Cyclohexylammonium 2-bromo-4-fluoro-3-methylpentanoate (29.0 g, 0.093 mole) was dissolved in 150 ml of 5% HCl with cooling. The mixture was extracted twice with 50-ml portions of chloroform. The solution was dried over sodium sulfate, and the solvent was evaporated under vacuum. The solid residue was crystallized from pentane (18.0 g, 10.9%), mp 72–74°. The analytical sample was crystallized from pentane, mp 74–76°; NMR (100 MHz, deuterochloroform, tetramethylsilane): δ 1.12 [d, C-3 CH_3, $J_{C\text{-}3}$ (H)—C-3 CH_3 = 7 Hz], 1.37 [dd, C-4 CH_3, $J_{C\text{-}4}$ (CH_3)—C-4 H = 6 Hz, $J_{C\text{-}4}$ (CH_3)—C-4 F = 29 Hz], 1.62–2.4 (m, C-3 H), 4.25 [d, C-2 H, $J_{C\text{-}2}$ (H)—C-3 H = 10 Hz], and 4.8–5.6 [m, C-4 H, $J_{C\text{-}4}$ (H)—C-4 F = 49 Hz, $J_{C\text{-}4}$ (H)—C-4 CH_3 = 7 Hz, $J_{C\text{-}4}$ (H)—C-3 H = 2 Hz] ppm.

Anal.—Calc. for $C_6H_{10}BrFO_2$: C, 33.82; H, 4.73; Br, 37.51; F, 8.92. Found: C, 33.59; H, 4.72; Br, 37.67; F, 8.92.

2-Bromo-4,4-dimethyl-4-butyrolactone (V)—The ether extract remaining after removal of 2-bromo-4-fluoro-3-methylpentanoic acid was dried over sodium sulfate and freed of solvent. The residue was distilled and yielded 90 g (60%) of product, bp 110–118°/5.0 mm. An analytical sample boiled at 88–90°/0.75 mm; NMR (60 MHz, deuterochloroform, tetramethylsilane): δ 1.48 [s, C-4 $(CH_3)_2$], 1.63 [s, C-4 $(CH_3)_2$], 2.47–2.79 (C-3 H_2, *AB* portions of *ABX* spectrum), and 4.7 (C-2 H, *X* portion of *ABX* spectrum, J_{AX} = 9 Hz, J_{BX} = 7 Hz, J_{AB} = 14.5 Hz) ppm.

Anal.—Calc. for $C_6H_9BrO_2$: C, 37.33; H, 4.70; Br, 41.40; O, 16.58. Found: C, 37.57; H, 4.72; Br, 41.48; O, 16.30.

4-Fluoroisoleucine (IX)—2-Bromo-4-fluoro-3-methylpentanoic acid (30 g, 0.14 mole) was dissolved in 175 ml of liquid ammonia and sealed in a stainless steel pressure vessel. After remaining at room temperature for 3 days, the excess ammonia was removed. The residue was dissolved in a small volume of water and adjusted to pH 5 with hydrobromic acid. The solution was evaporated under reduced pressure below 40°, and the residue was slurried repeatedly with methanol until a negative halogen test was obtained with silver nitrate.

The residue then was removed by filtration and dried under vacuum. The yield of product was 9.1 g (43.5%), mp 195.5–196° dec. An analytical sample was crystallized from a mixture of water and acetone, mp 202–202.5° dec.; NMR (100 MHz, deuterium oxide, sodium 2,2-dimethyl-2-silapentane-5-sulfonate): δ 1.13 [d, C-3 CH_3, $J_{C\text{-}3}$ (H)—C-3 CH_3 = 7 Hz], 1.36 [dd, C-4 CH_3, $J_{C\text{-}4}$ (CH_3)—C-4 H = 7 Hz, $J_{C\text{-}4}$ CH_3—C-4 F = 25 Hz], 1.9–2.4 (m, C-3 H), 3.78 [d, C-2 H, $J_{C\text{-}2}$ (H)—C-3 H = 4 Hz], and 4.4–5.2 [m, C-4 H, $J_{C\text{-}4}$ (H)—C-4 F = 50 Hz] ppm[6].

