4-Substituted Amino-2-(5-nitro-2-furyl)pyrimido[4,5-*d*]pyrimidine (13–19). A mixture of 50 g (0.18 mol) of crude **12** and 0.36 mol of the appropriately substituted amine in 500 ml of MeOH was refluxed with stirring for 10 min. The mixture was chilled and filtered, and the crude product was washed with H_2O, *i*-PrOH, and Et_2O, followed by drying and recrystallization from an appropriate solvent. The formation of a precipitate when **14** is treated with 5-nitro-2-furaldehyde in DMF supports the structure assignment of **14** as does γ_{max} 2.95, 3.05, and 6.1 μ (NH_2).

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Structure–Activity Studies on Narcotic Antagonists. 1. N-Substituted Ethyl 3-Phenylpyrrolidine-3-carboxylates and Ethyl 3-Phenylnipecotates†

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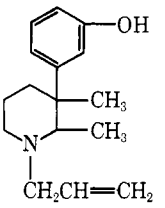
It is well established that replacement of the *N*-methyl group in potent opioid analgetics by certain small alkyl groups usually produces a compound possessing narcotic or opioid antagonist activity. Maximum antagonistic properties are found when the *N*-alkyl group is allyl, *n*-propyl, or cyclopropylmethyl, although the relative order of potency among these is dependent upon the analgesiophore.[2,3] That this type of group is not essential for opioid antagonism has been demonstrated by several (−) isomers of *N*-methylbenzomorphans.[4] These and other observations raise several questions in regard to the exact structural features and/or physicochemical properties necessary for potent opioid antagonism.

As part of a study into these questions, we prepared several *N*-alkyl derivatives of ethyl 3-phenylpyrrolidine-3-carboxylate (**8–13**) and ethyl 3-phenylnipecotate (**14–19**). These represent two series of analgetic analogs that possess a β-phenethylamine moiety, a structural feature that is present in almost all opioid antagonists.[2] Our attention to these series was drawn by the lack of antagonistic activity in the *N*-allyl[5,6] and *N*-dimethylallyl[6] derivatives of normeperidine. Archer and Harris[2] have suggested this may be due to the absence of the β-phenylethylamine moiety. Additional support for the β-phenethylamine hypothesis comes from the observations that the *N*-allyl compound **1** was found to be an antagonist devoid of analgetic activity[7] and that the *N*-methyl compound **2** was found to possess both analgetic and antagonist properties.[8] Both of these compounds contain a β-phenethylamine moiety.



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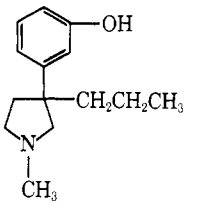

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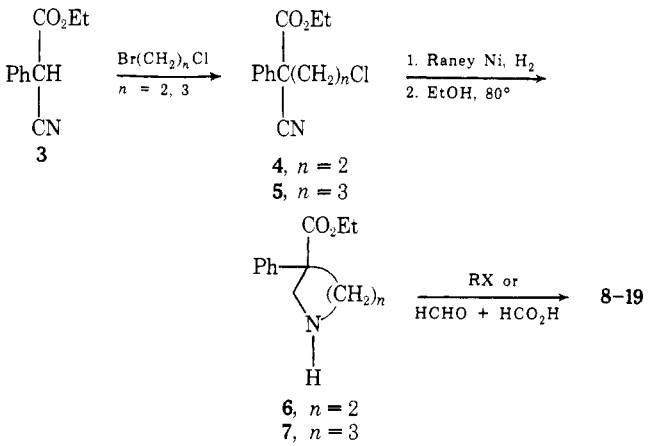
Chemistry. Of the published methods available for the synthesis of esters **6** and **7**, that used by Avison and Morrison[9] was selected over the earlier approaches of Bergel, *et al.*[10] Thus, ethyl phenylcyanoacetate (**3**) was alkylated with either 1-bromo-2-chloroethane or 1-bromo-3-chloropropane to yield the corresponding chloronitriles **4** and **5**, which were reduced to the corresponding primary amines. The primary amines were not isolated but were cyclized by refluxing in ethanol to give ethyl 3-phenylpyrrolidine-3-carboxylate (**6**) or ethyl 3-phenylnipecotate (**7**). It was found necessary to employ more rigorous hydrogenation conditions than Pd/C, as used earlier.[9] Satisfactory yields (45–60%) were obtained after 8 hr with Raney nickel in ammonia–ethanol solution. Addition of a catalyst promoter, platinic chloride, did not improve yields but reduced hydrogenation time to 1–2 hr. The *N*-methyl derivatives **8** and **14** were prepared by reductive methylation with formaldehyde and formic acid. The other N-substituted compounds (**9–13** and **15–19**) were prepared by treating the free base in ethanol in the presence of sodium bicarbonate or carbonate with the appropriate alkyl halide (Table I).



