7.73 (m, 4, C_6H_4), 7.12 (s, 2, NH_2), 8.17 (d, 1, NH), 8.58 (s, 1, 7-CH). Anal. ($C_{20}H_{21}N_7O_5S \cdot 0.9$ HCl $\cdot 0.2H_2O$) C, H, Cl, N, S.

N-[*p*-[[[**2-Amino-4-(methylthio)-6-pteridinyl]methyl]methylamino]benzoyl]-L-glutamic Acid (22). Methyl iodide (0.014 ml, 0.217 mmol) was added (Hamilton micro syringe) to a stirred solution of **21** (100 mg, 0.197 mmol) in 1 *N* NaOH (0.767 ml) and H_2O (2.7 ml) at 0°. The mixture was stirred for 1 hr at 0° and 18 hr at 25°. Acidification of the resulting solution with 1 *N* HCl to pH 2.5 gave an orange precipitate which was collected by filtration, washed with H_2O at pH 2.5, and dried in vacuo at 65° (P_2O_5): yield 90 mg (90%); λ_{max}, nm ($\epsilon \times 10^{-3}$) (solvent c), 0.1 *N* HCl, 308 (22.9), 362 (9.90), 377 (sh, 8.63); λ_{max} pH 7, 275 (22.4), 303 (25.2), 385 (8.36); λ_{max} 0.1 *N* NaOH, 275 (21.6), 303 (25.3), 384 (8.99); ν_{max} 1710, 1600, 1550, and 1505 cm^{-1}; ^1H NMR δ 1.8–2.4 (m, CH_2CH_2), 2.56 (s, SCH_3), 3.24 (s, 3, NCH_3), 4.36 (m, NCH), 4.86 (s, 2, NCH_2), 6.82, 7.74 (m, 4, C_6H_4), 7.48 (s, NH_2), 8.18 (d, 1, NH), 8.80 (s, 1, 7-CH). Anal. ($C_{21}H_{23}N_7O_5S \cdot 1.3H_2O$) C, H, N, S.

N-[*p*-[[(**2-Amino-4-hydrazino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic Acid (23). A solution of **22** (25.0 mg, 0.049 mmol) and 85% hydrazine hydrate (57.9 mg, 0.984 mmol) in H_2O (0.5 ml) was stirred for 5.5 hr and acidified to pH 4 with 1 *N* HCl. The yellow precipitate was collected by filtration, washed with H_2O at pH 4, and dried in vacuo (P_2O_5): yield 19.7 mg (78%); λ_{max}, nm ($\epsilon \times 10^{-3}$) (solvent c), 0.1 *N* HCl, 306 (23.3); λ_{max} pH 7, 221 (24.9), 302 (25.2), 372 (7.10). Anal. ($C_{20}H_{23}N_9O_5 \cdot 2.3H_2O$) C, H, N.

p-[[(**2-Amino-3,4,7,8-tetrahydro-4-thioxo-6-pteridinyl)methyl]methylamino]benzoic Acid (24). A solution of **11** (50.0 mg, 0.134 mmol) in 1 *M* mercaptoethanol (4 ml) and 1 *N* NaOH (6 ml) was treated with $Na_2S_2O_4$ (333 mg) and stirred in a stoppered flask under N_2 for 60 hr. The almost colorless solution was filtered under N_2 and acidified with 6 *N* HCl to pH 4. The yellow product was collected in a refrigerated centrifuge, washed with 1 *M* mercaptoethanol (4 ml) and then 0.01 *M* mercaptoethanol (4 ml), and dried in vacuo (P_2O_5): yield 47 mg; λ_{max}, nm (solvent d), 0.1 *N* HCl, 312, 370; λ_{max} pH 7, 251, 293, 328; λ_{max} pH 13, 283, 305.

N-[*p*-[[(**2-Amino-3,4,7,8-tetrahydro-4-thioxo-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic Acid (25). The reduction of **21** (12.0 mg) to give **25** (3.2 mg) was carried out as described above for **24** except that the time of reaction was 18 hr: λ_{max}, nm (solvent d), 0.1 *N* HCl, 310, 379 (sh); λ_{max} pH 7, 218, 307 (br); λ_{max} 0.1 *N* NaOH, 307 (br).

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References and Notes

(1) R. L. Blakley, "The Biochemistry of Folic Acid and Related Pteridines, Frontiers of Biology", Vol. 13, A. Neuberger and E. L. Tatum, Ed., American Elsevier, New York, N.Y., 1969.
(2) R. D. Elliott, C. Temple, Jr., J. L. Frye, and J. A. Montgomery, *J. Heterocycl. Chem.*, **10**, 1071 (1973).
(3) J. J. McCormack and H. G. Mautner, *J. Org. Chem.*, **29**, 3370 (1964).
(4) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Med. Chem.*, **17**, 553 (1974), and references cited therein.
(5) R. K. Robins, K. L. Dille, and B. E. Christensen, *J. Org. Chem.*, **19**, 930 (1954); C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, unpublished results.
(6) E. C. Taylor and W. R. Sherman, *J. Am. Chem. Soc.*, **81**, 2464 (1959).
(7) C. W. Mosher, E. M. Acton, O. P. Crews, and L. Goodman, *J. Org. Chem.*, **32**, 1452 (1967).
(8) B. R. Baker, B. T. Ho, and T. Neilson, *J. Heterocycl. Chem.*, **1**, 79 (1964).
(9) E. E. Snell, "Vitamin Methods, Microbiological Methods in Vitamin Research", P. Gyorgy, Ed., Academic Press, New York, N.Y., 1950, p 327.
(10) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3** (no. 2) (1972).
(11) A. Stuart and H. C. A. Wood, *J. Chem. Soc.*, 4186 (1963).
(12) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **35**, 1676 (1970).

