence of the aromatic nucleus or its replacement by an alkyl group resulted in compounds of little or no activity (6). On the other hand, iproniazide (7), a monamine oxidase (MAO) inhibitor, appears to reverse the action of reserpine.

Since maximum MAO inhibition and analeptic activity are shown by compounds similar to amphetamine, *e.g.*, phenipraxine and a nitrogenisostere of methamphetamine (8), the present work describes the synthesis of potential CNS-stimulating agents, which have both aminoalkane and heterocyclic structural systems, such as quinoline. A series of substituted amides derived from 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid, which appeared likely to possess a CNS-stimulating effect, were prepared. In addition, the unsubstituted hydrazide derivatives of the compounds were alkylated to overcome the insignificant MAO inhibitory properties of unsubstituted hydrazines (9, 10). In the present investigation, the 6,7-dimethoxyquinoline system was varied to obtain 3-carboxylic acid hydrazides and hydrazones (Scheme I) for evaluation as CNS stimulants.

EXPERIMENTAL SECTION

Chemistry—*6,7-Dimethoxy-2-hydroxyquinoline-3-carboxylic Acid Hydrazide (IX)*—Hydrazine hydrate (0.1 mol) was added to a suspension of 6,7-dimethoxy-3-ethoxycarbonyl-2-hydroxyquinoline (I) (11) (0.02 mol) in ethanol (200 mL). The mixture was heated at reflux for 3 h. The hydrazide was removed by filtration, washed with water, dried, and recrystallized (Table I).

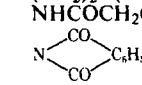
Interaction of 6,7-Dimethoxy-3-ethoxycarbonyl-2-hydroxyquinoline and Phenylhydrazines (X and XI)—Phenylhydrazine or 2,4-dinitrophenylhydrazine (0.02 mol) was added to a suspension of 6,7-dimethoxy-3-ethoxy-



I II–XVI

Scheme I

Table I—Newly Synthesized Alkoxyquinoline Derivatives (II–XVI)

Compound	R^1	R^2	mp, °C	Yield, %	Molecular Formula[a]
I[b]	—	—	275[c]	70	$C_{14}H_{15}NO_5$
II	H	CH_3	300[d]	75	$C_{13}H_{14}N_2O_4$
III	CH_2CH_3	CH_2CH_3	300[d]	80	$C_{16}H_{20}N_2O_4$
IV	H	$CH_2C_6H_5$	300[d]	70	$C_{19}H_{18}N_2O_4$
V	$(CH_2)_5$	$(CH_2)_5$	300[d]	85	$C_{17}N_{20}N_2O_4$
VI	$(CH_2)_2O(CH_2)_2$	$(CH_2)_2O(CH_2)_2$	300[d]	85	$C_{16}H_{18}N_2O_5$
VII	H	$NHCOCH_2CH_2CO_2H$	300[e]	60	$C_{16}H_{17}N_3O_7$
VIII	H		300[f]	80	$C_{20}H_{15}N_3O_6$
IX	H	NH_2	300[g]	80	$C_{12}H_{13}N_3O_4$
X	H	NHC_6H_5	300[h]	80	$C_{18}H_{17}N_3O_4$
XI	H	$NHC_6H_3(3,5\text{-}NO_2)$	300[h]	73	$C_{18}H_{15}N_5O_8$
XII	H	$N{=}CHC_6H_4(p\text{-}OCH_3)$	300[f]	73	$C_{20}H_{19}N_3O_5$
XIII	H	$N{=}CHC_6H_4(o\text{-}NO_2)$	300[f]	80	$C_{19}H_{16}N_4O_6$
XIV	H	$N{=}CHC_6H_4(p\text{-}OH)$	300[f]	75	$C_{19}H_{17}N_3O_5$
XV	H	$N{=}CHC_6H_3(3,4\text{-}OCH_3)$	300[f]	80	$C_{21}H_{21}N_3O_6$
XVI	H	$N{=}CHCH{=}CHC_6H_5$	300[f]	70	$C_{21}H_{19}N_3O_4$

[a] Elemental analyses for C and H were obtained for II–XVI; VII, VIII, X, and XI were also analyzed for N. Unless otherwise indicated, all values were within ± 0.4% of the theoretical value. [b] Calc. for C, 50.31; H, 4.97. Found: C, 50.26; H, 4.80. [c] Recrystallized from methanol (*cf.* Ref. 11). [d] Recrystallized from methanol. [e] Recrystallized from AcOH. [f] Recrystallized from dimethylformamide. [g] Recrystallized from water. [h] Recrystallized from ethanol-water.

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carbonyl-2-hydroxyquinoline (I) (0.01 mol) in ethanol (20 mL). The mixture was heated at reflux for 2 h. The solid was removed by filtration and recrystallized.

6,7-Dimethoxy-2-hydroxyquinoline-3-carboxylic Acid Hydrazones (XII-XVI)—The appropriate aldehyde (0.02 mol) was added to 6,7-dimethoxy-2-hydroxyquinoline-3-carboxylic acid hydrazide (IX) (0.01 mol) in glacial acetic acid. The mixture was heated at reflux for 1 h, and the material was removed by filtration and recrystallized.

