ethereal HCl was added. The hydrochloride salt which precipitated was collected by filtration and air-dried. The solid weighed 10 g and upon recrystallization from 2-propanol–isopropyl ether gave 8.1 g (42%) of white solid, mp 205–208 °C. Anal. ($C_{12}H_{14}Cl_3NO$) C, H, N.

References and Notes

(1) R. L. Duncan, Jr., G. C. Helsley, W. J. Welstead, Jr., J. P. DaVanzo, W. H. Funderburk, and C. D. Lunsford, *J. Med. Chem.*, **13**, 1 (1970).
(2) Lenperone, A. H. Robins Co., 4-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone monohydrochloride.
(3) Hungarian Patent 155 104; *Chem. Abstr.*, **70**, 47474t (1969).
(4) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(5) D. B. McKean and J. Pearl, *Physiol. Behav.*, **3**, 795–796 (1968).
(6) J. M. VanRossum in "The Neuroleptics. Modern Problems in Pharmacopsychiatry", Vol. 5, D. P. Bobon, P. A. J. Janssen, and J. Bobon, Ed., Liege, Karger, Basel, 1970, pp 23–32.

3-Benzazocine Amidinium Nitronates. An Unusual Type of Opiate Antagonist

Michael J. Strauss,* Raymond R. Bard,

Department of Chemistry

and Donald S. Robinson

Department of Pharmacology, College of Medicine, University of Vermont, Burlington, Vermont 05401.

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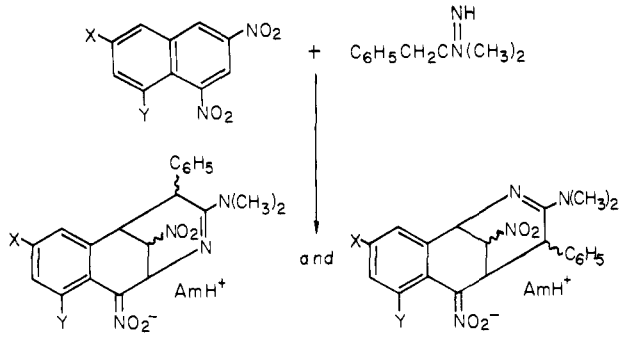
An interesting type of 3-benzazocine ring system which contains amidine functionality has been found to have significant narcotic antagonist activity. The isomeric 2-benzazocine, which incorporates similar structural features, except for the position of the ring nitrogen and adjacent phenyl substituent, is inactive. These 2- and 3-benzazocines can be synthesized in a single step from appropriately structured amidines and naphthalenes, and such syntheses may provide useful routes to new and interesting types of narcotic antagonists.

We recently reported the general synthesis and structure determination for a series of benzazocine amidinium nitronates prepared from 1,3-di- and 1,3,6,8-tetranitronaphthalenes.[1] We wish to report here the structure confirmation and pharmacological properties of certain isomeric 2- and 3-benzazocines in this series prepared from 1,3,6-trinitronaphthalene. A brief discussion of the interesting differences in activity between these isomers is presented. The 3-benzazocine amidinium nitronate may represent a new type of narcotic antagonist.

Two isomeric benzazocine amidinium nitronates (AmH^+ = α-phenyl-*N*,*N*-dimethylacetamidinium cation) **1** and **2** are formed by reaction of 1,3,6-trinitronaphthalene with 2 equiv of α-phenyl-*N*,*N*-dimethylacetamidine.[1] One



1, X = NO_2; Y = H
3, X = Y = NO_2

2, X = NO_2; Y = H
4, X = Y = H

isomer is obtained when the reaction is carried out in ethanol and the other is obtained when the reaction is carried out in Me_2SO.[1] When the reaction with 1,3,6,8-tetranitronaphthalene is carried out in Me_2SO, the 3-benzazocine **3** is formed, whereas with 1,3-dinitronaphthalene in Me_2SO the 2-benzazocine **4** is formed.[1] Using deuterium-labeled substrates the identity of **3** and **4** has previously been established.[1]

The structures of **1** and **2** are based solely on analogies with ^1H NMR chemical shifts for the di- and tetranitro analogues **3** and **4**. Confirmation of these assignments has now been obtained by deuterium labeling of the starting trinitronaphthalene, and the analgesic and analgesic–antagonist activity of **1–4** is reported here. We were specifically interested in the isomers **1** and **3** since the ring nitrogen and aromatic ring substituent are positioned similarly to those of frequently prepared pharmacologically active 3-benzazocines **5**.[2]

Pharmacological Results. Analgesia and analgesic–antagonism were measured using the mouse tail-flick test (see Experimental Section) as described by Harris and Dewey.[3] The antagonist screening results are summarized in Figure 1. The analgesic screening showed **1–4** all inactive. All were extremely insoluble and were administered intramuscularly or subcutaneously in Me_2SO.