Analgesic Activity of the Epimeric Tropane Analogs of Meperidine. A Physical and Pharmacological Study

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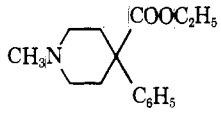
Condensation of *cis*-*N*-benzyl-2,5-bis(chloromethyl)pyrrolidine (**6**) and phenylacetonitrile afforded a mixture of epimers **7** and **8**. Compound **8** was readily converted to the meperidine analog **1** prepared earlier by Bell and Archer. Compound **7** was converted to a new tropane analog of meperidine, compound **3**. The ED_{50} of **1** and **3** in the D'Amour-Smith "tail flick" test for narcotic type analgesia, which differs by a factor of only 3 or 4 in potency, supports the accumulated data that suggest that the analgesic activity of the meperidine type is not very sensitive to the conformation of the phenyl group in 4-phenylpiperidines. A proton and ^{13}C magnetic resonance spectral comparison of **1** and **3**, as well as a reevaluation of the conformational requirements of **17–19**, leads to the conclusion that the differences in conformation of **1**, **3**, **17**, and **18** are due to the varying degrees of flattening of the piperidine ring. The ^1H NMR and ^{13}C NMR data are not consistent with the boat conformation suggested earlier for compound **17**.

Almost 15 years after the synthesis of the tropane analog **1** of meperidine (**2**) by Bell and Archer,[1] we have succeeded in preparing the epimeric tropane ester **3**. We hoped that with both epimeric tropane esters **1** and **3** in hand we could contribute to the accumulated information[2-4] relating to the conformational requirement of the phenyl group in the 4-phenylpiperidine analgesics, a topic that has been dealt with in several recent reviews.[5,6]

Chemistry. In 1961, Cignarella et al.[7] reported that *cis*-*N*-tosyl-2,5-bis(chloromethyl)pyrrolidine (**4**) and phenylacetonitrile in the presence of $NaNH_2$ and toluene afforded a single compound, **5**, in 28% yield. This in turn was converted in good yield to **1** (β-ester). We found that *cis*-*N*-benzyl-2,5-bis(chloromethyl)pyrrolidine (**6**)[8] and phenylacetonitrile in the presence of NaH and DMF yielded a 3:1 mixture (42%) of **7** and **8**. The preponderance of isomer **7** over isomer **8** is in complete concordance with the steric control suggested by Dreiding models in the ring closure of the intermediate shown in Scheme I. Fractional crystallization of their HCl salts separated **7** and **8**. The minor component **8** (β-nitrile), when treated with 80% H_2SO_4 at 150° for 1.5 hr followed by reflux with EtOH, afforded the β-



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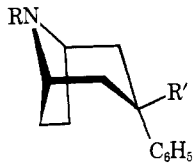
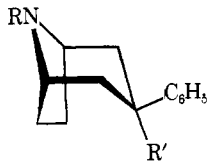
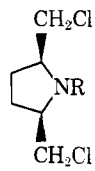


1, R = $-CH_3$; R' = $-COOC_2H_5$
5, R = -tosyl; R' = $-C{\equiv}N$
8, R = $-CH_2C_6H_5$; R' = $-C{\equiv}N$
9, R = $-CH_2C_6H_5$; R' = $-COOC_2H_5$
10, R = -H; R' = $-COOC_2H_5$
12, R = $-CH_2C_6H_5$; R' = $-CONH_2$
17, R = $-CH_3$; R' = $-COC_6H_5$
19, R = -H; R' = $-COC_6H_5$



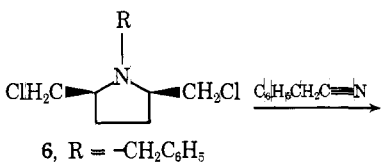
3, R = $-CH_3$; R' = $-COOC_2H_5$
7, R = $-CH_2C_6H_5$; R' = $-C{\equiv}N$
11, R = $-CH_2C_6H_5$; R' = $-CONH_2$
13, R = $-CH_2C_6H_5$; R' = -COOH
14, R = $-CH_2C_6H_5$; R' = -COCl
15, R = $-CH_2C_6H_5$; R' = $-COOC_2H_5$
16, R = -H; R' = $-COOC_2H_5$
18, R = $-CH_3$; R' = $-COC_6H_5$



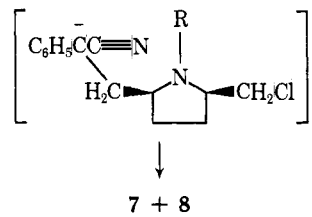
4, R = -tosyl
6, R = $-CH_2C_6H_5$

ester 9.[9] Debenzylation (Pd/C) followed by treatment with formic acid and formaldehyde gave the known compound 1.

