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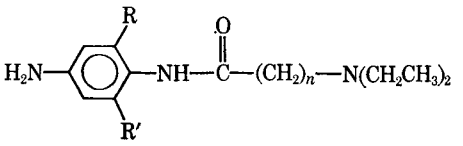
# Potential Antiarrhythmic Agents II: Effects of Amide Reversal and *ortho*-Methylation on Activity of Procaine Amide

**D. K. YUNG, M. M. VOHRA, and I. CHU**

**Abstract** □ Substitution of a methyl group at one or both of the *ortho*-positions of the benzene ring in procaine amide and procaine provides analogs that are more active in prolonging the refractory period of isolated rabbit atria than procaine amide itself. These analogs, however, fail to abolish ouabain-induced ventricular and aconitine-induced atrial arrhythmias in cats. On the other hand, analogs like 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide dihydrochloride monohydrate, 4-amino-*N*-(2-diethylaminoethyl)-2′,6′-dimethylbenzamide, 2-diethylaminoethyl 4-amino-2-methylbenzoate, and 2-diethylaminoethyl 4-amino-2,6-dimethylbenzoate produce a significant increase in the amount of ouabain required to elicit ectopic rhythm in cats when administered before the infusion of the glycoside. Of these four compounds, the last three also show local anesthetic activity in the corneal reflex test in rabbits. Reversal of the amide group in procaine amide significantly reduces the activity in prolonging the refractory period of cardiac tissue and does not seem to improve the antiarrhythmic activity of the parent compounds.

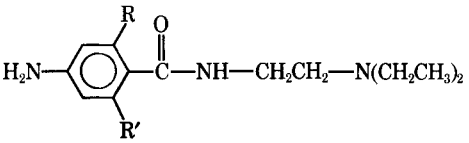
**Keyphrases** □ Antiarrhythmic agents, potential—synthesis □ Procaine amide activity—amide reversal, *ortho*-methylation, effects □ Structure-activity relationships—procaine amide derivatives □ IR spectrophotometry—identity

It is frequently noted that several pairs of compounds with analogous pharmacological activities can be obtained by reversing the position of the functional group. For example, a large increase in analgesic activity is reportedly caused by this type of reversal in the ester functional group of meperidine (1). As part of a continuing investigation on the structure–activity relationships of procaine amide (2), it was, therefore, considered of interest to determine whether this type of isosterism is possible in procaine amide. Accordingly, 3-diethylamino-4′-aminopropionanilide (I*a*) was synthesized. For comparative purposes, 2-diethylamino-4′-aminoacetanilide (I*b*), 3-diethylamino-4′-amino-2′,6′-dimethylpropionanilide (I*c*), and 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide (I*d*) were also prepared. Compounds I*c* and I*d* can be regarded as analogs of lidocaine, which is useful clinically in the prevention and treatment of cardiac arrhythmias.



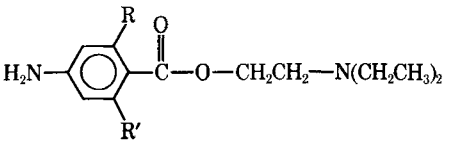
I*a*, $n = 2$; R and R′ = H
I*b*, $n = 1$; R and R′ = H
I*c*, $n = 2$; R and R′ = $CH_3$
I*d*, $n = 1$; R and R′ = $CH_3$

The fact that 4-amino-*N*-(2-diethylaminoethyl)-2-chlorobenzamide was 4 times as active as procaine amide in blocking atrial fibrillation in dogs (3) prompted the preparation of 4-amino-*N*-(2-diethylaminoethyl)-2-methylbenzamide (II*a*) and 4-amino-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide (II*b*) in an attempt to study the effect on activity of substitution of one or two methyl groups on the benzene ring *ortho* to the amide linkage in procaine amide.