Interaction of 6,7-Dimethoxy-2-hydroxyquinoline-3-carboxylic Acid Hydrazide and Acid Anhydrides (VII and VIII)—A mixture of the hydrazide (IX) (0.01 mol) and the appropriate acid anhydride (0.02 mol) in glacial acetic acid (30 mL) was heated at reflux for 3 h. The mixture was allowed to stand overnight. The material was removed by filtration and recrystallized. For VIII ^{1}H-NMR[1] ($CDCl_3$): δ 7.25 (s, 1, OH), 8.1-7.0 (m, 7, ArH), 4.3 (s, 1, NH), and 3.7 ppm (m, 6, 2 OCH_3).

Interaction of 6,7-Dimethoxy-3-ethoxycarbonyl-2-hydroxyquinoline and Different Amines (II-VI)—A mixture of 6,7-dimethoxy-3-ethoxycarbonyl-2-hydroxyquinoline (I) (0.01 mol) and the appropriate amine (0.02 mol) was heated at reflux in methanol (20 mL) for 3 h. Approximately 15 mL of the solvent was removed under reduced pressure, the residue was cooled, and the solid material was removed by filtration and recrystallized from a suitable solvent. For II, ^{1}H-NMR ($CDCl_3$): δ 6.8 (s, 1, OH), 8.1-7.03 (m, 3, ArH), 4.2 (s, 1, NH), 3.8 (m, 6, 2 OCH_3), and 1.5 ppm (s, 3, CH_3). For V [6,7-dimethoxy-3-(piperidinocarbonyl)-2-hydroxyquinoline], MS: *m/z* 316 (M^+), 232 ($M - C_5H_{10}N$), 204 [$M - (C_5H_{10}N + CO)$], 189 [$M - (C_5H_{10}N + CO + CH_3)$], and 173 [$M - (C_5H_{10}N + CO + OCH_3)$].

Biological Screening—Three compounds (III, V, and VII) of this series of alkoxyquinolines were used for preliminary pharmacological screening as CNS stimulants. Each was suspended in distilled water and administered to albino mice by oral intubation and intraperitoneal injection in doses up to 1 g/kg of body weight. The behavior and normal characteristics of the animals (heart rate, locomotor activity, reflexes, *etc.*) were recorded before and for 24 h after administration of the compounds.

RESULTS AND DISCUSSION

The animals given III showed transient increases in respiratory rate (from 198 to 300/min) 5 min after administration and returned to normal values 7 min later. Otherwise, there were no signs of CNS stimulation of the animals at the doses studied. There was no change in animal behavior, activity, and locomotion. None of the animals showed any signs of toxicity or mortality within 24 h after administration of the different compounds in the doses given.

From the biological screening, it is obvious that the tested compounds, although they are structurally related to the well-known carboxamide and *N,N*-alkylated derivatives of heterocyclic types of compounds, do not have a marked MAO inhibitory action. This leads to the conclusion that these bioisostere moieties of the fused heterocyclic systems structurally related to the quinoline series are biologically inactive as CNS stimulants.

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[1] ^{1}H-NMR and MS spectra were determined on Varian spectrometers.

Determination of Phenylbutazone in Tablets by Nuclear Magnetic Resonance Spectrometry

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Received April 18, 1983, from the *Food and Drug Administration, Department of Health and Human Services, New York Regional Laboratory, Brooklyn, NY 11232.* Accepted for publication October 6, 1983.

Abstract □ A method for the quantitative analysis of phenylbutazone in tablets using NMR is reported. The method is both accurate and precise. Using synthetic mixtures, the mean recovery value $\pm SD$ was 100.5 ± 0.86%. The NMR results of commercial preparations are compared with those obtained by the USP XX procedure. The NMR spectrum, in addition, provides a very specific means of identification for phenylbutazone.

Keyphrases □ Phenylbutazone—NMR analysis, comparative analyses □ NMR—phenylbutazone, comparative analyses

Phenylbutazone, 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (I), a synthetic pyrazolone derivative chemically related to aminopyrine, has anti-inflammatory, antipyretic, analgesic, and mild uricosuric properties (1). Approaches to the quantitative determination of phenylbutazone in tablets have varied. Tomaskova (2) reported a GC method using flame-ionization detection. A quantitative IR spectroscopic method was described by Pawelcyzk and Marciniec (3). Differential spectrophotometry, relying on the differences in absorption between acidic and basic species of phenylbutazone, was employed by Bezakova *et al.* (4). Other assay techniques have included separation on an ion-exchange column followed by titration (5) and acid hydrolysis to form benzidine, which was subsequently oxidized, and determined colorimetrically (6). The method of USP XX for the assay of phenylbutazone in tablets entails an ether-based extraction with a UV spectrophotometric determination (7). All these approaches require either lengthy sample preparations and/or nonspecific determinations. In contrast, nuclear magnetic resonance spectrometry (NMR) offers the advantages of minimal sample preparation, simplicity and specificity for the active ingredient.

NMR studies on phenylbutazone have dealt with its carbon-13 spectrum (8), degradation products (9, 10), and the monitoring of its dissolution kinetics (11). However, this technique has not been applied to the quantitative determination of the drug in pharmaceuticals. This paper describes a method in which a carbon tetrachloride–nitromethane mixture is used as the solvent and hexamethylcyclotrisiloxane

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