Scheme I



6, R = $-CH_2C_6H_5$



7 + 8

A striking difference in the reactivity of the 3α- and 3β-nitriles 7 and 8 became apparent when the conditions used earlier for the hydrolysis and esterification of the β-nitrile 8 gave only the α-amide 11 when applied to the α-nitrile 7. Furthermore, unsuccessful attempts at hydrolysis and esterification of the α-nitrile 7 under the following conditions pointed out further the difference in the reactivity of the nitriles and their transformation products: reflux with TsOH · H_2O–EtOH for 7.5 hr gave back starting material; reaction with 1.84 *N* BF_3–MeOH in a sealed tube at 106° for 18 hr gave back starting material; reaction with 80% H_2SO_4 for 48 hr at 150° followed by reflux with EtOH for 2 hr gave a trace of α-amide 11; similar conditions except prolonged reflux with EtOH (24 hr) produced a trace of α-ester 15. In fact, this difference in reactivity coupled with a substantial difference in polarity on silica gel between the β-ester 9 and the α- and β-amides 11 and 12 enabled us to obtain the β-ester 9 readily when a mixture of nitriles was subjected to the 80% H_2SO_4 treatment for 1 hr followed by reflux with EtOH.

A good yield of α-ester 15 was finally obtained by the following procedure. The α-nitrile 7 was heated at 150° in 80% H_2SO_4 for 48 hr and was added to ice–H_2O, whereupon the highly insoluble α-carboxylic acid 13 separated as its H_2SO_4 salt. This salt was converted to the acid chloride 14 which was refluxed in EtOH for 4 days producing the α-ester 15. Here again the sluggishness of reaction at the 3α site, apparently due to steric blockade, gave a very surprising result. Reflux of α-acid chloride 14 with EtOH for 3 hr, work-up with 2 *N* NaOH, and recrystallization of the HCl salt of the product from *i*-PrOH gave the HCl salt of the starting acid chloride 14. This salt could be converted to α-ester 15 by reflux with EtOH for 72 hr.

Debenzylation of α-ester 15 with Pd/C gave 8-nor compound 16 which was readily converted to α-ester 3 by means of HCOOH–CH_2O treatment.

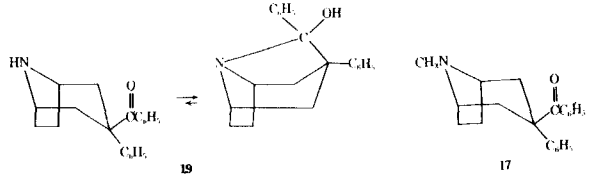
Physical–Chemical Studies. The availability of α-ester 3 gave us the opportunity to compare its ir and NMR spectral data with those of β-ester 1, with regard to substituent effects on ring conformation. Also, in view of the suggested conformational preference (boat conformation with resultant nitrogen–carbonyl interaction) of compound 17 (Table I), as reported by Archer and Bell[10] on the basis of ir and uv data,[11] it was of interest to determine if ^1H NMR data supported the conformational assignments of 17 and 18[10] (Table I). Table I lists ^1H NMR data for compounds 1, 3, 17, 18, and 19.[10]

Compound 19, which exists as an aminocarbinol epimeric mixture,[10] gave broad signals for all but the phenyl and C_6,C_7 hydrogens. This is attributable to the asymmetry which is introduced into the molecule by the carbinol carbon. The spectra of 1, 3, 17, and 18 do not show the broadening of the corresponding signals. On the basis of the equivalence of pairs of hydrogens (see Table I) it is safe to conclude that a plane of symmetry exists in these compounds.

A flattened chair has been found for the piperidine portion of 3β-tropanol by means of X-ray diffraction studies[12] and has been subsequently proposed for other tropanes.[13,14] The coupling constants (see Table II) of 3 and 18 are consistent with such a flattened piperidine ring. The coupling constants noted for 1 (decrease in the $H_1H_{2\,ax}$ and $H_5H_{4\,ax}$ angles and an increase in the $H_1H_{2\,eq}$ and $H_5H_{4\,eq}$ angles) are consistent with a ring flattening even more pronounced than that of 3 and 18. This distortion is also reflected in the increase of the H_1 and H_5 half-bandwidths (HBW) from 9 Hz for compound 3 to 16 Hz for compound 1. The comparison of *J* and HBW values for 17 with those of 3, 18, and 1 suggests that 17 has the most flattened conformation of all.

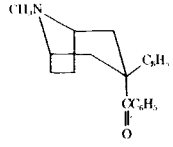
The ^1H NMR spectra of compounds 17 and 1 in CD_3OD showed no significant change in the positions of the NCH_3 signal when compared with spectra measured in $CDCl_3$: 17, 2.18 ($CDCl_3$), 2.22 ppm (CD_3OD); 1, 2.18 ($CDCl_3$), 2.20 ppm (CD_3OD). If indeed the type of nitrogen–carbonyl interaction suggested[10] to explain the ir and uv data[11] of compound 17 does occur in CD_3OD, a greater solvent shift

Table I. Proton NMR Chemical Shift Data[k]

