N-(2-Cyanoethyl) Derivatives of Meperidine, Ketobemidone, and a Potent 6,7-Benzomorphan

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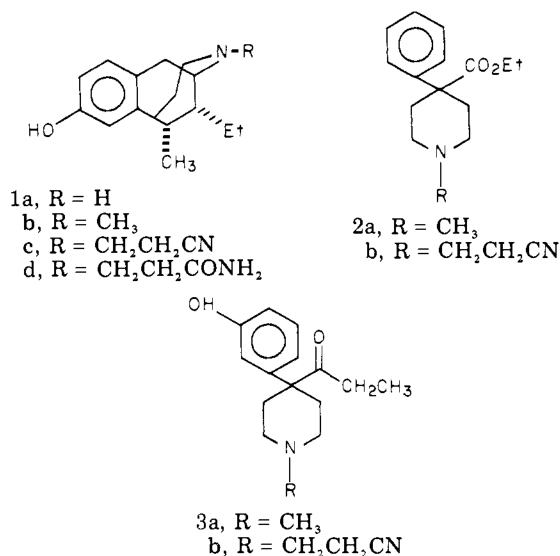
The N-(2-cyanoethyl)-9α-ethyl-5-methyl-6,7-benzomorphan (1c) is a more potent antinociceptive and has stronger receptor binding affinity than its N-methyl analogue **1b**. The N-(2-cyanoethyl)-4-phenylpiperidine compounds **2b** and **3b** were almost inactive compared to their N-methyl congeners **2a** and **3a**, respectively. It appears that the pharmacological effect of the N-(2-cyanoethyl) moiety is dependent on the opioid on which it is substituted.

Recently it was reported that replacement of the N-methyl substituent of (-)-3-hydroxy-N-methylmorphinan (levorphanol) and metazocine by 2-cyanoethyl resulted in a marked increase in antinociceptive potency without a corresponding increase in opiate receptor affinity and with a considerable decrease in acute toxicity.[2] Furthermore, the physical dependence capacity of the resultant compounds was nil. We wish to report our findings on a similar chemical alteration of three strong analgesics, meperidine (**2a**), ketobemidone (**3a**), and 2,5-dimethyl-9α-ethyl-2′-hydroxy-6,7-benzomorphan (**1b**), along with the carbamido compound **1d**.



Chemistry. The cyanoethyl derivatives **1c**, **2b**, and **3b** were prepared by alkylation of their respective nor bases with acrylonitrile. The carbamido analogue **1d** was similarly prepared by alkylation with acrylamide.

Biological Results and Discussion. Compounds **1c**, **1d**, **2b**, and **3b** were evaluated for analgesic activity in the hot-plate assay[2a,b] and for receptor affinity as determined by the capacity to displace bound, radiolabeled dihydromorphine from rat brain homogenates (Table I).[2c] Additionally **1c** and **1d** were evaluated in the tail-flick,[4] phenylquinone writhing (PPQ),[5] and tail-flick antagonism assays.[4] Also, **1c**, **1d**, **2b**, and **3b** were assayed by single-dose suppression tests (SDS) in morphine-dependent monkeys,[6] and **3b** was evaluated in the Nilsen assay.[7]

The N-(2-cyanoethyl)benzomorphan analogue **1c** was six times more potent than its N-methyl parent **1b**,[8] though the increase was not as large as that observed for the 9α-methyl (metazocines) congeners. There was a corresponding increase in receptor affinity; however, both **1b** and **1c** exhibit lower binding affinities than might be predicted from their hot-plate ED_{50} values when compared to morphine. This type of discrepancy may be rationalized on the basis of transport, such as for the case of meperidine