II*a*, R = $CH_3$; R′ = H
II*b*, R and R′ = $CH_3$

Two additional compounds, 2-diethylaminoethyl 4-amino-2-methylbenzoate (III*a*) and 2-diethylaminoethyl 4-amino-2,6-dimethylbenzoate (III*b*), were included in



III*a*, R = $CH_3$; R′ = H
III*b*, R and R′ = $CH_3$

Table I—3-Diethylamino-4′-amino-2′,6′-dimethylpropionanilide 2HCl (Ic) and Intermediates

| Compound | Yield, % | M.p. | Solvent of Recrystn. | Formula | Anal., % Calcd. | Found |
|---|---|---|---|---|---|---|
| 4-Nitro-2,6-dimethylaniline | 90 | 161.5–162°[a] | Ethanol (50%) | $C_8H_{10}N_2O_2$ | — | — |
| 3-Chloro-4′-nitro-2′,6′-dimethylpropionanilide | 69 | 218.5–220° | Ethanol | $C_{11}H_{13}ClN_2O_3$ | C, 51.47<br>H, 5.10<br>N, 10.92 | C, 51.55<br>H, 5.13<br>N, 10.74 |
| 3-Diethylamino-4′-nitro-2′,6′-dimethylpropionanilide | 80 | 80–82° | *n*-Hexane–acetone | $C_{15}H_{23}N_3O_3$ | C, 61.41<br>H, 7.90<br>N, 14.32 | C, 61.40<br>H, 7.84<br>N, 14.30 |
| 3-Diethylamino-4′-nitro-2′,6′-dimethylpropionanilide picrate | 72 | 174–176° | Methanol–acetone | $C_{21}H_{26}N_6O_{10}$ | C, 48.27<br>H, 5.02 | C, 48.30<br>H, 5.38 |
| 3-Diethylamino-4′-amino-2′,6′-dimethylpropionanilide 2HCl (Ic) | 60 | 237–238° | Absolute ethanol | $C_{15}H_{27}Cl_2N_3O$ | C, 53.57<br>H, 8.09 | C, 53.34<br>H, 8.23 |
| 3-Diethylamino-4′-amino-2′,6′-dimethylpropionanilide dipicrate | 68 | 207–209° | Methanol–acetone | $C_{27}H_{31}N_9O_{15}$ | C, 44.93<br>H, 4.33 | C, 45.00<br>H, 4.41 |

[a] Reported m.p., 163.5–164.5° (8).

Table II—4-Amino-*N*-(2-diethylaminoethyl)-2-methylbenzamide (IIa) and Intermediates

| Compound | Yield, % | B.p. | Formula | Anal., % Calcd. | Found |
|---|---|---|---|---|---|
| 4-Nitro-2-methylbenzoic acid | 91 | –[a] | — | — | — |
| 4-Nitro-2-methylbenzoyl chloride | 90 | 164–168°/18 mm.[b] | $C_8H_6ClNO_3$ | C, 48.12<br>H, 3.03<br>N, 7.02 | C, 48.40<br>H, 3.27<br>N, 6.86 |
| 4-Nitro-*N*-(2-diethylaminoethyl)-2-methylbenzamide | 82 | 170–174°/0.1 mm.[c] | $C_{14}H_{21}N_3O_3$ | C, 60.19<br>H, 7.58 | C, 60.20<br>H, 7.67 |
| 4-Nitro-*N*-(2-diethylaminoethyl)-2-methylbenzamide picrate | 84 | –[d] | $C_{20}H_{24}N_6O_{10}$ | C, 47.24<br>H, 4.76 | C, 47.24<br>H, 4.86 |
| 4-Amino-*N*-(2-diethylaminoethyl)-2-methylbenzamide (IIa) | 87 | 182°/0.25 mm. | $C_{14}H_{23}N_3O$ | C, 67.45<br>H, 9.30<br>N, 16.86 | C, 66.87<br>H, 9.05<br>N, 17.11 |

[a] M.p. 150–151°, reported m.p. 153° (9). [b] M.p. 33–34°. [c] M.p. 63–64°. [d] M.p. 162–164°, after recrystallization from methanol and acetone.

this study to determine whether or not steric protection of the ester group in procaine can produce active antiarrhythmic substances. The observation of activity in 2-diethylaminoethyl 2,3,5,6-tetramethylbenzoate (4) made the proposed structural modification appealing.

## EXPERIMENTAL

### Chemical Synthesis[1]

Compounds Ia (3-diethylamino-4′-aminopropionanilide HCl) and Ib (2-diethylamino-4′-aminoacetanilide HCl) were prepared according to the procedure reported by DiGangi (5) and Lofgren and Lundquist (6), respectively. The procedure of Dahlbom *et al.* (7) was followed in preparing Compound Ic (3-diethylamino-4′-amino-2′,6′-dimethylpropionanilide 2HCl) and 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide. Compound Ic and its intermediates are new compounds whose physical data and yields are listed in Table I. The dihydrochloride salt of 2-diethylamino-4′-amino-2′,6′-dimethylacetanilide (Id) has not been reported previously.

