of 1.3 mg/kg for 7 days in combination with 5 (mg/kg)/day of chloroquine.

Antileishmanial Test Method. The antileishmanial activity of **2d** was determined in golden hamsters by the method of Hanson et al.[13] Male golden hamsters were inoculated intracardially with 10^7 amastigotes of the Khartoum strain of *Leishmania donovani*. Administration of the drug was begun 3 days after inoculation and was continued twice daily for 4 days. On day 6 the hamsters were sacrificed and the ratio of the number of amastigotes per host liver cell nucleus was determined. Comparison was made of the suppressive effects of the test compound to that of the reference compound, glucantime (*N*-methylglucamine antimonate), and a glucantime index, *G*, was calculated using the formula: G = dose (SD_x) of glucantime/dose (SD_x) of test drug.

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References and Notes

(1) This is contribution no. 1540 to the Army Research Program on Malaria.
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4-Anilidopiperidine Analgesics. 2. A Study of the Conformational Aspects of the Analgesic Activity of the 4-Anilidopiperidines Utilizing Isomeric N-Substituted 3-(Propananilido)nortropane Analogues

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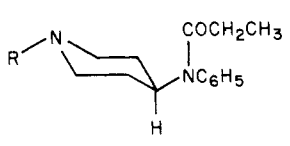
Relatively little information is available concerning the influence of conformational factors on the potent analgesic actions of the 4-anilidopiperidines. A series of N-substituted 3α- and 3β-(propananilido)nortropanes have been designed, synthesized, and stereochemically characterized as semirigid analogues of the 4-anilidopiperidine analgesics in an attempt to study the influence of certain stereochemical factors on analgesia in this class of compounds. Conformational analysis of 3α-propananilides (**4**) reveals a boat conformation for the preferred conformation of the piperidine ring of these tropane analogues. Evaluation of the analgesic potencies of the isomeric N-substituted 3-(propananilido)nortropanes of this study indicates greater potency for the 3β-(propananilido) isomers (**5**) with *N*-benzyl and *N*-phenethyl substitution as compared to the corresponding N-substituted 3α-propananilides. Analysis of relative solubility differences among these isomers suggests that both structural and stereochemical influences predominate in affecting analgesic potency.

The 4-anilidopiperidine class of synthetic narcotic analgesics (**1**) is characterized by high analgesic potency,



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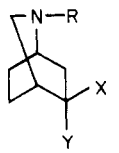
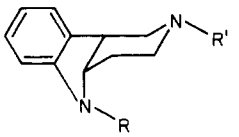


2, X = H; Y = $N(C_6H_5)COCH_2CH_3$
X = $N(C_6H_5)COCH_2CH_3$; Y = H
R = CH_3 and $C_6H_5CH_2CH_2$



3, R′ = $-CH_2CH_2C_6H_5$; R = H or $COCH_2CH_3$

rapid onset of action, and relatively high therapeutic indices.[1,2] Extensive SAR studies of the 4-anilidopiperidines have adequately defined optimal structural features for these synthetic analgesics relative to pharmacological activity.[3-5] On the other hand, relatively few studies have been performed to characterize the stereochemical requirements for 4-anilidopiperidine analgesic activity. First-order approximations of NMR spectral data obtained for a series of N-substituted 4-anilidopiperidine derivatives[3] and for certain 3-methyl-4-(propananilido)-piperidines[6] suggest a preferred piperidine ring chair conformation with an equatorially oriented 4-anilido moiety (**1**). Studies with chiral 3-methyl-4-(propananilido)piperidines indicate a significant dependence of analgesic activity on both optical and geometric isomerism in these 4-anilidopiperidine derivatives. Investigations of conformationally restricted analogues of the 4-anilidopiperidine analgesics have included the use of isomeric N-substituted 5-(propananilido)-2-azabicyclo[2.2.2]octanes (**2**), which were found to be devoid of measurable analgesic activity at ip doses of 100 mg/kg in mice.[7,8] Berger and co-workers[9] have studied isomeric pyrido[4,3-*b*]indoles (**3**)