Of interest in the nmr spectra of these compounds was the nonequivalence of the protons on the 2- and 4-methylenes of the pyrrolidine and piperidine rings. In the spectra of unsubstituted esters **6** and **7**, only the C-2 protons are sufficiently resolved to allow assignment of coupling constants. The low field α-H in the pyrrolidine was analyzed as an AB system giving ^2J = 11.5 Hz. The corresponding α-H in the piperidine gave ^2J = 13 Hz, with further long-range coupling with the C-6 proton, ^4J = 2.5 Hz. The coupling was unchanged either after D_2O treatment or in the *N*-methyl **14**. This is indicative of diaxial coupling[11] and provides tentative evidence that the axial C-2 proton, which is almost 1 ppm downfield, is cis to an equatorial phenyl. Further experiments using decoupling techniques are in progress to confirm these observations and to provide additional conformational information.

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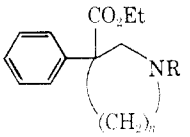
Table I. N-Substituted Ethyl 3-Phenylpyrrolidine-3-carboxylates and Ethyl 3-Phenylnipecotates



Compd	R	n	Alkylating agent	Yield, %	Bp, °C (mm)	Salt	Mp, °C	Crystn solvent[a]	Formula[b]
8	Methyl	2	HCHO + HCO_2H	75	87–88 (0.05)[c]	Fumarate	153–155	A	$C_{14}H_{19}NO_2 \cdot C_4H_4O_4$
9	Allyl	2	RBr	63	102–103 (0.05)	Oxalate	160–161	A	$C_{16}H_{21}NO_2 \cdot C_2H_2O_4$
10	Dimethylallyl	2	RCl	90	117–119 (0.05)	Maleate	124–126	A	$C_{18}H_{25}NO_2 \cdot C_2H_2O_4$
11	Cyclopropylmethyl	2	RBr[d]	68	116–118 (0.05)	HCl	117–119	B	$C_{17}H_{23}NO_2$
12	*n*-Propyl	2	RBr	88	100–101 (0.05)	HCl	114–115	B	$C_{16}H_{23}NO_2$
13	Methylthioethyl	2	RCl[e]	59	150–152 (0.2)	HCl	98–99	B	$C_{16}H_{24}NO_2S \cdot HCl$
14	Methyl	3	HCHO + HCO_2H	84	96–97 (0.05)[f]	HCl	178–180[g]	A	$C_{15}H_{21}NO_2$
15	Allyl	3	RBr	79	*h*	HCl	134	A	$C_{17}H_{23}NO_2 \cdot HCl$
16	Dimethylallyl	3	RCl	68	*h*	HCl	149–151	A	$C_{19}H_{27}NO_2 \cdot HCl$
17	Cyclopropylmethyl	3	RBr[d]	49	124–126 (0.2)	HCl	174–176	A	$C_{18}H_{25}NO_2$
18	*n*-Propyl	3	RBr	67	104–105 (0.05)	HCl	146–166	A	$C_{17}H_{25}NO_2$
19	Methylthioethyl	3	RCl[e]	61	156–158 (0.2)	HCl	97–98	A	$C_{17}H_{25}NO_2S$

[a] A, EtOAc–EtOH; B, EtOAc. [b] Analyses for C, H, and N were within ±0.4% of the theoretical values. [c] Previously synthesized (see ref 10), bp 114° (0.4 mm). [d] Cyclopropylmethyl bromide synthesized according to J. S. Meek and J. W. Rowe, *J. Amer. Chem. Soc.*, **77**, 6675 (1955). [e] β-Chloroethyl methyl sulfide synthesized according to W. R. Kirner and W. Windus in "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 136. [f] Previously synthesized (see ref 9 and 10), bp 104° (0.2 mm), 160° (12 mm). [g] Previously prepared (see ref 10), mp 178–180°. [h] Isolated and purified as the hydrochloride salt.

Pharmacology. All of the compounds (8–19) have been tested for analgetic activity by ip administration of aqueous solutions of the amine salts to mice using the standard hot-plate method.[12] Only the known β-pethidine (14) showed analgetic activity, being about one-half as active as meperidine, as previously reported.[13] The inactivity of the *N*-methylpyrrolidine 8 confirmed the earlier report.[14] The lack of analgetic activity by the remaining compounds was not unexpected if they are nalorphine-like, as the hot-plate method is insensitive to antagonist–analgetics such as nalorphine or pentazocine.