**2-Diethylamino-4′-amino-2′,6′-dimethylacetanilide 2HCl**—Yield was 95%, m.p. 250–252°, after recrystallization from absolute ethanol.

*Anal.*—Calcd. for $C_{14}H_{21}N_3O \cdot 2HCl \cdot H_2O$: C, 49.41; H, 8.00; N, 12.35. Found: C, 49.41; H, 7.86; N, 12.28.

Compound IIa [4-amino-*N*-(2-diethylaminoethyl)-2-methylbenzamide] was synthesized by the reaction of 4-nitro-2-methylbenzoic acid, which was prepared according to the method of Peltier (9), with thionyl chloride, followed by condensation of the acid chloride with *N*,*N*-diethylethylenediamine and reduction of the resultant 4-nitro-*N*-(2-diethylaminoethyl)-2-methylbenzamide with iron-hydrochloric acid. Attempts to make the hydrochloride salt of Compound IIa failed because of the hygroscopic nature of the salt. The physical data and yields of Compound IIa and its intermediates are summarized in Table II.

The preparation of Compound IIb [4-amino-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide] was analogous to that of Compound IIa. 4-Nitro-2,6-dimethylbenzoic acid was obtained by converting 4-nitro-2,6-dimethylaniline to 4-nitro-2,6-dimethylbenzonitrile *via* the Sandmeyer reaction, followed by acidic hydrolysis of the nitrile. Attempts to prepare the hydrochloride salt of Compound IIb were unsuccessful because of the hygroscopic nature of the salt. Compound IIb and its intermediates have been reported in the literature (10). The intermediate 4-nitro-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide and Compound IIb are liquids; for purpose of identification, picrate salts were prepared.

**4-Nitro-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide Picrate**—Yield was 85%, m.p. 189–191°, after recrystallization from acetone and methanol.

*Anal.*—Calcd. for $C_{21}H_{26}N_6O_{10}$: C, 48.27; H, 5.02. Found: C, 48.15, H, 5.43.

**4-Amino-*N*-(2-diethylaminoethyl)-2,6-dimethylbenzamide Dipicrate**—Yield was 90%, m.p. 200–203°, after recrystallization from acetone and methanol.

*Anal.*—Calcd. for $C_{27}H_{31}N_9O_{15}$: C, 44.93; H, 4.33. Found: C, 44.80; H, 4.51.

Compounds IIIa (2-diethylaminoethyl 4-amino-2-methylbenzoate) and IIIb (2-diethylaminoethyl 4-amino-2,6-dimethylbenzoate) were synthesized by a previously reported procedure (10). While Compound IIIb and its intermediates have appeared in the literature (10), Compound IIIa and its intermediates are new compounds. The physical data and yields of Compound IIIa and its intermediates are listed in Table III. Compounds IIIa and IIIb failed to form stable hydrochloride salts. Since 2-diethylaminoethyl 4-nitro-2,6-dimethylbenzoate and Compound IIIb are liquids, picrate salts were prepared.

[1] Melting points were taken with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Weiler and Strauss, Oxford, England. The absorption peaks of IR spectra of all compounds synthesized were as expected. IR spectra were recorded on a Perkin-Elmer model 237B spectrophotometer.

Table III—2-Diethylaminoethyl 4-Amino-2-methylbenzoate (III*a*) and Intermediates

| Compound | Yield, % | B.p. | Formula | Anal., % Calcd. | Anal., % Found |
|---|---|---|---|---|---|
| 4-Nitro-2-methylbenzoyl chloride | | | See Table II | | |
| 2-Diethylaminoethyl 4-nitro-2-methylbenzoate | 82 | 122–124°/0.05 mm. | $C_{14}H_{20}N_2O_4$ | C, 59.98<br>H, 7.19<br>N, 10.00 | C, 60.21<br>H, 7.45<br>N, 9.64 |
| 2-Diethylaminoethyl 4-nitro-2-methylbenzoate picrate | 62 | —[a] | $C_{20}H_{23}N_5O_{11}$ | C, 47.17<br>H, 4.55 | C, 47.28<br>H, 4.75 |
| 2-Diethylaminoethyl 4-amino-2-methylbenzoate (III*a*) | 98 | 146–150°/0.1 mm. | $C_{14}H_{22}N_2O_2$ | C, 67.17<br>H, 8.86<br>N, 11.19 | C, 67.15<br>H, 9.10<br>N, 11.26 |
| 2-Diethylaminoethyl 4-amino-2-methylbenzoate picrate | 56 | —[b] | $C_{20}H_{25}N_5O_9$ | C, 50.10<br>H, 5.26 | C, 49.66<br>H, 5.40 |

[a] M.p. 173.5–175°, after recrystallization from methanol and acetone. [b] M.p. 155–157°, after recrystallization from methanol and acetone.