Table I. Pharmacology of N-(2-Cyanoethyl) Compounds

compd	ED_{50}[a]	EC_{50}[b]	PDC[c]
(±)-1b[d]	1.3 (0.9–2.0)[d]	15	high[d]
(±)-1c	0.21 (0.15–0.30)[e]	4	intermed
(±)-1d	19.3 (13.3–27.9)[f]	9	none
2a	4.7 (4.2–5.4)[g]	700[h]	high
2b	inact to 100	8000	none
3a	0.8 (0.7–0.9)	2	high
3b	[i]	1500	low
(−)-morphine	1.2 (0.9–1.3)	3	high
(±)-metazocine	1.18 (1.05–1.33)[j]	9	high

[a] Hot-plate assay in mg/kg. Parentheses indicate 95% SE limits on probit analysis, subcutaneous injection in mice.[3a,b] [b] Binding constant from rat-brain homogenates in nM.[3c] [c] Physical dependence capacity in rhesus monkeys from SDS (single-dose suppression).[6] [d] Reference 8a, 6.4 (3.1–12.8) in tail-flick assay and 0.2 (0.008–0.7) in PPQ. [e] 0.8 (0.4–1.5) in the tail-flick assay and 0.09 (0.04–0.2) in the PPQ. [f] Inactive in the tail-flick assay and PPQ. [g] Reference 9. [h] W. A. Klee, N.I.H., personal communication. [i] Erratic dose–response curve in the hot plate assay; ED_{50} > 50 in the Nilsen assay. [j] Reference 7.

(**2a**), or possibly metabolism. Such discrepancies might also be expected if, perhaps, the receptor is somewhat distorted in its in vitro environment. A potential metabolite of **1c**, the carbamido analogue **1d**, was only weakly active as an analgesic. However, the affinity of **1d** for the binding site is equal to that of (±)-metazocine, reflecting perhaps a decreased ability to cross the blood–brain barrier. Compounds **1c** and **1d** did not show antagonist activity in the tail-flick assay, an interesting observation since short chains on the nitrogen in analgesics having tricyclic or larger ring systems usually induce antagonist activity. In SDS tests, **1d** did not substitute for morphine at the doses tested (to 16 mg/kg), and **1c** partially substituted (briefly) for morphine at 1.2 mg/kg, while **1b** substituted completely[8a] for morphine.

The N-(cyanoethyl)-substituted 4-phenylpiperidines **2b** and **3b** showed a complete loss of analgesic activity for **2b**, and only minor activity remained for **3b**, which gave an erratic dose–response curve in the hot plate assay. These results were reflected in their binding constants. In SDS tests, **2b** was inactive (to 20 mg/kg) and **3b** showed a partial suppression of abstinence signs at 20 mg/kg that was complete at 40 mg/kg. The low activity observed with **2b** and **3b** is somewhat surprising in view of the substantial analgesic activity of the N-propyl and N-butyl analogues of **2a**[9] and **3a**.[10] Thus, short to moderate length chains on the nitrogen atom of **2a** and **3a** continue to show intriguing and unexplained variations in opiate effects.

In conclusion, our results further substantiate the finding of a recent report that the effect of substituting the N-(2-cyanoethyl) moiety in strong analgesics is dependent on the parent opiate employed.[2] It appears that the utility of this group as an analgesic pharmacophore may be limited to tricyclic and larger ring systems.

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Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt, capillary, melting point apparatus and are uncorrected. IR spectral data were obtained on a Perkin-Elmer 257 and NMR spectral data were obtained on a Perkin-Elmer R-24. Spectra were obtained on all compounds and these are compatible with the structural assignments. Microanalyses obtained as indicated by the symbols of the elements are within ±0.4% of the theoretical values.

2-(2-Cyanoethyl)-9α-ethyl-2′-hydroxy-5-methyl-6,7-benzomorphan (1c). Compound **1a** (1 g, 4.3 mmol),[8] acrylonitrile (0.3 g, 5.6 mmol), absolute EtOH (10 mL), and Et_3N (5 drops) were stirred overnight at room temperature (23–25 °C), after which TLC showed no **1a**. Evaporation to dryness at 20–26 mm and cooling gave a solid which crystallized from EtOAc (5 mL)–ligroin (30–60 °C, 3–4 mL) in prisms: yield 0.96 g, 90%; mp 95-96 °C (gas evolution). Anal. ($C_{18}H_{24}N_2O$) C, H, N.