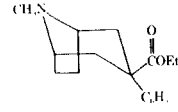


19

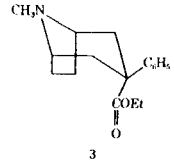
17



18



1



3

Assignments	δ(CDCl$_3$),[a,f] ppm	δ(CDCl$_3$),[a,f] ppm	δ(CD$_3$OD),[b] ppm	δ(CDCl$_3$),[a] ppm	Δ ppm[c]	δ(CDCl$_3$),[a] ppm	δ(CD$_3$OD),[b] ppm	Δ ppm[c]	δ(CDCl$_3$),[a] ppm	Δ ppm[e]
H$_2$, H$_4$ ax	2.60[c]	3.5[d]	3.3[i]	2.86[g]	0.26	3.15[d,g] } *h*	2.76[g]	0.05	2.96[g]	0.18
H$_1$, H$_5$	3.65[c]	3.06[g]	3.15	3.16[g]	0.56	3.2[g] }	3.12[g]	0.32	3.22[g]	0.54
NCH$_3$		2.18	2.22	2.28	0.56	2.18	2.20	0.29	2.28	0.57
H$_6$, H$_7$[j]	1.70	2.10	2.06	1.90	0.30	2.0	1.90	0.12	1.94	0.38
H$_2$, H$_4$ eq	2.00[c]	1.66[g]	1.88	2.35[d,g]	0.40	1.8[g]	2.28[g]	0.04	2.16[d,g]	0.33
H$_6$, H$_7$[j]	1.32	1.55	1.59	1.60	0.25	1.38	1.36	0.12	1.72	0.01
C$_6$H$_5$	7.0–7.7	7.2–7.6	7.2–7.6	7.2–7.5	Part of signal shifts	7.1–7.6	7.1–7.6	No shift	7.1–7.5	Part of signal shifts
OH	4.0[c]									
OCH$_2$CH$_3$						4.08 1.18	4.00 1.10		4.08 1.14	

[a] 5% w/v CDCl$_3$, internal reference Me$_4$Si. [b] 5% w/v CD$_3$OD, internal reference Me$_4$Si. [c] Broad unresolved signals. [d] Signals deshielded by C=O. [e] Shifts caused by addition of Eu(fod)$_3$d$_{30}$ to give a 0.1:1 mole ratio of reagent to compound (CDCl$_3$ solution). [f] Addition of Eu(fod)$_3$d$_{30}$ to CDCl$_3$ solution causes signal broadening only. [g] See Table II. [h] Signals overlap. [i] Signal overlaps CD$_3$OD blank. [j] The signals for the 6,7 hydrogens were unambiguously identified by comparison with the spectra of 2,4-tetradeuterio-*N*-benzyltropanone and tropanone [*N*-benzyl, C(6H,7H) δ 2.18, 1.63 ppm; *N*-methyl, C(6H,7H), δ 2.14, 1.68 ppm]. Studies with Eu(fod)$_3$d$_{30}$ produced as expected larger shifts for 2,4 hydrogens than for 6,7 hydrogens. [k] See ref 22.

Table II. Comparison of Coupling Constants of Protons at Positions 1, 2, 4, and 5

	17 ($CDCl_3$)	18 ($CDCl_3$)	1 (CD_3OD)	3 ($CDCl_3$)
$J_{2,2}$; $J_{4,4}$	14	14	14	14
$J_{1,2\,eq}$; $J_{5,4\,eq}$	1–2	3	2–3	3
$J_{1,2\,ax}$; $J_{5,4\,ax}$	Complex coupling[a]	2–3	5.5	2–3
HBW, H_1 and H_5	18	10	16	9

[a]The H_2H_4 axial hydrogens of 17 gave a more complex pattern than that found for 1. To establish whether the complexity was due to coupling or chemical shift differences resulting from nonequivalence, the signal was recorded on both A-60 and HA-100 instruments. The patterns obtained were identical, confirming the former.

would have been expected for the NCH_3 due to the necessary proximity of the benzoyl aromatic ring. The CD_3OD spectra also showed decreased deshielding of the $H_{2\,ax}H_{4\,ax}$ and increased deshielding of $H_{2\,eq}H_{4\,eq}$ for 17 and similar but much larger effects for 1. This might well be due to interaction of the solvent with the carbonyl in each case. The unchanged signal patterns indicate that the planes of symmetry have been retained here in contrast to the loss of symmetry in **19**. The nitrogen–carbonyl interaction as suggested by Archer and Bell[10] would cause the tropane molecule to lose its plane of symmetry since the structure in question would resemble compound **19**.

Additions of $Eu(fod)_3d_{30}$ to $CDCl_3$ solutions of compounds 3 and 18 gave similar results. The largest shifts were observed for NCH_3 and H_1 and H_5 signals with weaker but significant shifts for $H_{2\,eq}$ and $H_{4\,eq}$ signals. Complexing apparently takes place at both of the competitory sites, nitrogen and carbonyl. The latter is further substantiated by a change in the aromatic pattern of both compounds. This same experiment, when carried out with compound 1, resulted in shifts of the NCH_3 and H_1 and H_5 signals but without noticeable shifts of the H_2 and H_4 signals or shifting of part of the aromatic signals. Steric factors apparently prevent complex formation at the carbonyl in this case. Addition of $Eu(fod)_3d_{30}$ to a $CDCl_3$ solution of compound 17 only broadened but did not shift the signals. One must conclude from this experiment that steric factors in compound 17 prevent complexing at both the nitrogen and carbonyl.

The ^{13}C NMR spectra of compounds 1, 3, 17, and 18 showed sharp peak signals for the C_1C_5, C_2C_4, and C_6C_7 pairs of carbons, a characteristic that is indicative of a plane of symmetry in these compounds. The similarity in the position of the carboxyl, NCH_3, and benzoyl carbonyl signals in these epimers (see Table III) together with the downfield shifts of the C_2C_4 and C_6C_7 ^{13}C signals in compounds 1 and 17 supports the ^1H NMR spectral data, indicating a larger degree of flattening of the piperidine ring in compounds 1 and 17 than in 3 and 18.