Table IV—Effect of Compounds on the Maximum Stimulation Rates (MSR) of Isolated Rabbit Atria

| Compound | Concn., mcg./ml. | Average Percent Depression, MSR | Activity |
|---|---|---|---|
| Procaine amide | 10 | 10.4 ± 1.5 | 1 |
| | 20 | 15.1 ± 2.2 | 1 |
| | 30 | 19.8 ± 4.7 | 1 |
| 3-Diethylamino-4′-amino-propionanilide HCl (I*a*) | 30 | 5.1 ± 1.0 | 0.3 |
| 2-Diethylamino-4′-amino-acetanilide HCl (I*b*) | 30 | 5.4 ± 1.2 | 0.3 |
| 3-Diethylamino-4′-amino-2′,6′-dimethylpropion-anilide 2HCl (I*c*) | 10 | 18.2 ± 4.4 | 1.8 |
| | 20 | 24.9 ± 2.5 | 1.7 |
| | 30 | 34.4 ± 4.7 | 1.7 |
| 2-Diethylamino-4′-amino-2′,6′-dimethylacetani-lide 2HCl $H_2O$ (I*d*) | 10 | 18.5 ± 2.8 | 1.8 |
| | 20 | 26.0 ± 3.6 | 1.7 |
| | 30 | 33.5 ± 5.3 | 1.7 |
| 4-Amino-*N*-(2-diethylamino-ethyl)-2-methylbenzamide (II*a*) | 10 | 14.6 ± 1.1 | 1.4 |
| | 20 | 21.9 ± 3.4 | 1.5 |
| | 30 | 28.0 ± 2.6 | 1.4 |
| 4-Amino-*N*-(2-diethylamino-ethyl)-2,6-dimethyl-benzamide (II*b*) | 10 | 17.1 ± 1.7 | 1.6 |
| | 20 | 30.7 ± 1.4 | 2.0 |
| | 30 | 36.3 ± 2.2 | 1.8 |
| 2-Diethylaminoethyl 4-amino-2-methylbenzoate (III*a*) | 5 | 26.7 ± 2.0 | — |
| | 10 | 42.4 ± 6.8 | 4.1 |
| 2-Diethylaminoethyl 4-amino-2,6-dimethylbenzoate (III*b*) | 5 | 23.4 ± 2.2 | — |
| | 10 | 48.0 ± 7.6 | 4.6 |

**2-Diethylaminoethyl 4-Nitro-2,6-dimethylbenzoate Picrate**—Yield was 96%, m.p. 169–171°, after recrystallization from acetone and methanol.

*Anal.*—Calcd. for $C_{21}H_{25}N_5O_{11}$: C, 48.18; H, 4.81; N, 13.37. Found: C, 48.17; H, 4.86; N, 13.70.

**2-Diethylaminoethyl 4-Amino-2,6-dimethylbenzoate Dipicrate**—Yield was 83%, m.p. 107–111°, after recrystallization from acetone and methanol.

*Anal.*—Calcd. for $C_{27}H_{30}N_8O_{16}$: C, 44.88; H, 4.18. Found: C, 45.14; H, 4.50.

**Determination of pKa Values**—An accurately weighed amount of the compound (about 120 mg.) was dissolved in a stoichiometric quantity of 0.1 *N* HCl or in water, and the solution was diluted to 200 ml. with freshly boiled distilled water. To the solution was added a known amount of 0.1 *N* NaOH. The pH of the solution was then determined by means of a pH meter. The pKa value of the compound was calculated, using the formula $pKa = pH - \log [B]/[BH^+]$.