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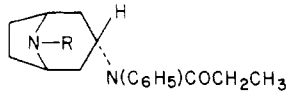
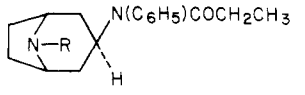
as conformationally restricted analogues of the 4-anilidopiperidines and report their compounds to lack analgesic activity. It is conceivable that the lack of analgesic activity observed in these studies of conformationally restricted analogues of the 4-anilidopiperidines could be ascribed to deviations from the preferred stereochemistry of the parent molecule **1**, as, for example, a boat conformation of the piperidine ring as required by the azabicyclooctane analogues **2** and/or axial orientation of the anilido moiety as found in both analogues **2** and **3**. In any regard, it is apparent that the opiate receptor exerts a relatively high stereochemical demand for efficacious interaction by the 4-anilidopiperidine class of synthetic narcotic analgesics.

In an attempt to design analogues of the 4-anilidopiperidine analgesics that would exhibit measurable analgesic activity and would allow for a determination of conformational influences on this activity, we have undertaken a study of tropane analogues of this class of basic anilide analgesics. The tropane ring system was chosen for this study because it has been used successfully in other studies of conformational influences on analgesic activity[10] and because this ring system allows for the facile incorporation of the important structural features of the 4-anilidopiperidines via N^8-alkylation or aralkylation and substitution of a propananilido moiety at the 3 position. Hence, a series of N-substituted 3α- (**4**) and 3β-(propananilido)nortropane (**5**) derivatives have been synthesized and conformationally characterized in this study. Further, these analogues have been evaluated for analgesic activity and, in the case of the *N*-propyl, *N*-allyl, and *N*-(cyclopropylmethyl) derivatives, evaluated for potential opiate antagonistic activities.

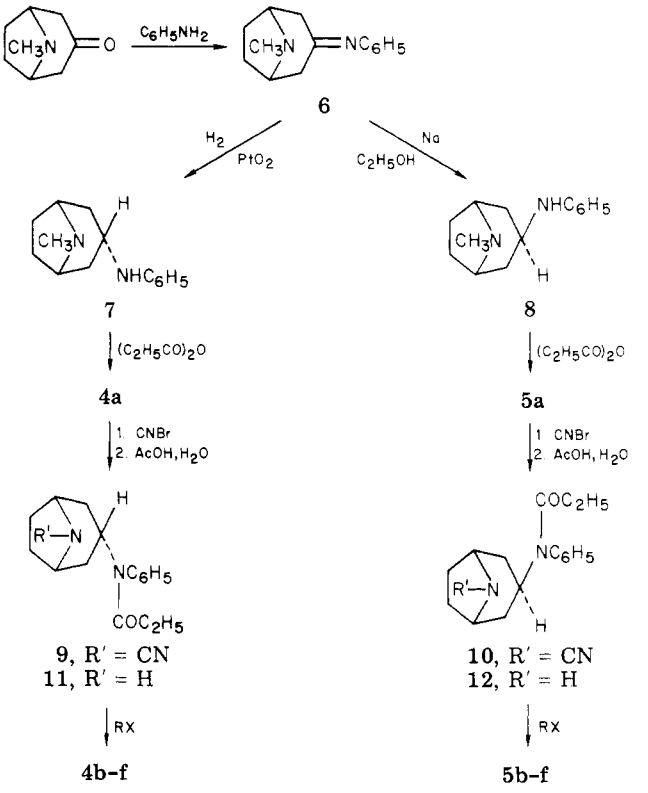


4a, R = CH_3
b, R = $CH_2C_6H_5$
c, R = $CH_2CH_2C_6H_5$
d, R = $CH_2CH{=}CH_2$
e, R = CH_2-c-C_3H_5
f, R = $CH_2CH_2CH_3$

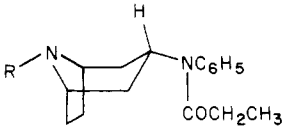


5a, R = CH_3
b, R = $CH_2C_6H_5$
c, R = $CH_2CH_2C_6H_5$
d, R = $CH_2CH{=}CH_2$
e, R = CH_2-c-C_3H_5
f, R = $CH_2CH_2CH_3$

