Table I—Assay Results on Commercial Dosage Forms

Dosage Form	I per Dosage, mg	Other Active Ingredients, mg	Results on I, % Modified Method[a]	Results on I, % NF Method[a]
Green tablet	20	None	97.0	96.5
Yellow tablet	10	Phenobarbital, 15	98.4	98.0
White tablet	10	None	99.2	99.5
Orange tablet	20	Meprobamate, 200	99.2	98.9
Light-red tablet	20	Hydroxyzine hydrochloride, 10	99.2	99.5
Sustained-release capsule (white pellets)	30	None	105.9	105.2

[a] Average of two determinations.

DISCUSSION

The results (Table I) for various dosage forms indicate that the NF method (1) can be modified to save 75% of the time required for the analysis of I and to assure quantitative recoveries. The only precaution is that the powder must be finely ground, as required also by the NF method. It is recommended that this change be made in the NF procedure.

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Synthesis of an Anti-Inflammatory 10,10a-Dihydro-1*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3(2*H*)-dione

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Received April 15, 1977, from the *Scientific Affairs Department, Norwich-Eaton Pharmaceuticals Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication August 10, 1977.

Abstract □ A new synthesis of imidazo[1,5-*b*]isoquinolines is reported. 2-[2-(Piperidino)ethyl]-10,10a-dihydro-1*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3(2*H*)-dione hydrochloride was found to possess anti-inflammatory activity.

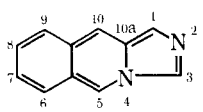
Keyphrases □ Imidazo[1,5-*b*]isoquinolines, substituted—synthesized, evaluated for anti-inflammatory activity □ Anti-inflammatory activity—evaluated in substituted imidazo[1,5-*b*]isoquinolines

The imidazo[1,5-*b*]isoquinoline ring system (I) has received little attention. Prior to work in this laboratory (1), all known members of this class of compounds were prepared by reaction of the appropriate 2,4-imidazolidinedione with a functionalized benzaldehyde (2–5). Since this sequence gives rise to compounds containing an oxo or thio group in the 5-position as well as a double bond at the 10–10a-position, it is not suitable for the synthesis of the projected compound, II, a derivative of III (Scheme I) containing the water-solubilizing piperidinoethyl function.

DISCUSSION

The target compound was readily prepared in a two-step sequence originating with the *d,l*-acid IV (6). Acid-catalyzed treatment of IV with potassium cyanate gave the unsubstituted III, and treatment of III with *N*-(2-chloroethyl)piperidine (V) afforded *d,l*-II.

Compound II was studied for anti-inflammatory activity in the conventional manner by determining its effectiveness in reducing the edematous inflammation induced by an injection of carrageenan (0.05 ml of a 1% solution) into the plantar surface of the rat hindpaw (7). At a dose of 300 mg/kg po, administered 1 hr before carrageenan, II caused moderate (44.2%) antagonism of edema formation 4 hr after the carrageenan injection; this antagonism decreased to 26.3% after 6 hr. Thus,



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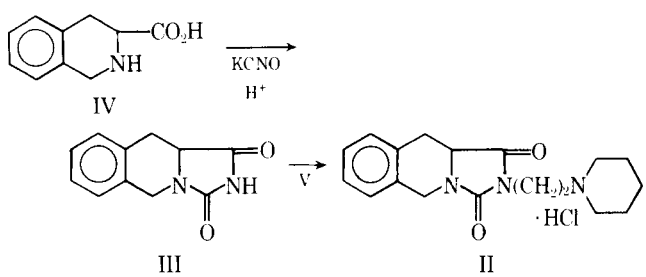

Scheme I

II possesses anti-inflammatory activity but with a shorter duration than that evoked by some standard anti-inflammatory drugs such as phenylbutazone (58% at 6 hr), indomethacin (49% at 6 hr), and ibuprofen (55% at 6 hr).

EXPERIMENTAL[1]

10,10a-Dihydro-1*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3(2*H*)-dione (III)—To a suspension of 53.1 g (0.30 mole) of *d,l*-IV (6) in 1000 ml of acetic acid was added quickly a solution of 48.6 g (0.60 mole) of potassium cyanate in 150 ml of water. The mixture was stirred and heated on a steam bath at 90–95° for 90 min, and all solids were dissolved. Hydrochloric acid (3 *N*, 2400 ml) was added, and the resulting solution was stirred and refluxed for 20 hr. The solution was filtered while hot through a coarse sintered-glass funnel to remove mechanical impurities, and the filtrate was stored in the refrigerator for 18 hr; 44 g of the crude product was obtained.

Recrystallization from 1400 ml of alcohol gave 29.9 g (49%) of III, mp 225–231°. Further recrystallization from alcohol gave an analytical sample, mp 227–230°; IR: 3.14 (NH), 5.63, and 5.85 (C=O, imidazolidinedione) μm; NMR (dimethyl sulfoxide-d_6): δ 2.73–3.06 (m, 2, C-10 H_2), 4.05–4.96 (m, 3, C-5 H_2 and C-10a H), 7.25 (s, 4, aromatic CH), and 10.5–11.1 (broad s, 1, exchangeable, NH) ppm; mass spectrum M^+: *m/e* 202.

[1] Melting points were determined on a Mel-Temp apparatus, and those below 230° are corrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. NMR spectra were obtained on a Varian A-60A instrument and were compared with tetramethylsilane as an internal standard. The mass spectrum was run on a Finnigan model 3300 mass spectrometer at the Mass Spectrometry Facility at Cornell University.