The lack of nitrogen–carbonyl interaction is also borne out by the almost identical positions of the benzoyl carbonyl ^{13}C signals of 17 and 18. According to Nakashima and Maciel[15a] the nitrogen–carbonyl interaction of the type suggested by Archer and Bell[10] introduces a very large upfield shift in the carbonyl ^{13}C signal. The difference in the position of the ^{13}C signal for C_1 in the aromatic rings of 1 and 17 vs. 3 and 18 is compatible with the pseudoaxial nature of the 3α-phenyl group in compounds 1 and 17.[15b]

Table III. ^{13}C NMR Chemical Shift Data[a] (ppm) in $CDCl_3$

Assignments	1	3	17	18
$COOC_2H_5$	175.4	175.7		
COC_6H_5			202.3	203.6
	142.5	145.8	141.7	143.9
			141.5	137.3
	128.1	128.1	128.8	130.0
	126.7	126.6	128.3	129.8
		126.0	127.3	128.1
			127.0	127.8
			126.5	126.7
				125.4
OCH_2	60.4	61.1		
C_1C_5	59.1	60.4	57.9	60.7
C_3	46.1	45.6	50.1	51.2
NCH_3	39.8	39.2	39.4	39.2
C_2C_4	41.3	38.1	44.7	38.6
C_6C_7	28.1	24.4	29.2	24.4
CH_2CH_3	14.2	13.8		

[a]For assignments see L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, and G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972. See also ref 22.

Table IV. Narcotic Analgesic Screen

Compd	D'Amour–Smith "tail flick", ED_{50} (sc)[a]	Straub tail rxn
3	60–120[b]	Negative
1	25 ± 3.6[c]	Positive
Meperidine (**2**)	27 ± 4.3[c]	Positive

[a]mg/kg of free base. [b]The rat tails did not respond to the stimulus for 8% of the maximum time of 20 sec at 15 mg/kg; 18% at 30 mg/kg; 30% at 60 mg/kg, 1/6 dead, convulsions; 73% at 120 mg/kg, 3/6 dead. [c]Study on 1 and 2 was done at an earlier date.

It is noteworthy that the position of the carbonyl absorption in the ir for compounds 1 and 3 in $CHCl_3$ is identical (1713 cm^{-1}) reflecting no difference in the inter- or intramolecular interaction at this carbonyl.

Pharmacology. The new tropane analog of meperidine reported here (3) showed a D'Amour–Smith tail flick response[16] ED_{50} of 60–120 mg/kg sc. An accurate ED_{50} could not be determined owing to the toxicity of the compound; 1/6 rats died at 60 mg/kg. The reality of the analgesia noted was substantiated in that this effect was reversed by nalorphine. Tropane analog 1 and meperidine (2) were shown earlier in our laboratories to have an ED_{50} of 25 and 27 mg/kg, respectively (Table IV).

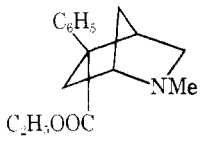
Portoghese[4] prepared the pair of rigid meperidine analogs **20** and **21** shown below. In terms of the ester groups being separated from the nitrogen by a blocking carbon bridge, compounds 21 and 3 have parallel structure. They are the less active and more toxic members of the epimeric pairs. Another difference between 3 and 1 was that 3 pro-

Table V. Local Anesthetic Activity in Guinea Pigs Intradermal Wheal Method

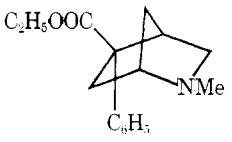
Compd	Concn, %	No. positive / no. tested	Mean anesthetic score	TAC_5,[a] %/ml	Act. ratio
Procaine	0.125	4/6	5.5		
	0.25	6/6	15	0.125	
	0.5	6/6	26		
					1
3	0.125	1/5	6.5		
	0.25	6/6	19	0.1	
	0.5	6/6	27		
Procaine	0.125	6/8	5.5		
	0.25	8/8	13.8	0.13	
	0.5	8/8	30.9		
					1
1	0.125	6/8	6.3		
	0.25	7/8	7.6	0.13	
	0.5	8/8	17.9		
Procaine	0.125	2/4	3		
	0.25	4/4	18	0.13	
	0.5	4/4	30		
					1
Meperidine (2)	0.125	3/4	4		
	0.25	4/4	14	0.14	
	0.5	4/4	29		

[a] The average threshold anesthetic concentration (TAC_5) was obtained from the dose-effect curve (semilogarithmic plot of duration in minutes vs. dosage) as described by Luduena and Hoppe.[20]

duced no Straub tail reaction,[17] whereas 1 and meperidine did so.



20



21

Table V compares the local anesthetic action of these compounds in parallel with procaine using an intradermal anesthetic test in guinea pigs.[18]

Conclusions

The ^1H and ^{13}C magnetic resonance spectra are inconsistent with a boat structure for compounds 1 and 17 as suggested earlier.[10] These spectra, however, are consistent with a piperidine ring that is flatter than one in a normal chair conformation.[19] Although the pharmacological data appear to indicate that compound 1 is more effective at the narcotic receptor than compound 3, the difference in activity, as was the case with compounds 20 and 21 studied by Portoghese,[4] could be due to differences in rate of passage into the brain. The difference in potency between 1 and 3 in the D'Amour-Smith "tail flick" test (a factor of only 3 or 4), a series which may not interact with analgesic receptors in the same way as morphine, suggests that the analgesic activity in the case of meperidine-like compounds is not very sensitive to the conformation of the phenyl group in 4-phenylpiperidines. These results would tend to support the results of other workers[2-4] who have also suggested that the steric relationship of the phenyl group with respect to the piperidine ring is of little importance in meperidine like compounds. It is also apparent in this series that there is little conformational requirement for local anesthetic activity. The difference in the Straub tail reaction cannot be explained with the available data.