Chemistry. An approach to the synthesis of the tropane analogues of the 4-anilidopiperidine analgesics was employed that would allow both isomer separation and stereochemical characterization of the isomers in one step (Scheme I). Hence, the isomeric 3-(propananilido)tropane analogues **4a** and **5a** were initially synthesized, configurationally and conformationally characterized, and then converted via N-demethylation to the remaining *N*-alkyl and *N*-aralkyl derivatives of the series. Catalytic reduction of tropananil (**6**), prepared by refluxing tropinone and aniline in toluene in the presence of 4 Å molecular sieves, provided isomerically pure samples of 3α-anilinotropane (**7**), whereas reduction of the anil using Na–EtOH provided a 70:30 mixture of 3β-anilinotropane (**8**) and the 3α-isomer, respectively. Recrystallization of the mixture from petroleum ether provided pure samples of 3β-anilinotropane. The relative configurations of the anilino isomers were inferred by reference to previous reports of stereoselective reductions of tropinones and tropinimines[11-13] and by interpretation of GLC retention times and NMR spectral data.[14] The 3-(propananilido)tropane isomers **4a** and **5a** were prepared from the corresponding 3-anilino isomers via propionylation in refluxing propionic anhydride. N-Demethylation of the 3-(propananilido)nortropane isomers was readily accomplished using fresh CNBr in benzene, followed by hydrolysis of the cyanamide isomers **9** and **10** in aqueous AcOH to provide 3α- (**11**) and 3β-(propananilido)nortropane (**12**). The appropriate N-substituent was incorporated into the tropane structures via treatment of **11** and **12** with an alkyl or aralkyl halide to provide the desired N-substituted 3-(propananilido)-nortropane isomers **4b–f** and **5b–f** (Table I).



Examination of the NMR spectral data obtained for the isomeric 3-(propananilido)tropanes **4a** and **5a** revealed an apparent anomaly in the chemical shifts of the H_3 signals. The H_3 signal in the NMR spectrum of the 3α-isomer **4a** appeared at δ 4.60 (nonet, J = 8 and 11 Hz), whereas this signal in the NMR spectrum of the 3β-isomer **5a** was at δ 4.98 (J = 7 and 10 Hz). These data, taken in conjunction with other NMR spectral characteristics of these isomers, were interpreted in terms of a preferred conformation of the 3α isomer in which the piperidine ring exists in a boat conformation (**13**) with resultant pseudoequatorial disposition of the 3-(propananilido) moiety.[14] Presumably, steric repulsion between an axially oriented 3-(propananilido) moiety and the 6,7-bimethylene bridge of the tropane ring system is relieved by adoption of a piperidine boat conformation. A preferred conformation of the 3β-isomer **5a** in which a slight degree of flattening of the piperidine ring about the C_2–C_3–C_4 bonds occurs (**14**) is supported by NMR spectral data for this compound. The NMR spectral characteristics of the isomeric N-substituted 3-(propananilido)nortropane derivatives support similar conformational preferences for both the 3α (boat) and the 3β isomers (flattened chair).



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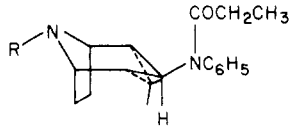
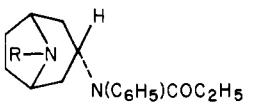


14

Pharmacological Results and Discussion. The isomeric N-substituted 3-(propananilido)nortropane analogues prepared in this study were evaluated for an-

Table I. Isomeric N-Substituted 3-(Propananilido)nortropane Analogues



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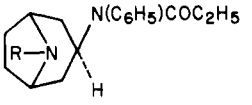