The *N*-allyl, -cyclopropylmethyl, and -*n*-propyl derivatives (9, 11, 12, 15, 17, and 18) were tested for antagonistic activity against meperidine and phenazocine by the rat tail-flick method.[15] By this procedure, the compounds showed no significant narcotic antagonism.‡ The lack of significant antagonistic action exhibited by these compounds indicates that structural features other than β-phenethylamine are required for a compound to be a potent antagonist. The result of this work does not exclude the moiety from being a structural prerequisite for narcotic antagonism but it does preclude it from being of sole importance. Perhaps the introduction of a phenolic hydroxyl into these compounds would confer antagonistic properties, a possibility that we are presently investigating.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Baron Consulting Co., Orange, Conn. Ir spectra were taken on a Beckman Microspec and were as expected. Nmr spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ with TMS as internal standard. All nmr spectra were as expected except for those of compounds 6 and 7 which are discussed in the Chemistry section. Nmr spectra for 6 and 7 were obtained with a JEOL PS-100 spectrometer in $CDCl_3$ with TMS as internal standard.

Ethyl 4-Chloro-2-cyano-2-phenylbutyrate (4). This compound was prepared according to the known procedure used for synthesis of 5.[9] The crude reaction product was distilled *in vacuo* to afford the title ester (69%), bp 108–112° (0.2 mm). The colorless oil solidified on standing and was found to melt at 35–36°. *Anal.* ($C_{13}H_{14}ClNO_2$) C, H, N.

Ethyl 3-Phenylpyrrolidine-3-carboxylate (6). This compound was prepared from ethyl 4-chloro-2-cyano-2-phenylbutyrate (4, 6.0 g, 0.024 mol) by catalytic hydrogenation in EtOH (100 ml) and saturated NH_3–EtOH (100 ml) using Raney nickel (2 tbs, W. R. Grace & Co.) as the catalyst. The above mixture was shaken in a Parr low-pressure hydrogenation apparatus at 50 psi until the hydrogen uptake stopped (*ca.* 8 hr). After the Ni was removed by filtration, the solution was concentrated under reduced pressure. The residue was dissolved in cold 1 *N* HCl and extracted twice with Et_2O. The aqueous solution was made strongly basic with ice-cold 30% NaOH, extracted three times with Et_2O, dried rapidly over Drierite, filtered, and concentrated *in vacuo*. The residue was dissolved in anhydrous EtOH (150 ml) and refluxed for 8 hr to afford the cyclized product. The reaction mixture was cooled and concentrated *in vacuo*. The residual oil was dissolved in H_2O and made strongly basic with 30% NaOH. The separated oil was extracted with Et_2O, dried (Na_2SO_4), filtered, concentrated *in vacuo*, and distilled. The desired ester 6 distilled at 96–98° (0.05 mm) [lit.[10] bp 97° (0.1 mm)] as a colorless oil (2.6 g, 50%): nmr ($CDCl_3$) δ 1.15 (t, 3, CH_3), 2.04–2.44 [m, 2, one 4-H and N-H (s, 2.23)], 3.68–3.32 (m, 3, one 4-H and two 5-H), 3.10 (d, 1, ^2J = 11.5 Hz, 2-H), 3.97 (d, 1, ^2J = 11.5 Hz, 2-H), 4.18 (q, 2, OCH_2), 7.50 (s, 5, aromatic).

Ethyl 3-Phenylnipecotate (7). Ethyl 5-chloro-2-cyano-2-phenylvalerate (5, 6 g, 0.023 mol), EtOH (100 ml), Raney nickel (2 tbs, W. R. Grace & Co.), and saturated NH_3–EtOH (100 ml) were placed in a Parr low-pressure hydrogenation bottle. Just before the reduction was started, platinic chloride solution (3 ml of a solution containing 1.6 g of $H_2PtCl_6 \cdot 6H_2O$ in 30 ml of H_2O) was added to the hydrogenation mixture. This mixture was then hydrogenated at 50 psi. Hydrogen uptake was complete within 1 hr and then the intermediate chloroamine was cyclized as in the previous procedure. The cyclized material was distilled as above to yield 3.3 g (63%) of 7: bp 107–108° (0.075 mm) [lit.[9] bp 105° (0.1 mm)]; nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3), 1.40–2.20 [m, 4, one 4-H, two 5-H and N-H (s, 1.92)], 2.24–3.52 (m, 3, one 4-H and two 6-H), 2.85 (d, 1, ^2J = 13 Hz, 2-H), 3.82 [d, 1, ^2J = 13 Hz (showing long-range coupling, ^2J = 2.5 Hz), 2-H], 4.26 (d of q, 2, OCH_2), 7.5 (s, 5, aromatic).

The HCl salt of 7 was prepared in anhydrous Et_2O and recrystallized from EtOH–EtOAc: mp 142–143° (lit.[9] mp 143°).

