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Screening Nornuciferine Derivatives for Apomorphine-Like Activity

Keyphrases □ Nornuciferine derivatives—screened for apomorphine-like activity, dogs, pigeons, mice □ Apomorphine-like activity, potential—nornuciferine derivatives screened, dogs, pigeons, mice

Sir:

A substantial number of apomorphine analogs and derivatives were examined in an attempt to define the chemorphological requisites for biological activity, notably activity relating to emesis and behavioral stereotypy (1–3). In a continuing study of apomorphine derivatives having "potential" emetic activity, Vavrek *et al.* (4) prepared a series of 1,2-dimethoxylated noraporphines (nornuciferines) for biological evaluation. These compounds recently were screened for several apomorphine-related activities: (*a*) emesis in dogs, (*b*) compulsive pecking in pigeons, and (*c*) compulsive gnawing in mice. Gross acute toxicity in mice, in terms of convulsions and lethality, were also evaluated.

The method for assessing emetic activity was described previously (2) and involves comparison of the threshold emetic dose of a compound with the threshold emetic dose of apomorphine reference standard in the same animals. Compounds that do not provoke emesis in doses 100 times the apomorphine threshold emetic dose are judged to be inactive. Cumulative pecking responses in birds were recorded with an electromechanical monitor (5), and gnawing activity in mice was assessed as a dose-related quantal response. Drugs were administered as hydrobromide or hydrochloride salts in saline by the following routes: dogs and pigeons, intramuscular; and mice, intraperitoneal.

All of the nornuciferine derivatives were inactive as emetics and exerted no overt behavioral effects in either mice or pigeons. They were devoid of all ability to generate compulsive behavioral responses so characteristic of apomorphine.

The compounds, however, do provoke intense clonic convulsions as does apomorphine. Estimates of convulsant and lethal potencies are presented in Table I. Sparingly soluble compounds, VI–VIII and XIII–XVI, could not be administered in sufficiently high doses to

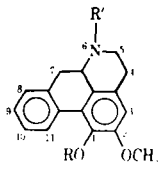

Table I—Comparative Toxicities of Nornuciferine Derivatives in Mice[a]

Compound	Number[b]	R	R'	CD_{50}[c], μmoles/kg.	LD_{50}[d], μmoles/kg.
Apomorphine	—	—	—	328 ± 13	559 ± 33
Nornuciferine	I	CH_3	H	123 ± 4	323 ± 18
Nuciferine	II	CH_3	CH_3	70 ± 2	142 ± 6
(−)-Nuciferine	(−)II	CH_3	CH_3	237 ± 9	280 ± 9
N-Ethylnornuciferine	III	CH_3	CH_2—CH_3	164 ± 12	291 ± 3
N-*n*-Propylnornuciferine	IV	CH_3	CH_2—CH_2—CH_3	363 ± 24	851 ± 60
N-Cyclopropylmethylnornuciferine	V	CH_3	CH_2—	212 ± 15	385 ± 8
N-Allylnornuciferine	VI	CH_3	CH_2—CH=CH_2	>1010	>1010
N-Propargylnornuciferine	VII	CH_3	CH_2—C≡CH	>1010	>1010
N-Benzylnornuciferine	VIII	CH_3	CH_2—C_6H_5	>900	>900
1-Hydroxy-2-methoxynoraporphine	IX	H	H	339 ± 29	469 ± 32
1-Hydroxy-2-methoxyaporphine	X	H	CH_3	217 ± 3	235 ± 4
1-Hydroxy-2-methoxy-*N*-ethylnoraporphine	XI	H	CH_2—CH_3	227 ± 8	272 ± 8
1-Hydroxy-2-methoxy-*N*-*n*-propylnoraporphine	XII	H	CH_2—CH_2—CH_3	404 ± 27	>650
1-Hydroxy-2-methoxy-*N*-cyclopropylmethylnoraporphine	XIII	H	CH_2—	>650	>650
1-Hydroxy-2-methoxy-*N*-allylnoraporphine	XIV	H	CH_2—CH=CH_2	>650	>650
1-Hydroxy-2-methoxy-*N*-propargylnoraporphine	XV	H	CH_2—C≡CH	>650	>650
1-Hydroxy-2-methoxy-*N*-benzylnoraporphine	XVI	H	CH_2—C_6H_5	>650	>650

[a] Female Harlan ICR. [b] Code as designated in *Reference 4*. [c] Median convulsant dose ± *SE* in μmoles of base/kg. body weight, intraperitoneal. [d] Median lethal dose.

permit reliable estimates of either CD_{50} or LD_{50}. Racemic nuciferine (II) proved to be the most toxic member of the series.