5

no.	R	% yield[a]	recrystn solvent[b]	mp, °C	formula[c]
			3α-propananilides		
11	H	92	MeOH/Et_2O	230-232	$C_{16}H_{22}N_2O\cdot HCl\cdot 0.25H_2O$
4a	CH_3	77	EtOH/Et_2O	196-197	$C_{17}H_{24}N_2O\cdot HCl$[d]
4b	$CH_2C_6H_5$	71	EtOH/Et_2O	205-206	$C_{23}H_{28}N_2O\cdot C_2H_2O_4\cdot H_2O$
4c	$CH_2CH_2C_6H_5$	71	MeOH/Et_2O	244-247	$C_{24}H_{30}N_2O\cdot HCl$
4d	$CH_2CH{=}CH_2$	41	MeOH/Et_2O	203-206	$C_{19}H_{26}N_2O\cdot HCl$
4e	CH_2-c-C_3H_5	71	EtOAc	168-170	$C_{20}H_{28}N_2O\cdot HCl\cdot 0.25H_2O$
4f	$CH_2CH_2CH_3$	66	MeOH/Et_2O	207-208	$C_{19}H_{28}N_2O\cdot HCl$
			3β-propananilides		
12	H	63	MeOH/Et_2O	269-270	$C_{16}H_{22}N_2O\cdot HCl$
5a	CH_3	66	EtOH/Et_2O	172-173	$C_{17}H_{24}N_2O\cdot HCl$[d]
5b	$CH_2C_6H_5$	83	EtOH	235-236	$C_{23}H_{28}N_2O\cdot C_2H_2O_4$
5c	$CH_2CH_2C_6H_5$	88	EtOH	221-222	$C_{24}H_{30}N_2O\cdot C_2H_2O_4$
5d	$CH_2CH{=}CH_2$	85	MeOH/Et_2O	168-169	$C_{19}H_{26}N_2O\cdot HCl\cdot 0.75H_2O$
5e	CH_2-c-C_3H_5	82	EtOH/Et_2O	195-196	$C_{20}H_{28}N_2O\cdot C_2H_2O_4\cdot 0.25H_2O$
5f	$CH_2CH_2CH_3$	64	EtOH/Et_2O	204-205	$C_{19}H_{28}N_2O\cdot C_2H_2O_4$

[a] Based on the weight of the free base obtained from immediate synthetic precursor. [b] Solvent used to purify indicated salt. [c] All compounds were analyzed for C, H, and N, with results obtained for these elements within ±0.4% of theoretical values. [d] See ref 13.

Table II. Analgesic Activities of Isomeric N-Substituted 3-(Propananilido)nortropane Analogues

compd[a]	log P	AD_{50}, mg/kg sc (95% CL)[b]	naloxone antag		antag of morph analg	
			dose, mg/kg	results[c]	dose, mg/kg	results[d]
		3α-propananilides				
11	2.71	>100			100	0/6
4a	2.82	>100			100	0/2
4b	3.95	35.5 (22.2-56.8)	100	6/6	70.6	0/6
4c	3.90	2.22 (0.92-5.33)	11.0	6/6	5.0	0/6
4d	3.04	>100			100	0/6
4e	2.95	>100			100	0/6
4f	2.94	>100			100	0/6
		3β-propananilides				
12	2.52	>100			100	0/6
5a	2.70	>100			100	2/2
5b	3.30	1.80 (0.78-4.14)	14.8	6/6	3.8	0/6
5c	3.35	0.047 (0.017-0.131)	10.6	6/6	0.1	0/6
5d	2.71	>100			100	2/6
5e	2.67	>100			100	0/6
5f	2.70	>100			100	1/6
pentanyl citrate	3.15	0.024 (0.014-0.043)				
morphine sulfate		1.90 (1.29-2.79)				

[a] Assayed as HCl salts. [b] CL = confidence limits. [c] Number of mice in which analgesia was abolished by naloxone pretreatment/number of mice tested. [d] Number of mice in which morphine analgesia was abolished by test compound/number of mice tested.

algesic activity in mice using the tail-flick procedure[15] (Table II). The opiate receptor site of analgesic action of the active tropane derivatives was established by measuring the effect of naloxone pretreatment on the analgesic potency of the compounds when administered at AD_{100} dose levels (Table II). Potential opiate antagonistic actions of the compounds of this study were evaluated by the administration of the test compounds to morphine-pretreated mice and any reductions in the level of morphine analgesia noted (Table II).