Experimental Section[21]

8-Benzyl-3ξ-phenyl-1αH,5αH-nortropane-3ξ-carbonitrile (7 and 8). A solution of 23.1 g (0.09 mol) of *N*-benzyl-*cis*-2,5-bis(chloromethyl)pyrrolidine (6)[8] and 16.5 g (0.14 mol) of $PhCH_2CN$ in 500 ml of DMF was stirred vigorously at ice bath temperature while 17.7 g of a 57% w/w dispersion of NaH in mineral oil (0.42 mol) was added, carefully controlling the H_2 evolution. The ice bath was removed and the mixture was stirred at room temperature for 3 hr and finally was heated on a steam bath for 2 hr. The mixture, after being cooled, was added to 2.5 l. of ice-H_2O and was extracted with $CHCl_3$ several times. The $CHCl_3$ was washed with 2 *N* HCl. The acid was made alkaline with concentrated NaOH and extracted several times with $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and evaporated by warming in vacuo leaving 25 g of residue. TLC showed a single band at R_f 0.5; GLC showed two close but resolved peaks, a major early peak (74%) and a minor peak (26%). The residue was distilled at 145–185° (0.50–0.45 mm) affording 11.2 g (41.5%) of a mixture of isomers (GLC indicated a 3:1 early-late mixture).

The distillate was dissolved in ether and treated with ethereal HCl. The precipitated mixture of salts was recrystallized from EtOH yielding 6.02 g of 8-benzyl-3β-phenyl-1αH,5αH-nortropane-3α-carbonitrile (7) hydrochloride salt: mp 255–260° dec; GLC showed a major early peak (96%) and a minor late peak (4%).

Further recrystallization from EtOH afforded the analytical sample of 7 HCl salt: mp 276–278° dec; GLC 99% early peak. Anal. ($C_{21}H_{22}N_2 \cdot HCl$) C, H, Cl.

The free base 7 melted at 102–103° (from Et_2O): M^+ 302; GLC showed only the early peak.

The mother liquors of 7 HCl salt upon further concentration afforded 1.0 g of impure 8-benzyl-3α-phenyl-1αH,5αH-nortropane-3β-carbonitrile (8) HCl salt: mp 238–240°; GLC showed a minor early peak (14%) and a major late peak (86%).

The free base 8 after recrystallization from Et_2O melted at 117–118°: M^+ 302; GLC indicated that this sample was 99% pure.

The analytical sample melted at 118–120° (Et_2O). Anal. ($C_{21}H_{22}N_2$) C, H.

Ethyl 8-Benzyl-3α-phenyl-1αH,5αH-nortropane-3β-carboxylate (9).[9] A solution of 300 mg (1.0 mmol) of 8 in 200 mg of H_2O and 800 mg of H_2SO_4 was heated in an oil bath at 150° (internal temperature) for 1.5 hr. The temperature was dropped to 130° and enough absolute EtOH was added so that reflux maintained an internal temperature of 103–108° for 4 hr. The reaction mixture was added to ice. NaOH (2 *N*) and Et_2O were added. The separated Et_2O was dried (Na_2SO_4) and evaporated (warmed in vacuo) affording 130 mg (mechanical loss) of 9 as an oil. Conversion to the HCl salt by treatment with ethereal HCl and recrystallization of the precipitated salt from isopropyl alcohol afforded 100 mg of 9 HCl: mp 204–205°; GLC showed a single peak; M^+ 349; ir (KBr) 1710 cm^{-1}. Anal. ($C_{23}H_{27}NO_2 \cdot HCl$) C, H, N.

8-Benzyl-3β-phenyl-1αH,5αH-nortropane-3α-carboxamide (11). A solution of 600 mg (1.8 mmol) of 7 HCl salt in 200 mg of H_2O and 800 mg of H_2SO_4 was heated in an oil bath at 145° (internal temperature) for 1.5 hr. The temperature was reduced to 120° and enough EtOH was added to maintain reflux at 103–108° for 2 hr. The reaction mixture was worked up as for 9 affording 0.46 g of crystalline 11 (72%): mp 128–130°; TLC showed a single band R_f 0.3; M^+ 320; ir (KBr) 1660 cm^{-1}.

Similar results were obtained when the reaction mixture was heated at 145–150° for 5.5 hr followed by reflux with EtOH at 103–108° for 4 hr.

The HCl salt of 11 (from EtOH) melted at 302–305°. Anal. ($C_{21}H_{24}N_2O \cdot HCl$) C, H, Cl.