Anal.—Calc. for $C_6H_{12}FNO_2$: C, 48.31; H, 8.11; F, 12.74; N, 9.39. Found: C, 48.09; H, 8.10; F, 12.73; N, 9.30.

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[6] The NMR spectrum of 3-fluorovaline as reported in Ref. 1 is now corrected to: δ 1.56 [d, C-3 CH_3, $J_{C\text{-}3}$ (CH_3)—F = 23 Hz] and 1.70 [d, C-3 $(CH_3)_2$, $J_{C\text{-}3}$ $(CH_3)_2$—F = 23 Hz] ppm. These results are based on a comparison of the 60- and 100-MHz spectra.

Modified NF Method for Quantitative Determination of Pentaerythritol Tetranitrate

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Received July 11, 1977, from the *College of Pharmacy, University of Houston, Houston, TX 77004.* Accepted for publication August 11, 1977.

Abstract □ A modified NF method for the quantitative determination of pentaerythritol tetranitrate is reported. A solution of powder is made directly from the dosage form in glacial acetic acid and is then reacted with phenoldisulfonic acid TS. The proposed method saves approximately 75% of the time required with the NF method. The results on six different commercial dosage forms with four different colors and three other active ingredients are reported.

Keyphrases □ Pentaerythritol tetranitrate—colorimetric analysis in dosage forms, NF method modified □ Colorimetry—analysis, pentaerythritol tetranitrate in dosage forms, NF method modified □ Vasodilators—pentaerythritol tetranitrate, colorimetric analysis in dosage forms, NF method modified

The NF method (1) for the quantitative determination of pentaerythritol tetranitrate (I) in dilutions and tablets is lengthy and tedious. The method requires boiling the powder in acetone at 60°, cooling it, centrifuging, and then evaporating the decanted solution at 35°. In the hands of inexperienced analysts, the recovery may not be quantitative. By eliminating these steps, 75% of the time required can be saved. This paper reports a modified NF method for the quantitative determination of I in dosage forms.

EXPERIMENTAL

Reagents and Chemicals—All chemicals and reagents were USP, NF, or ACS grade and were used without further purification.

Solutions—All solutions were prepared according to NF directions (1).

Assay—The dosage form was ground to a fine powder in a mortar. An appropriate quantity (accurately weighed), representing 0.5 mg of I, was transferred to a dry, clean, 150-ml beaker. Then 1 ml of glacial acetic acid was added, and the mixture was stirred for several minutes. A 2-ml quantity of phenoldisulfonic acid TS was added, and the mixture was allowed to stand for 5 min. Then 25 ml of water and 25 ml of ammonia TS were added, and the solution was allowed to cool.

The mixture was transferred to a 100-ml volumetric flask and brought to volume with water. The absorbance value of the clear solution was measured[1] at 409 nm against a reagent blank. For increased accuracy, the quantity of powder may be doubled. If so, all volumes should be doubled.

The modified method was tried on six commercial dosage forms containing four different colors; some contained another active ingredient. The results were calculated according to the NF formula (1) (Table I). The results obtained by the NF method (1) are also presented in Table I.

[1] Bausch & Lomb Spectronic 20.

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.

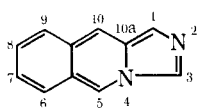
Keyphrases □ Imidazo[1,5-*b*]isoquinolines, substituted—synthesized, evaluated for anti-inflammatory activity □ Anti-inflammatory activity—evaluated in substituted imidazo[1,5-*b*]isoquinolines

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.

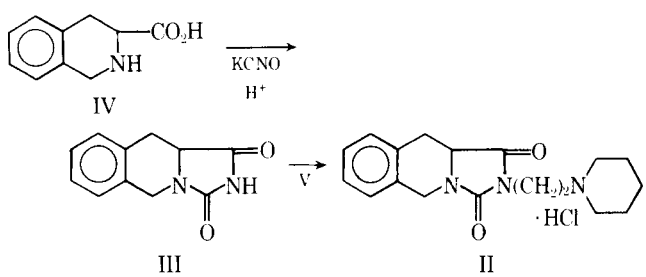
DISCUSSION

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,



I



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.