Previous SAR studies of the 4-anilidopiperidine analgesics suggest that measurable analgesic activity is largely confined to those derivatives having an *N*-aralkyl substituent on the basic N atoms.[3,4] SAR results in the current study are consistent with these observations in that only the *N*-benzyl (**4b** and **5b**) and the *N*-phenethyl (**4c** and **5c**) derivatives exhibit analgesia at dose levels of <100 mg/kg. The greater potency of the *N*-phenethyl derivatives **4c** and **5c** in both the 3α- and 3β-(propananilido) isomers as compared to the corresponding *N*-benzyl derivatives **4b** and **5b** is also consistent with the above-cited SAR studies. It is perhaps noteworthy that the potency of **5c** is not significantly different from that of the prototype 4-anilidopiperidine analgesic, fentanyl (1, R = $C_6H_5CH_2CH_2$), and that the potencies of **4c** and **5b** are similar to that exhibited by morphine. A definite stereochemical influence on analgesic potency can be observed for the isomeric 3-(propananilido)nortropane analogues of this study in that the 3β-isomers **5b** and **5c** are significantly more potent than the correspondingly N-substituted 3α-isomers **4b** and **4c**. In an attempt to evaluate the contribution of relative solubility differences among the test compounds, the log *P* values (Table II) of the various N-substituted 3-(propananilido)nortropane isomers and the standard analgesic, fentanyl, were determined. It is conceivable that solubility differences among the test compounds could account, to a significant degree, for observed potency differences as a result of differential

translocation into the CNS.[16] However, the results of this study indicate a lack of correlation between relative solubility and analgesic activity of the test compounds. Measurable analgesic activity is restricted to those 4-anilidopiperidine analogues having a log P value of ≥ 3.15. Further, the relatively large differences in potency seen for the N-benzyl (**4b** and **5b**) and N-phenethyl (**4c** and **5c**) analogues can best be accounted for in terms of structural differences in view of the relatively small differences in log P values found for these compounds. The important role of stereochemical factors as opposed to relative solubility in influencing analgesic potency of the isomeric N-benzyl- and N-phenethyl-3-(propananilido)nortropane analogues is apparent from the inverse relationship noted between log P values and analgesic potencies of these analogues.

The results of this study of conformationally restricted analogues of the 4-anilidopiperidines support earlier findings that the analgesic activity of this class of compounds is highly dependent on stereochemical factors. It is possible that the lesser analgesic potency of the N-benzyl- and N-phenethyl-3α-(propananilido)nortropanes (**4b** and **4c**) is related to the preferred piperidine boat conformation of these analogues. Examination of molecular models of the preferred conformations of **1**, **4**, and **5** indicates an equatorial (**1**) or pseudoequatorial (**4** and **5**) orientation of the propananilido moiety positioned approximately equidistant from the basic N atom in each model. The less analgesically active 3α isomers (**4**), however, differ from **1** and **5** in having a piperidine boat conformation. These results suggest that the pharmacophoric conformation of the 4-anilidopiperidine analgesics is identical with the thermodynamically preferred conformation, that is, a chair piperidine ring conformation with equatorial orientation of the 4-anilido moiety.

The results of this study also indicate the lack of favorable opiate antagonistic properties of these conformationally restricted analogues of the 4-anilidopiperidine analgesics. In particular, those analogues having N substituents known to confer antagonistic activity in other narcotic analgesic classes, **4d–f** and **5d–f**, were devoid of measurable opiate antagonistic activity. Certain derivatives (Table II) exhibited minor reductions in morphine analgesia in our assay but only at the highest dose levels (100 mg/kg) tested.

Experimental Section

Log P Determinations. The relative solubilities of the HCl salts of the test compounds and of fentanyl citrate were determined by a partitioning procedure using a reverse-phase high-pressure LC column (3.9 mm i.d. × 30 cm, 10-μm μ-Bondapak C_{18} column, Waters Associates, Inc.) and a pH 7.0 mobile phase (3.3 g of K_2HPO_4, 4.2 g of KH_2PO_4, 2.8 L of MeOH, and 1.2 L of H_2O). A flow rate of 2.0 mL/min was used, and the column was operated at room temperature. Two UV detectors (Model 440, Waters Associates, Inc.) were employed in series with the column and they were operated at 254 and 280 nm and the chromatograms were obtained on a dual-pen recorder. Samples (0.1–2.0 μL) of the test compounds (1.0 mg/mL) in MeOH were manually injected into the chromatographic system. The procedure of Baker and co-workers was used in determining the retention indices and log P values of the test compounds.[17,18]