H_2SO_4 Treatment of a Mixture of 7 and 8. A solution of 8.6 g (0.025 mol) of a mixture of 7 and 8 (3:2) in 4 g of H_2O and 16 g of H_2SO_4 was heated in an oil bath at 150–165° (internal temperature) for 1 hr. The temperature was reduced to 130° and enough EtOH was added to maintain reflux at 102–108° for 3 hr. The mixture was worked up as for 9 leaving 5.6 g of residue; TLC showed a less polar band at R_f 0.7 and a more polar band at R_f 0.3. The residue was chromatographed on 300 g of silica gel using a 50:47:3 *n*-C_5H_{12}-Et_2O-*i*-$PrNH_2$ solvent system for elution. The early eluent gave 2.3 g of ester 9. Its HCl salt (2.0 g) melted at 204–205° and was identical by ir and NMR with 9 HCl prepared from pure 8.

The later fractions afforded 2.7 g of a mixture of amides which were separated by plate chromatography (nine plates, 20 × 40 cm × 1 mm, Brinkmann Instruments silica gel grade PF-254, *i*-$PrNH_2$–Et_2O 3:97). The least polar band afforded 1.2 g of α-amide **11**, mp 126–128°, and 0.9 g of the more polar β-amide **12**, mp 118–120° (from Et_2O). The crude HCl salt of **12** melted at 265° dec.

The analytical sample of **12** HCl salt from Me_2CO melted at 260–261° dec; M^+ 320; ir (KBr) 1650 cm^{-1}. Anal. ($C_{21}H_{24}NO \cdot HCl$) C, H, Cl.

Ethyl 3α-Phenyl-1αH,5αH-nortropane-3β-carboxylate (10).[1,22] A solution of 1.4 g (3.6 mmol) of **9** HCl in 300 ml of 95% EtOH was hydrogenated with 0.5 g of 10% Pd-on-C catalyst on the Parr shaker at 50 lbs/in.^{2}. When the theoretical uptake was complete the catalyst and solvent were removed and the residue (0.87 g) was recrystallized from *i*-PrOH yielding crystalline **10** HCl salt, mp 229–230°. Its identity was established by ^1H NMR, GLC, TLC, and melting point comparison with a sample prepared by Bell and Archer.[1]

Ethyl 3α-Phenyl-1αH,5αH-tropane-3β-carboxylate (1).[1,22] A solution of 320 mg (1.1 mmol) of **10** in 5 ml of formic acid (98–100%) and 2 ml of formaldehyde (35% aqueous) was heated on the steam bath for 2 hr. The excess reagents were removed by warming in vacuo; 2 *N* NaOH and Et_2O were added. The Et_2O layer was separated, washed (saturated NaCl), dried (Na_2SO_4), and concentrated, affording 350 mg of **1**: ir (10% $CHCl_3$) 1713 cm^{-1}. Treatment with ethereal HCl and recrystallization of the precipitated salt from *i*-PrOH gave **1** HCl: mp 190–191°; identical by ^1H NMR, ir, and melting point with a sample prepared by Bell and Archer.[1]

Ethyl 8-Benzyl-3β-phenyl-1αH,5αH-nortropane-3α-carboxylate (15). A solution of 18.5 g (0.052 mol) of **7** HCl in 13.1 g of H_2O and 52.4 g of H_2SO_4 was heated at 150° (internal temperature) for 48 hr and the cooled mixture was added to ice-H_2O. The precipitated solid was dissolved in EtOH and the solution was filtered and concentrated by warming in vacuo, leaving 24.4 g of carboxylic acid sulfate salt **13**.

This salt was heated under reflux in 300 ml of $SOCl_2$ for 20 hr. The excess reagent was removed by warming in vacuo. The solid residue was dissolved in 300 ml of absolute EtOH and heated under reflux for 4 days. The excess EtOH was evaporated. Et_2O and concentrated NH_4OH were added to the solid residue. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and evaporated affording 12.6 g of **15** (66.5%). The analytical sample (from EtOH) melted at 89–90°: M^+ 349; ir (KBr) 1710 cm^{-1}. Anal. ($C_{23}H_{27}NO_2$) C, H, N.

8-Benzyl-3β-phenyl-1αH,5αH-nortropane-3α-carboxylic Acid Chloride (14). A solution of 1.23 g of **13** as the carboxylic acid sulfate salt in 40 ml of $SOCl_2$ was heated under reflux for 3 hr. The excess reagent was removed by warming in vacuo and 50 ml of EtOH was added carefully. The mixture was heated under reflux for 3 hr and then warmed in vacuo to remove the excess EtOH. H_2O, 2 *N* NaOH, and Et_2O were added. The Et_2O layer was separated, dried (Na_2SO_4), and concentrated, affording 600 mg of an oily residue that was converted to an HCl salt. Recrystallization from *i*-PrOH gave 350 mg of crude **14** HCl salt: mp 236–237° dec; M^+ 341, 339; ir (KBr) 1760 cm^{-1}.

Heating this solid under reflux in EtOH for 72 hr followed by evaporation of the EtOH afforded 350 mg of **15** HCl salt: mp 186–188°; M^+ 349; ir (KBr) 1710 cm^{-1}.

Ethyl 3β-Phenyl-1αH,5αH-nortropane-3α-carboxylate (16). A solution of 12.6 g (0.032 mol) of **15** and 16.4 ml of 2 *N* HCl (0.032 mol) in enough 95% EtOH to bring the volume to 300 ml was hydrogenated with 2 g of 10% Pd/C on the Parr shaker at 55 lbs/in.^{2}. After theoretical uptake the catalyst and solvent were removed, Et_2O and NaOH were added, and the layers were separated. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and evaporated affording 8.0 g of **16** (75%): mp 88–93°; M^+ 259; ir (KBr) 3200, 1710 cm^{-1}. This product was used in the next experiment without further purification.