General Procedures for Preparation of N-Substituted Ethyl 3-Phenylpyrrolidine-3-carboxylates (8–13) and N-Substituted Ethyl 3-Phenylnipecotates (14–19). The *N*-methyl compounds 8 and 14 were prepared by methylation of the appropriate free base (6 or 7) with HCHO and HCO_2H using a known procedure.[9] All

‡ See paragraph at end of paper regarding supplementary material.

other N-substituted compounds (9–13 and 15–19) were prepared as follows. Ethyl 3-phenylpyrrolidine-3-carboxylate (6) or ethyl 3-phenylnipecotate (7) was dissolved in EtOH (*ca.* ten times the weight of the free amine) and $NaHCO_3$ or Na_2CO_3 (a weight equal to that of the free amine) was added. The appropriate alkyl halide (10% molar excess) was added dropwise to the warm (*ca.* 50°) reaction mixture. The stirred mixture was refluxed and the progress of the reaction was followed by tlc (Eastman 6060 silica gel, 5% EtOH in C_6H_6). When the reaction was complete (2–4 hr), the mixture was cooled and allowed to stir overnight. The precipitated solids were filtered off and washed with Et_2O. The filtrate was concentrated under reduced pressure and the residue was dissolved in anhydrous Et_2O. After filtration and concentration of the ethereal solution, the residual oil was distilled to give the free bases 9–13 and 17–19. Crude 15 and 16 were not distilled but were dissolved in anhydrous Et_2O and treated with HCl gas to give the salt of 15 and 16. See Table I for details.

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Supplementary Material Available. The results of the antagonist testing will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-453.

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A Cyclopentane Analog of Muscarone

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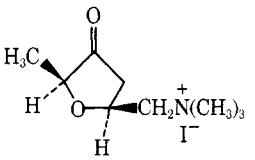
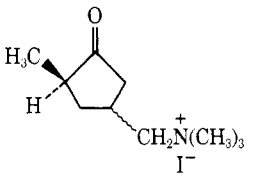
Muscarine and related compounds have played a major role in studies on cholinergic receptors. Among the other compounds, muscarones are particularly interesting because of their activity which is higher than that of muscarine and because of a different importance of steric factors on the activity.[1] For instance, muscarone and *allo*-muscarone have nearly the same potency and D(−)-muscarone is about three times more active than L(+)-muscarone while in the muscarine series the L(+)-muscarine is a hundred times more potent than D(−)-muscarine and the other stereoisomers.[1]

Various rationalizations of these facts have been proposed by Waser,[2] Belleau,[3] and recently by Pauling.[4] Although Belleau's theory seemed more consistent with the current knowledge of cholinergic receptors, no definite conclusions could be drawn.

Therefore, it appeared to us of some importance to have a compound such as 1 which, by substitution of the ether oxygen with a methylene group, would allow us to check the role of both the ether and the keto group on the activity and cast further light on the problem. This paper reports the synthesis and some preliminary pharmacological data of compound 1.



(±)-muscarone



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While concluding this research, a paper[5] reporting the synthesis and pharmacological evaluations of a cyclopentane analog of muscarine appeared. The results of this work, which challenge the current theories of muscarinic receptors, prompted us to publish our results as a contribution to a further understanding of the problem.

Chemistry. The synthesis of compound 1 was achieved through the pathways shown in Scheme I. Although time consuming, if compared to that involving the amide 2, synthesis through compounds 9, 11, and 12 was performed to explore the possibility that more hindered compounds could bring to the separation of cis and trans isomers.

Because of the strongly equilibrating conditions used in the synthesis of the starting material, 4-methyl-3-oxocyclopentane-1-carboxylic acid,[6,7] the nmr spectrum showed it to be a mixture of cis and trans isomers (roughly 60:40) that could not be separated by chromatography.

Although Hardegger, *et al.*,[8] report that, in a very similar case, complete conversion into the trans isomer was observed, the reaction of 4-methyl-3-oxo-1-carbomethoxycyclopentane with dimethylamine gave a mixture of cis and trans isomers of 2. The same was found for 3 whose nmr spectrum, as well as that of 6 and 7, shows a double doublet for 4-CH_3, while 4, 5, and in general all compounds where the substituent in 1 is not a carbonyl group show a single doublet. Yet this cannot be considered evidence of the presence of a single isomer as a consequence of isomerization but it is probably due to the equivalence of 4-CH_3 in the two isomers.

This was confirmed by nmr spectrum of *p*-toluenesulfonate 11 which again shows the double doublet, while its starting material (10) does not.

Consequently, compound 1 should be considered a mixture of cis and trans isomers. Because of the overlapping of the signals, even at 100 MHz, the ratio of the two isomers could not be directly obtained but it is safe to say that it should not be different from that of the equilibrated starting material.

Repeated efforts to evidence the isomers by tlc at every