Chemistry. All melting points are uncorrected and were determined with a Mel-Temp apparatus. IR spectra were determined with a Beckman IR-33 spectrophotometer. NMR spectra were taken on a Jeolco C-60HL spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

The isomeric 3-anilino-1αH,5αH-tropanes **7** and **8** and 3-(N-propananilido)-1αH,5αH-tropanes **4a** and **5a** were prepared and characterized as reported in an earlier publication.[14]

3α- and 3β-(N-Propananilido)-1αH,5αH-nortropane (11 and 12). A solution of 1.1 g (4.0 mmol) of **4a** or **5a** in 10 mL of dry C_6H_6 was added slowly to a stirred solution of 1.0 g (9.0 mmol) of CNBr in 10 mL of dry C_6H_6 maintained at 55–60 °C. The reaction was stirred at this temperature for 2 h and then allowed to stand at room temperature overnight. The reaction was washed with three 25-mL portions of saturated NaCl solution and dried (Na_2SO_4). Evaporation of solvent gave a yellow solid which was cleaned with repetitive petroleum ether washings. The cyanamide (ν^{NCN} 2200 cm^{-1}) isomers **9** and **10** were used without further purification. A mixture of 2.6 g (9.2 mmol) of **9** or **10**, 45 mL of AcOH, and 15 mL of H_2O was refluxed for 5 h. The reaction mixture was cooled and concentrated in vacuo, and the residual oil was dissolved in 50 mL of $CHCl_3$ (or CH_2Cl_2 in the case of the preparation of **12**). The organic solution was washed with 25 mL of 50% NH_4OH and dried (Na_2SO_4). Removal of solvent in vacuo provided an oily product that was distilled to give 2.5 g (92%) of **11**: bp 142–147 °C (0.05 mm); NMR δ 7.27 (m, 5 H, C_6H_5), 4.82 (nonet, 1 H, J = 8 and 11 Hz, 3β-H), 3.63 (m, 2 H, HBW = 18 Hz, 1α,5α-H). Preparation of **11**·HCl in the usual manner and recrystallization from MeOH/Et_2O gave a white, crystalline solid, mp 230–232 °C. Similarly, distillation of the oily product obtained from **10** gave 1.7 g (63%) of **12**: bp 160–185 °C (0.1 mm); NMR δ 7.22 (m, 5 H, C_6H_5), 5.16 (nonet, 1 H, J = 7 and 10 Hz, 3α-H), 3.63 (m, 2 H, HBW = 8 Hz, 1α,5α-H). The HCl salt of **12** was prepared and recrystallized from MeOH/Et_2O, mp 272–273 °C.

General Procedure for the Preparation of 4b–f and 5b–f. In a typical preparation, 9.2 mmol of the appropriate alkyl halide ($PhCH_2Cl$, c-$C_3H_5CH_2Cl$, $PhCH_2CH_2Br$, $H_2C{=}CHCH_2Br$, $CH_3CH_2CH_2I$) in 10 mL of CH_3CN was added to a stirred, ice-cooled mixture of 8.4 mmol of **11** or **12**. Anhydrous Na_2CO_3 (40 mmol) and a few crystals of KI (except in the preparation of **4f** and **5f**) were added to the reaction mixture along with 20 mL of CH_3CN. The reaction mixture was refluxed for 24 h, cooled, and filtered, and the filter cake was washed with CH_3CN. The filtrate was concentrated in vacuo and the residual oil dissolved in 25 mL of 10% HCl. The acidic solution was washed with 2 × 15 mL portions of Et_2O and then neutralized with 6 N NaOH. The free amine was extracted into Et_2O (3 × 20 mL portions), and the ethereal solution was washed with 3 × 15 mL portions of H_2O and dried (Na_2SO_4). Removal of solvent yielded a nearly colorless oil which was converted into either a HCl or oxalate salt (Table I) for purposes of elemental analysis. The distinguishing NMR spectral characteristics of the various N-substituted 3-(propananilido)nortropane isomers (**4a–f** and **5a–f**) are found in the 3-H and 1α,5α-H signals. In the case of the 3α-propananilide isomers the 3β-H signal appears as a nonet (δ 4.82–5.18, $J \simeq 8$ and 11 Hz), and for the 3β-propananilide isomers the 3α-H signal appears as a poorly resolved nonet (δ 5.06–5.10, $J \simeq 7$ and 10 Hz). In the NMR spectra of the N-substituted derivatives of **4** the 1αH,5αH signal appears as a broad multiplet (δ 3.26–3.46, HBW = 17–19 Hz), and for the N-substituted derivatives of **5** this signal appears as a multiplet (δ 3.22–3.46, HBW = 8–10 Hz).