Anal.—Calc. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.41; H, 4.80; N, 13.90.

2-[2-(Piperidino)ethyl]-10,10a-dihydro -1*H*,5*H*- imidazo[1,5-*b*]isoquinoline-1,3(2*H*)-dione Hydrochloride (II)—A mixture of 26.5 g (0.131 mole) of III, 48.2 g (0.262 mole) of V, 54.2 g (0.393 mole) of potassium carbonate, and 19.7 g (0.131 mole) of sodium iodide in 900 ml of dimethyl sulfoxide was stirred at 50–55° for 48 hr. An additional 24.1 g (0.131 mole) of V was added to the mixture, and stirring was continued at 50–55° for an additional 24 hr. Then the mixture was cooled, poured into 2.0 liters of cold water, and extracted with 4 × 400 ml of chloroform. The combined extracts were washed with 2 × 800 ml of water, dried (magnesium sulfate), and concentrated to dryness. The oil was boiled with 180 ml of ethanol, and the resulting suspension was stored in the refrigerator for 2 weeks. Filtration gave 9.0 g of unreacted III.

To the filtrate was added 40 ml of methanol saturated with hydrogen chloride. The resulting solid was recrystallized from 125 ml of ethanol to yield, after drying at 100° for 4 hr, 7.9 g (26% based on consumed III) of the product, mp 204–207°. An analytical sample, mp 237–239°, was obtained by recrystallization from ethanol; IR: 5.70 and 5.90 (C=O, imidazolidinedione) μm; NMR (dimethyl sulfoxide-d_6): δ 1.46–1.96 (broad m, 6, piperidine 3-CH_2, 4-CH_2, and 5-CH_2), 3.05–3.20 (m, 2, C-10 H_2), 3.16–3.50 (broad m, 4, piperidine 2-CH_2 and 6-CH_2), 3.73–5.00 (m, 7, C-5 H_2, C-10a H, and NCH_2CH_2N), 7.28 (s, 4, aromatic CH), and 10.9–11.4 (broad s, 1, exchangeable NH) ppm.

Anal.—Calc. for $C_{18}H_{23}N_3O_2$·HCl: C, 61.79; H, 6.91; N, 12.01. Found: C, 61.78; H, 7.02; N, 11.86.

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dc Polarographic Determination of Hydroxylaminoeverninomicin D

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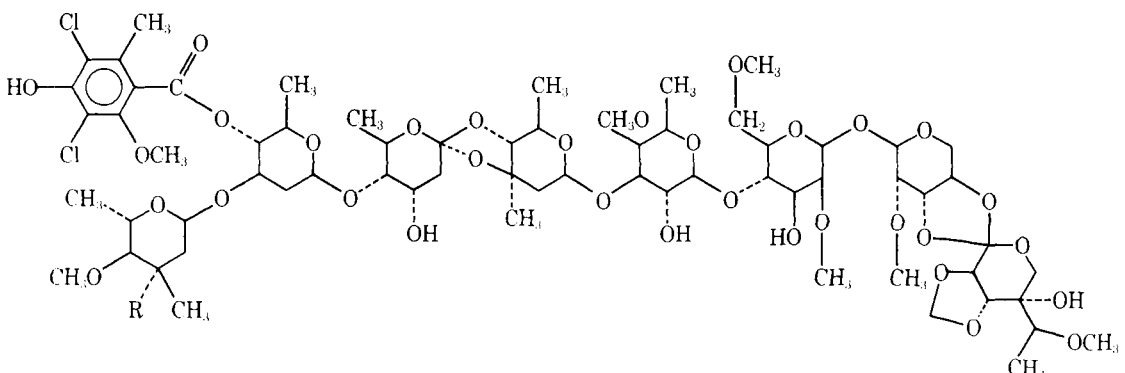
Received June 24, 1977, from the *Development Division, Schering Corporation, Bloomfield, NJ 07003.* Accepted for publication August 18, 1977.

Abstract □ An analytical procedure for a tertiary alkylhydroxylamine, hydroxylaminoeverninomicin D, was developed. It involved the autoxidation of the compound in the presence of Cu(II) and subsequent polarographic reduction. Conditions are described for the quantitative determination of the possible impurities (everninomicin D and nitrosoeverninomicin D) in hydroxylaminoeverninomicin D.

Keyphrases □ Hydroxylaminoeverninomicin D—polarographic analysis, bulk drug □ Polarography—analysis, hydroxylaminoeverninomicin D, bulk drug □ Antibacterials—hydroxylaminoeverninomicin D, polarographic analysis, bulk drug

Everninomicins (1–3) produced by *Micromonospora carbonaceae* are highly active oligosaccharide antibiotics against Gram-positive bacteria including strains resistant to penicillins, tetracyclines, lincomycins, rifampin, macrolides, and chloramphenicol. The major component of the everninomicin complex (4) is everninomicin D (I). The chemical (5) or electrochemical (6) reduction of the tertiary nitro group in I yields hydroxylaminoeverninomicin D (II). Nitrosoeverninomicin D (III), undergoing similar reductions, also yields II. Compounds I–III possess equal *in vitro* activity against Gram-positive bacteria. However, II gives the highest blood level when administered intramuscularly to dogs.

A reported polarographic determination of alkylhydroxylamines was based on the formation of reproducible



I: R = NO_2
II: R = NHOH
III: R = NO