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Technique for Preparing Simulated Coated Dosage Forms and Preliminary Evaluation of Sprayed and Cast Films

Keyphrases ☐ Films, sprayed and cast, from the same coating solution—method, apparatus ☐ Simulated coated dosage forms—free films, method and apparatus ☐ Coating solutions—method and apparatus for preparing both cast and sprayed free films

Sir:

Numerous investigations have appeared in the literature evaluating polymeric films either on the basis of their performance on coated tablets prepared by conventional spraying techniques or as unsupported free films prepared by casting techniques.

In a publication dealing with free films, Kanig and Goodman (1) pointed out the benefits of studying the properties of free films without introducing the variables arising from the coating technique or the nature of the dosage form.

In contrast, Zatz *et al.* (2) stated that free films only provide a model for evaluating gross properties of applied films, with limited information in other areas, while Banker *et al.* (3) concluded that free film evaluations should not be used as the sole criterion for accepting or rejecting potential film coatings.

Table I—Free Film Profiles[a]

Property	Cast Film	Sprayed Film
Percent volatiles[b]	8.12 ± 0.28	9.16 ± 0.34
Tear strength, g.[c]	7.20 ± 0.44	5.85 ± 0.32
Thickness range, mm.	0.048–0.052	0.043–0.048
Water vapor permeability[d]	0.8817 ± 0.0362	0.8977 ± 0.0126
Weight/unit area, g.[e]	0.3968	0.3728

[a] These numbers represent mean values of at least four determinations. [b] Measured weight loss under vacuum at 40° to constant weight. [c] Elmendorf Tear Tester, modified ASTM, D687. [d] Modified ASTM, E96-66, units = g. cm. cm.$^{-2}$ × 10^{-6}/24 hr. *Reference 5.* [e] Area of test strip = 80 cm.^{2}.

These reports suggest the importance of a technique or method that would afford the investigator the opportunity to prepare both cast and sprayed free films from the same coating solution and also permit application to simulated dosage forms during a single experiment. In fact, Allen *et al.* (4) recently pointed out the need for a method of preparing free films which simulate, more realistically, those deposited on dosage forms.

To attempt such studies, we devised an apparatus and developed techniques which afford us the options mentioned. The apparatus consists basically of a Teflon-coated metal plate with holes carefully machined to accommodate accurately tablets so that only the tablet surfaces are exposed to the coating formulation. The plate used was 16.5 cm. wide and 56.0 cm. long, with a thickness of 0.385 cm. It consisted of four pairs of holes, each having a diameter of 3.2 cm., with each pair of holes located 9.0 cm. from the next pair in the direction of casting. The holes were spaced in this manner to allow maximum recovery of unsupported free film samples at the same time coated tablets were prepared. The actual spacings are not critical and were selected to provide film samples of adequate size for selected ASTM test procedures.

The tablets used were 3.2 cm. in diameter and were prepared on a Carver press[1] at a weight of approximately 3.0 g., using 11,000 lb./sq. in. pressure. This combination yielded a thickness optimal for use in the coating plate and subsequent test procedures. At this point in the studies, any clearance variation between tablet and hole did not interfere with preparation or recovery of samples so long as a relatively tight fit was maintained.

Experiments were conducted using a casting knife[2] following a technique similar to that outlined by Munden *et al.* (5) and also using a spray[3] process outlined by Allen *et al.* (4). The Teflon plate can be modified into a rotating device where the spray distance, spray rate, and spray time can be varied as well as the revolutions per minute of the device.

Our first concerns were testing the uniformity and investigating the equivalency of cast and sprayed free films as well as developing control tests for these free films. Typical results of these studies for a film consisting of methylcellulose[4] are summarized in Table I.

[1] Model B, Fred S. Carver Inc., Summit, N. J.
[2] Gardner Laboratory Inc., Bethesda, Md.
[3] E. G. A. Type Spray Gun, DeVilbiss Co., Broomall, Pa.
[4] Methocel HG, Dow Chemical Co., Midland, Mich.