2-(2-Carbamidoethyl)-9α-ethyl-2′-hydroxy-5-methyl-6,7-benzomorphan (1d). A mixture of 1.0 g (4.33 mmol) of **1a**,[8] 0.41 g (5.76 mmol) of acrylamide, 5 drops of Et_3N, and 10 mL of absolute EtOH was stirred at room temperature (4 days) and monitored by TLC [EtOAc–MeOH–concentrated NH_4OH (16:3:1) and $CHCl_3$–MeOH–concentrated NH_4OH (74:24:2), silica gel, iodoplatinate reagent]. The reaction mixture was then filtered and the filtrate concentrated (in vacuo) to a brownish oil. Et_2O was added, and the resulting crystals from overnight standing were recrystallized from EtOAc/Me_2CO (3:1): yield 1.07 g, 90.7% (based on covered starting material); mp 171.5–172.5 °C. Anal. ($C_{18}H_{26}N_2O_2$) C, H, N.

***N*-(2-Cyanoethyl)normeperidine (2b).** A solution of normeperidine (norpethidine,[11] 3.00 g, 10.7 mmol), acrylonitrile (0.81 mL, 12.25 mmol), and anhydrous K_2CO_3 in absolute EtOH (50 mL) was stirred for 6 h at room temperature. The solution was filtered and evaporated in vacuo to yield a brown oil. The oil was dissolved in Et_2O (50 mL), washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated in vacuo to yield an oil from which the hydrobromide salt was made. Recrystallization twice from Me_2CO afforded 0.88 g (29%), mp 207–208 °C. Anal. ($C_{17}H_{23}N_2O_2Br$) C, H, N.

***N*-(2-Cyanoethyl)norketobemidone (3b).** A solution of norketobemidone[10] (3.00 g, 12.9 mmol) and acrylonitrile (1.26 mL, 19.3 mmol) in absolute EtOH (50 mL) was stirred for 2 h at room temperature. The solvent was evaporated in vacuo, yielding a brown tar from which the hydrobromide salt was made. Recrystallization twice from absolute EtOH afforded 3.45 g (73%), mp 130–131 °C. Anal. ($C_{17}H_{23}N_2O_2Br$) C, H, N.

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Active-Site Studies of Neurohypophyseal Hormones: Synthesis and Pharmacological Properties of [5-(N^4,N^4-Dimethylasparagine)]oxytocin[1]

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Synthesis and biological properties of [5-(N^4,N^4-dimethylasparagine)]oxytocin are reported. In this analogue, the hydrogens of the primary carboxamide moiety in the side chain of the asparagine residue in position 5 of the posterior pituitary hormone oxytocin have been replaced by two methyl groups. The protected nonapeptide intermediate was prepared by a stepwise procedure using solution techniques. The analogue possesses 4.60 ± 0.03 units/mg (mean ± SEM) uterotonic activity on the isolated rat uterine horn and 9.14 ± 0.03 units/mg of avian vasodepressor activity. Moreover, it displays an identical intrinsic activity in the in vitro rat uterotonic assay as oxytocin, when tested in the presence of either 0.5 mM Ca^{2+} (standard assay conditions) or at reduced levels of Ca^{2+} (0.3, 0.15, and 0.05 mM). This result is significant in view of the proposed biologically active model of oxytocin, in which the side chain of the 5 position residue was assigned to contain an "active element" responsible for the intrinsic activity of the hormone when bound to the uterine receptor.

The 5-position asparaginyl residue plays a key role in the preferred solution conformation of oxytocin[2] and in the proposed "biologically active" model of the hormone (Figure 1) at the uterine receptor.[3-5] Both in Me_2SO and aqueous medium[6] the peptide NH of the asparagine residue helps to stabilize the β turn involving the sequence

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