Ethyl 3β-Phenyl-1αH,5αH-tropane-3α-carboxylate (3). A solution of 7.9 g of **16** (0.031 mol) in 120 ml of formic acid (98–100%) and 48 ml of formaldehyde (35% aqueous) was heated on a steam bath for 2 hr. The mixture was worked up as for **1** yielding 8.0 g (94%) of **3**: ir (10% $CHCl_3$) 1713 cm^{-1}. The crude HCl salt **3** melted at 179–180° dec.

Recrystallization from Me_2CO afforded the analytical sample **3** HCl: mp 184–184.5° dec; M^+ 273; ir (KBr) 1710 cm^{-1}. Anal. ($C_{17}H_{23}NO_2 \cdot HCl$) C, H, Cl.

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References and Notes

(1) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4638 (1960).
(2) A. Ziering, A. Motchane, and J. Lee, *J. Org. Chem.*, **22**, 1521 (1957).
(3) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).
(4) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, 11, 219 (1968).
(5) P. S. Portoghese, *Annu. Rev. Pharmacol.*, **10**, 51 (1970).
(6) A. F. Casy, *Prog. Med. Chem.*, **7**, 265 (1971).
(7) G. Cignarella, G. G. Gallo, and E. Testa, *J. Am. Chem. Soc.*, **83**, 4999 (1961).
(8) G. Cignarella and G. G. Nathansohn, *Gazz. Chim. Ital.*, **90**, 1495, (1960); N. Albertson, U.S. Patent 3,202,675 (1965).
(9) S. Archer and M. Bell, U.S. Patent 3,073,829 (1965).
(10) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960).
(11) The abnormal spectral behavior of **17** in the ultraviolet in both CH_2Cl_2 and CH_3OH is characterized by the absence of absorption peaks (only shoulder) in the 240–250- and 320-nm regions and by a decreased intensity of absorption in the 240–250-nm region. There is a significant decrease in absorption intensity when the solvent is changed from CH_2Cl_2 to CH_3OH. The piperidine analog is unaffected by this change. Archer and Bell reported[10] that a 1% solution of **17** in MeOH exhibited no infrared absorption in the 5.9–6.25-μ range. (In CH_2Cl_2 there is a carbonyl peak at 6.02 μ.) Cignarella, Gallo, and Testa[7] later reported that a *3% solution* of **17** in MeOH did indeed show absorption at 6 μ and the latter observation was verified by Archer and Bell.
(12) H. Schenk, C. H. MacGillvary, S. Skolnik, and J. Laan, *Acta Crystallogr.*, **23**, 423 (1967).
(13) (a) G. S. Choppell, B. F. Grabowski, R. A. Sandmann, and D. M. Yourtree, *J. Pharm. Sci.*, **62**, 414 (1973); (b) P. Scheiber, G. Kraiss, and K. Nador, *J. Chem. Soc. B*, 1366 (1970).
(14) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(15) (a) T. T. Nakashima and G. E. Maciel, *Org. Magn. Reson.*, **4**, 321 (1972); (b) A. J. Jones, A. F. Casy, and K. M. J. McErlane, *J. Chem. Soc., Perkin Trans. 1*, 2576 (1973).
(16) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, **143**, 141 (1964).
(17) M. D. Aceto, D. B. McKean, and J. Pearl, *Brit. J. Pharmacol.*, **36**, 225 (1969), and references cited therein.
(18) E. Bülbring and I. Wajda, *J. Pharmacol. Exp. Ther.*, **85**, 78 (1945).
(19) A paper by A. F. Casy and J. E. Coates, *Org. Magn. Reson.*, **6**, 441 (1974), came to our attention after our manuscript had already been submitted to the editor of the *J. Med. Chem.* Casy and Coates concur that **1** exists in a flattened chair conformation when protonated. However, they conclude that **17** exists in a boat conformation. Their main argument is based on 1H,5H half-bandwidths. We feel that with the lack of sufficient information on boat conformations in the tropane series, together with the undetermined distortions of both the piperidine and pyrrolidine rings which affect the dihedral angles C(2)–C(1)–C(7) and C(4)–C(5)–C(6), an argument based on half-bandwidths, is inconclusive.
(20) F. P. Luduena and J. O. Hoppe, *J. Pharmacol. Exp. Ther.*, **104**, 40 (1952).
(21) All melting points are uncorrected. The mass spectra reported were measured with a Joelco JMS-1-OCS mass spectrograph. Infrared spectra were determined on a Model-21 Perkin-Elmer infrared spectrophotometer. EM Reagents precoated silica gel F-254 plates were used with an *i*-$PrNH_2$–Et_2O (3:97) developing system for TLC analysis. GLC was done on a 3% OV-1 100–120 mesh GCQ column. Analytical results for indicated elements are within ±0.4% of the theoretical values.
(22) ^1H NMR spectral measurements were made on Varian A-60 or HA-100 spectrophotometers using $CDCl_3$ as solvent unless otherwise indicated. Me_4Si was used as an internal standard. Spin-decoupling experiments were done with a Varian HA-100 instrument using a Hewlett-Packard audio oscillator 4204A. The ^{13}C NMR spectra were determined using a Varian Associates CFT-20 spectrometer and $CDCl_3$ as solvent at concentrations of ca. 0.5 *M* except for compound **18** which was ca. 0.03 *M* (Me_4Si as 0 ppm).