Pharmacology. All compounds were evaluated as saline solutions of their HCl salts in this study. A modification of the D'Amour–Smith tail-flick method was employed in the evaluation of analgesic activity.[15] Male albino ICR mice weighing 15–25 g were given a thermal stimulus challenge 20 min postadministration (sc) of the test compounds. Positive analgesia was defined as a tail-flick response time greater than or equal to the mean response time of the control group of 10 mice plus two standard deviations of their mean. All median analgesic doses (AD_{50}) and their 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[19] The mice used in the analgesic assay were closely observed for physical and behavioral changes during the test period and were examined for lethality 24 h after testing. While the analgesically active compounds **4b**, **5b**, and **5c** produced immediate lethal effects at 100 mg/kg, none of the other test compounds produced acute or chronic (24 h) lethalities at 100 mg/kg. A depression of locomotor activity was elicited by **4b** and **4c** only at dose levels greater than the AD_{50} values, while stimulation of locomotor activity was observed in mice treated with **5b** and **5c** at dose levels greater than the respective AD_{50} values of these compounds. All of the analgesically active compounds except **4b** elicited Straub tail reactions in the test animals, although this reaction was absent at the AD_{50} dose levels.

Naloxone hydrochloride (4 mg/kg, sc) was administered to groups of six mice, followed by sc AD_{100} doses of **4b**, **4c**, **5b**, and **5c** after a 5-min period. Analgesic activity was then measured 15 min after administration of the test compounds using the tail-flick procedure. Naloxone pretreatment completely abolished the analgesic responses of the test compounds. Groups of six mice were pretreated with morphine sulfate (5 mg/kg, AD_{100}, sc), followed 10 min later by a sc dose of 100 mg/kg of the analgesically inactive compounds or a sc dose of $2 \times AD_{50}$ of the analgesically active compounds. The mice were then evaluated for analgesia using the tail-flick procedure 20 min after administration of the test compounds.

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New Antiarrhythmic Agents. 1. Primary α-Amino Anilides

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Thirty-two α-amino anilides with various substituents in the aromatic ring and in the α position are described. Their abilities to protect mice against chloroform-induced fibrillation and to elicit toxicity were determined. Substitution of an alkyl or aryl group in the α position enhanced the antifibrillatory activity. In most cases, increased potency was accompanied by increased toxicity. Eleven compounds were tested in dogs with surgically induced myocardial infarction; most showed antiarrhythmic activity. 2-Aminopropiono-2′,6′-xylidide, tocainide, was chosen for clinical investigation.

Cardiac arrhythmias are common causes of death in man. In particular, ventricular tachycardia and ventricular fibrillation contribute to the mortality associated with myocardial infarction, digitalis intoxication, and a number of other clinical conditions.[1] Moreover, cardiac arrhythmias have been implicated in a large percentage of unexplained "sudden deaths".[2]

Antiarrhythmic agents have long been used in the treatment and prevention of life-threatening arrhythmias. While the judicious use of these drugs is of benefit, the presently available antiarrhythmic agents provide less than optimum therapy for a number of reasons.[3] In the first place, not all patients are responsive to antiarrhythmic drugs. In the second place, side effects quite commonly accompany treatment: quinidine and procainamide, the two agents most widely used chronically for oral therapy, both interfere with intracardiac conduction and both produce hypotension. Quinidine also produces a wide variety of other adverse effects, including gastrointestinal disturbances and idiosyncratic and allergic reactions. Procainamide produces, among other adverse effects, a lupus-like syndrome. Newer and less widely used agents, such as phenytoin, bretylium tosylate, and disopyramide, also produce a high incidence of adverse effects.[3]

Lidocaine is the third antiarrhythmic agent in widespread clinical use.[3] When given intravenously or in-

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