### Pharmacological Testing

For the biological testing, compounds that formed hydrochloride salts were dissolved in distilled water. The others were dissolved in a stoichiometric amount of 0.4 *N* HCl. All solutions were then buffered with potassium phosphate solution of pH 7.4, followed by dilution with normal saline to give the desired concentrations. Procaine amide and procaine were used in the form of hydrochloride salts.

**Determination of Maximum Stimulation Rate (MSR)**—The method of determination was that reported by Dawes (11). The rate and amplitude of contraction of the rabbit atria were recorded by a force displacement transducer on an E & M model DMP-4A physiograph. Four or more determinations were carried out, using at least two isolated atria for each compound. The average percent depression on the MSR for procaine amide was arbitrarily set to have an activity of 1 unit.

**General Methods for Experiments on Cats**—Cats of either sex, weighing from 2 to 4 kg., were anesthetized with pentobarbital[2] (35 mg./kg. i.p.). Artificial respiration was maintained throughout the experiment. Mean atrial blood pressure was recorded from the femoral artery with a Statham P-23C pressure transducer. Electrocardiograms were recorded on a standard Lead II. All recordings were made on a direct ink-writing Beckman type R dynograph. The solutions of the test compounds were injected intravenously through indwelling polyethylene catheters in the femoral vein, followed by a 2-ml. saline flush.

Prior to the testing for antiarrhythmic activity, the cardiotoxicity of Compounds I*c*, I*d*, II*a*, II*b*, III*a*, and III*b* was studied by injecting the compound intravenously at increasing doses of 1, 2.5, 5, and 10 mg./kg. at 10-min. intervals until ectopic rhythm appeared in the electrocardiograms. The total dose was taken as the maximum tolerated dose.

**Determination of Activity in Termination of Ouabain-Induced Arrhythmias**—The method used to induce arrhythmias with ouabain was that described by Raper and Wale (12). An initial loading dose of ouabain (40 mcg./kg.) was injected intravenously into cats; starting 30 min. later, doses of 10 mcg./kg. were repeated at 15-min. intervals until a persistent ventricular tachycardia was produced. When arrhythmias had persisted for 10 min., increasing doses of the compound to be tested were given every 10 min. until the maxi-

[2] Nembutal.

Table V—Arrhythmic and Lethal Doses of Ouabain[a] in Cats Pretreated with Compounds

| Compound[b] | Approx. $LD_{50}$, mg./kg. | Dose of Compd,[c] mg./kg. | No. of Cats | Average Dose to Ectopic Rhythm, mcg./kg. | $p$[d] | Average Lethal Dose, mcg./kg. | $p$[d] |
|---|---|---|---|---|---|---|---|
| Control | — | — | 3 | 104 ± 6 | — | 158 ± 10 | — |
| Procaine amide | 290 | 18.5 | 2 | 143 ± 15 | <0.01 | 228 ± 1 | <0.01 |
| Ic | 194 | 8.5 | 1 | 110 | — | 162 | — |
| Id | 192 | 18.5 | 3 | 131 ± 4 | <0.01 | 212 ± 23 | <0.05 |
| IIa | 186 | 18.5 | 1 | 118 | — | 168 | — |
| IIb | 209 | 8.5 | 3 | 129 ± 11 | <0.05 | 215 ± 20 | >0.01 |
| IIIa | 86 | 18.5 | 3 | 143 ± 5 | <0.01 | 210 ± 27 | <0.05 |
| IIIb | 67 | 8.5 | 3 | 128 ± 5 | <0.01 | 193 ± 31 | >0.05 |

[a] Ouabain administered by intravenous infusion at a rate of 5 mcg./kg./min. [b] Compounds administered by slow intravenous injection before ouabain infusion. [c] Maximum tolerated dose of the compounds. [d] $p$ values compared with control.

mum tolerated dose was reached. The criterion used to define antiarrhythmic activity was the reversion to sinus rhythm for a period of not less than 30 min.

**Determination of Activity in Prevention of Ouabain-Induced Arrhythmias**—In this series of experiments the compound to be tested was injected intravenously in cats in one single dose. Ouabain was administered 10 min. later by intravenous infusion at the rate of 5 mcg./kg./min. The amount of ouabain required to produce ectopic rhythm and death was determined.

**Determination of Activity in Termination of Aconitine-Induced Arrhythmias**—Atrial arrhythmias were produced in cats according to the procedure described by Schmid and Hanna (13). A 0.05% solution of aconitine nitrate in normal saline was used. Compounds Id and IIIa were administered intravenously at the rate of 1 mg./kg./min., and Compounds IIb and IIIb were administered at the rate of 0.5 mg./kg./min.