The most definitive aspect of the data summarized in Figure 1 is the dose-related narcotic antagonism observed for **1** and the complete lack of activity (even at the high dose level of 20 mg/kg) for isomer **2** and the analogue **4**. This is evidence for a quite specific interaction resulting in narcotic antagonism from **1** and not a general CNS toxicity resulting from structures like **1–4**.

Interestingly, while **1** does contain the 3-benzazocine ring system, it also has a number of unusual structural features not associated with any previously reported narcotic antagonists. It is a nitronate salt with trigonal hybridization at C-1, analogous to ketazocine,[4] and the benzazocine nitrogen is trigonally hybridized in the form of amidine functionality. This ring nitrogen is unsubstituted and **1** does not contain a quaternary C-6 carbon. These latter structural features are usually found in benzazocine analgesics and analgesic–antagonists.[2]

The long delay in onset of maximum activity and extended duration of activity of **1** and **3** is probably related to slow absorption from the injection site. The extremely low solubility of these compounds in water makes it very likely that this factor is primarily responsible for the slow onset and sustained narcotic antagonism shown by **1** and **3**. The maximum antagonist activity occurs at about 8 h

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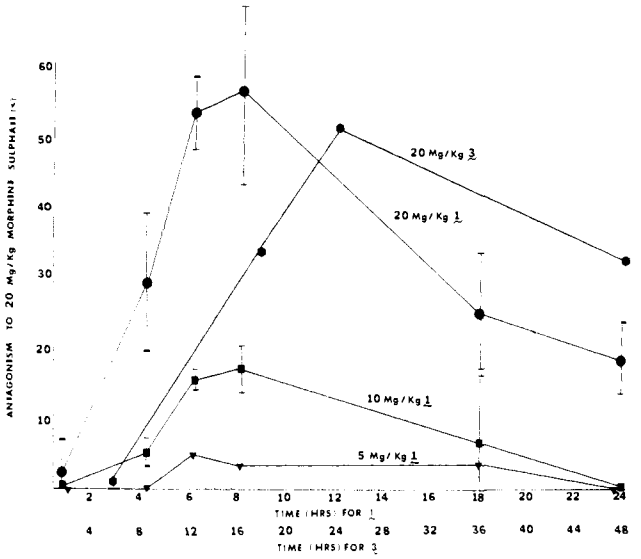
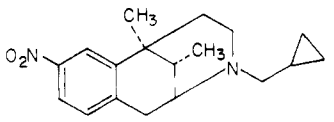


Figure 1. Duration of antagonist activity for 1 and **3** against a 20 mg/kg dose of morphine sulfate.

for 1 and 24 h for **3**, and at the maximum dose of each (20 mg/kg) is only 50–60%. This might be expected for such water-insoluble compounds. Another factor which could contribute to the slow onset and sustained activity is metabolism to an active compound.

In a control study which we carried out with naloxone hydrochloride, 100% antagonism is observed at a dose of 0.4 mg/kg at 40 min (sc in Me_2SO). The dose required for 50–60% antagonism at 40 min is 0.04 mg/kg. Thus for each drug, at the time of maximum activity, naloxone is at least 500 times as potent an antagonist as 1 or **3**. Naloxone antagonism drops off rapidly, however, reaching 10% at 8 h. At 24 h it is 0%,[5] where both 1 and **3** still show significant antagonist activity. The tetranitro compound **3** shows significant 48-h antagonism at a level exceeding that of the insoluble salt complexes of naloxone we have prepared previously in an attempt to develop long-acting antagonist preparations.[5]

The only other nitroaromatic 3-benzazocine antagonist previously studied is the cyclazozcine analogue **5**.[6] This



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compound was reported to have an AD_{50} of 9.6 mg/kg sc (vs. meperidine).[7] It was prepared as a precursor to the 8-aminocyclazocine analogue. These compounds were reportedly prepared to increase the duration of narcotic antagonist activity of cyclazocine-like antagonists by hindering glucuronide formation which occurs at the 8-hydroxyl in cyclazocine.

The activity shown by 1 is not due to the counter α-phenyl-*N*,*N*-dimethylacetamidinium ion since the hydrochloride is inactive.

Experimental Section

Synthesis. The preparation of both 1 and **2** has previously been described.[1] The synthesis of C-1 deuterated 1 was achieved as follows. 1-Chloro-2,4,7-trinitronaphthalene was prepared according to the procedure of Fendler.[3] This aromatic (0.2 g) and deuteriobenzoic acid (0.6 g) were stirred in a 5-mL round-bottom flask fitted with a drying tube. The mixture was heated to 150 °C (*caution*: higher temperatures result in decomposition) and small portions of electrolytic copper dust (0.2 g) were added over a period of 5 min. After addition of the copper was completed, the temperature was maintained at 150 °C for 5 min. The mixture was then cooled and the flask and contents were placed in a beaker containing 50 mL of 8% sodium bicarbonate. The solid was broken up and crushed until effervescence ceased, filtered off, and then stirred with 200 mL of acetone. The insoluble copper was filtered off and the filtrate was reduced in volume on a rotary evaporator. The residue was dissolved in absolute ethanol, decolorized with activated carbon, filtered, and cooled to yield 30 mg of 1-deuterio-2,4,7-trinitronaphthalene. The ^1H NMR (Me_2SO-d_6) showed absorptions at δ 8.75 (d, J = 1.5 Hz, H_5 and H_6), 9.02 (s, H_3), 9.41 (d, J = 1.5 Hz, H_8), and 9.56 (d, J = 2 Hz, 0.2 residual H_1; ~80% deuteration).

The adduct of 1-deuterio-2,4,7-trinitronaphthalene with α-phenyl-*N*,*N*-dimethylacetamidine was prepared as follows. To an ethanolic solution containing 20 mg of the deuterated aromatic was added 28 mg of amidine. After 2 days the orange crystals were filtered off, washed with cold ethanol, pulverized, and stirred in anhydrous ether. The resulting powder was filtered off and dried under vacuum at 65 °C for 4 h to yield 15 mg of C-1 deuterated 1. The ^1H NMR spectrum of this product in Me_2SO-d_6 was identical with that of 1 reported previously[1] except for the H-1 absorption. Peaks were observed at δ 2.60 (s, 6 H, NCH_3), 3.14 (s, 6 H, NCH_3), 3.77 (m, 0.2 H, bridgehead next to carbon), 4.03 (s, 2 H, CH_2 of cation), 4.46 (s, 1 H, CHC_6H_5), 4.87 (d, J = 5 Hz, 1 H, $CHNO_2$), 6.32 (d, J = 5 Hz, 1 H, bridgehead next to nitrogen), 7.48 (m, 10 H, C_6H_5), 7.93 (dd, J = 7 and 2 Hz, 1 H, nitroaromatic H), 8.38 (d, J = 2 Hz, 1 H, peri to bridgehead), 9.11 (d, J = 7 Hz, 1 H, peri to nitronate).

Pharmacology. Solutions of drug (1–**3**) were administered to Swiss albino mice, obtained from Canadian Breeding Laboratories, St. Constant, Quebec. Mice were equilibrated for at least 1 week in the laboratory environment before screening. At that time they weighed approximately 25 g each. Drug dosage was adjusted to animal weight and the drug was given intramuscularly in Me_2SO solution. Compound **3** was administered subcutaneously.

Analgesic activity of morphine sulfate was determined by adaptation to the mouse tail-flick procedure of the method of Harris and Pierson.[8] Antagonism of analgesia was evaluated by intramuscular administration of antagonist at 5, 10, and 20 mg/kg doses. Duration of antagonist activity was evaluated by dosing mice with the drug preparation, and by taking groups of 12 mice at each dose and time interval and challenging these with a 20 mg/kg intraperitoneal dose of morphine sulfate, and testing their reaction time in the tail-flick test 30 min thereafter. At least 12 mice were used for each individual determination. A group of 12 mice was included as a control at each dose level. These received only the ED_{80} dose of morphine sulfate.

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References and Notes

(1) R. R. Bard and M. J. Strauss, *J. Org. Chem.*, 41, 2421 (1976).
(2) D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 77, 1 (1977).
(3) For a review of this method see L. Harris and W. Dewey in "Methods in Narcotics Research", Ehrenpreis and Neidle, Ed., Marcel Dekker, New York, N.Y., 1975, Chapter 5.
(4) W. F. Michne and N. F. Albertson, *J. Med. Chem.*, 15, 1278 (1972).
(5) A. P. Gray and D. S. Robinson, *Adv. Biochem. Pharmacol.*, 8, 555 (1973).
(6) N. F. Albertson, A. K. Pierson, and M. P. Wentland, paper presented at the 7th Northeast Regional Meeting of the American Chemical Society, Albany, N.Y., 1976.
(7) M. P. Wentland, personal communication.
(8) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, 143, 141 (1964).