**Determination of Surface Anesthesia in Rabbits**—Albino rabbits of either sex, weighing 2 to 3 kg., were used. The eyelashes of the rabbit were clipped off; into each conjunctival sac was instilled 0.5 ml. of a 2% solution of the test compound. Normal saline solution was used as a control. The corneal reflex was elicited by touching the cornea with a feather five times at 2, 5, 10, 15, 20, 30, and 35 min. after the compound was applied. The degree of anesthetic activity was expressed in terms of percent anesthesia. For example, a score of 50 failures of corneal reflex out of a possible maximum of 120 gave 41.7% anesthesia.

**Acute Toxicity Studies in Mice**—Male albino mice, weighing 20 to 35 g., were used in the tests. Compounds were injected intraperitoneally. The median lethal dose ($LD_{50}$) for each compound was calculated by the method of Litchfield and Wilcoxon (14) and was based on 1 day's observations.

## RESULTS AND DISCUSSION

Results in Table IV indicate that although Compound Ia showed some activity in prolonging the refractory period of isolated rabbit atria at a concentration of 30 mcg./ml., the activity, being only one-third of the activity of procaine amide, was hardly significant. Shortening the hydrocarbon chain length between the carbonyl carbon and the terminal amino nitrogen atoms in Compound Ia failed to improve the activity of the parent compound. This suggests that reversing the amide functional group in procaine amide does not improve the antiarrhythmic activity of the compound.

The activity of procaine amide to depress the MSR of isolated rabbit atria was increased significantly ($p < 0.05$) when one or two methyl groups were substituted at the *ortho*-positions of the benzene ring. This information led to the synthesis of the two lidocaine analogs, Compounds Ic and Id. These two compounds had an activity of about 1.7 times that of procaine amide in depressing the MSR. Compared with the corresponding nonmethylated compounds, Ia and Ib, the methylated ones were at least 5 times more active.

In view of the favorable effect of the methyl substituents, it was considered of interest to modify the structure of procaine in the same fashion. Accordingly, Compounds IIIa and IIIb were prepared. When tested on isolated rabbit atria, both compounds demonstrated marked depressant action on the force and rate of contraction of the atria at a concentration of 30 mcg./ml. Determinations of MSR were, therefore, carried out at lower concentrations, 5 and 10 mcg./ml. Results showed that Compounds IIIa and IIIb were about 4 times more active than procaine amide.

Since Compounds Ic, Id, IIa, IIb, IIIa, and IIIb showed significant prolongation of the refractory period of isolated rabbit atria, they were tested for their ability to antagonize or prevent ouabain-induced arrhythmias. Prior to these experiments, the maximum tolerated dose of the compounds was determined. For Compounds Ic, IIb, and IIIb, the maximum tolerated dose was found to be 8.5 mg./kg.; for Compounds IIa and IIIa, the maximum was 18.5 mg./kg. It appeared that compounds with a methyl substituent at both *ortho*-positions of the benzene ring had a higher cardiotoxicity, as indicated by the lower maximum tolerated dose value, than those that were only mono-*ortho* substituted.

None of the compounds tested appeared to show any activity in terminating arrhythmias induced by ouabain. To make certain that the animals were not refractory, procaine amide was given after each experiment in doses of 28.5 to 38.5 mg./kg., and this resulted in the successful conversion to sinus rhythm. It should be noted, however, that procaine amide was also ineffective at doses of 8.5 and 18.5 mg./kg.

The effectiveness of the compounds in preventing ouabain-induced arrhythmias was determined by the increase in the amount of the glycoside needed to evoke ectopic rhythm, as indicated in the electrocardiograms by three successive QRS complexes not clearly related to a preceding P wave (15), and to cause the death of the animal. Results of the determinations are listed in Table V. On a weight basis, the di-*ortho*-methyl-substituted procaine amide analog (IIb) showed a higher prophylactic activity against arrhythmias than procaine amide, whereas the monosubstituted analog (IIa) did not appear to have any activity at all. The corresponding analogs of procaine, Compounds IIIa and IIIb, also showed protective action against ouabain-induced arrhythmias. Again, on a weight basis, the di-*ortho*-methyl-substituted compound (IIIb) was more active than the monosubstituted analog (IIIa).

After Compounds Id, IIb, IIIa, and IIIb were found to be active prophylactically against ventricular arrhythmias caused by ouabain, it was decided to test them for activity in abolishing established atrial arrhythmias induced by aconitine. None of the compounds showed any activity.

The effects of Compounds Ic, Id, IIa, IIb, IIIa, and IIIb on blood pressure were studied. The compounds did not demonstrate any significant effect on the blood pressure, although a transient lowering of blood pressure was observed with Compounds IIb and IIIa at cumulative doses of 6 mg./kg.

Table VI—Local Anesthetic Activity of Compounds and Their Ionization Constant ($H_2O$, 25°)

| Compound | No. of Tests | Average Percent Anesthesia | pKa |
|---|---|---|---|
| Saline (control) | – | — | — |
| Procaine | 6 | 34.6 | 8.86[a] |
| Id | 3 | Inactive | 8.24 |
| IIb | 3 | 54.1 | 8.68 |
| IIIa | 2 | 41.3 | 8.80 |
| IIIb | 3 | 41.7 | 8.64 |

[a] Reported pKb value, 5.2 (16).

Since many antiarrhythmic agents seem to possess some degree of local anesthetic action, those compounds, namely, Id, IIb, IIIa, and IIIb, were tested for local anesthetic activity. Table VI is the summary of the results of the testing. Due to the limited number of tests, the data in this table were not analyzed statistically to determine if the average percent anesthesia of the compounds was significantly higher than that of procaine. Therefore, the results should be treated qualitatively rather than quantitatively. It is not surprising that Compounds IIb, IIIa, and IIIb showed local anesthetic activity, because in addition to structural similarity these compounds had a pKa value very close to that of procaine.

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# *In Vivo* Evaluation of Absorption and Excretion of Pentylenetetrazol-10-$^{14}$C from Sustained-Release and Nonsustained-Release Tablets


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**Abstract** □ Sustained-release and nonsustained-release tablets containing pentylenetetrazol-10-$^{14}$C were administered orally to human volunteers. The levels of the drug and/or its labeled metabolites in the plasma and urine were determined by liquid scintillation counting. These data showed that the sustained-release tablets provided a consistent plasma level of $^{14}$C for about 12 hr. and that the drug and/or its labeled metabolites were excreted in the urine at a fairly constant rate during this period. The nonsustained-release tablets given in divided doses resulted in three separate peak plasma-$^{14}$C levels and a urinary excretion pattern similar to that of the sustained-release tablet. A single dose of the nonsustained-release tablet was followed by a peak plasma-$^{14}$C level, which decreased during the 12 hr. after administration, and by a fairly constant rate of urinary excretion of $^{14}$C during this period.



**Keyphrases** □ Pentylenetetrazol-10-$^{14}$C—absorption, excretion □ Tablets, sustained-, nonsustained-release—pentylenetetrazol-10-$^{14}$C □ Absorption, excretion—pentylenetetrazol-10-$^{14}$C from sustained-, nonsustained-release tablets □ Scintillometry—analysis


Sustained-release[1] and nonsustained-release tablets containing pentylenetetrazol and niacin in common therapeutic dosages have been evaluated for their *in vivo* performance in humans by following niacin–plasma levels (1). This evaluation was accomplished by using $^{14}$C-labeled niacin in the tablets and determining the plasma and urine levels of niacin-$^{14}$C and/or its labeled metabolites subsequent to oral administration of the tablets. The results of this study showed that after ingestion of sustained-release tablets, the plasma level of niacin-$^{14}$C and/or its labeled metabolites was sustained for a 12-hr. period. In contrast, three doses of nonsustained-release tablets, administered at 4-hr. intervals, resulted in three peak plasma levels. The drug excretion patterns observed after both dosage regimens were similar.

Because of the various chemical, pharmacological, and metabolic differences between niacin and pentylenetetrazol, different absorption and excretion patterns for the two drugs were expected. The present paper reports a study of the absorption and excretion patterns characteristic of pentylenetetrazol administered orally, combined with niacin, in both sustained-release and nonsustained-release dosage forms. Pentylenetetrazol-10-$^{14}$C was used in this study to permit determination of these patterns by radiotracer techniques similar to those originally reported by Rosen and Swintosky (2) for following the appearance of a drug in human plasma and urine.

[1] Geroniazol TT, Philips Roxane Laboratories, Columbus, Ohio.