filtration. The $CHCl_3$ extract of the broth showed no acronycine metabolites when chromatographed on thin-layer plates. The cells were extracted with two 3-l. portions of MeOH and the methanolic extracts were combined and concentrated to give 7.39 g of a yellow powdery precipitate. Tlc indicated that the precipitate was a mixture of **1** (R_f 0.55) and **2** (R_f 0.22). A sample of this mixture was treated with ethereal diazomethane to convert **2** to the corresponding methyl ether. Vapor-phase chromatography (hydrogen flame, 270°, 4-ft glass column packed with 3.8% W-98 methylvinyl silicone gum on 80–100 mesh Diatoport S) of this mixture indicated an approximate 1:4 ratio of **1** and the methyl ether derivative of **2**. Silica gel (Grace 62) column chromatography of the methanol precipitate failed to remove the last traces of **1** from **2**. However, compound **1** proved to be slightly more soluble than **2** in hot MeOH. Repeated crystallization of column preparations of **2** finally gave **2** free of **1**, as shown by vpc of its methyl ether derivative: yield 4.8 g. The material was identical in all respects with that reported for 9-hydroxyacronycine. *Anal.* ($C_{20}H_{19}O_4N$) C, H, O.

Preparation of 3-Hydroxymethylacronycine (3). A total of 3 g of acronycine, 100 μg/ml, was added to erlenmeyer flasks containing 100 ml of a 48-hr culture of *Strept. spectabilicus*, NRRL 2494. The culture was grown at 30° in a medium containing (g/l.): cerelose 25, corn starch 10, peptone (Wilson) 10, NA-Amine A (Sheffield) 4, molasses (Black Strap) 5, $MgSO_4 \cdot 7H_2O$ 0.5, $CaCO_3$ 2. After incubation for an additional 72 hr, the resulting cells and broth were separated by filtration. The cells were extracted with MeOH and the extract was concentrated by vacuum to an aqueous solution. This solution was added to the filtered broth and the combined solution was extracted (volume/volume) with $CHCl_3$. The $CHCl_3$ extract was concentrated by vacuum to give 6.53 g of noncrystalline material which was chromatographed on a column of 500 g of Grace 62 silica gel packed in benzene. The column was eluted with benzene and benzene–EtOAc mixtures. Elution with benzene–EtOAc (9:1) gave 460 mg of acronycine. Elution with benzene–EtOAc (2:3) gave 930 mg of a material which showed one spot on tlc, R_f 0.38. Recrystallization from $CHCl_3$–hexane gave 430 mg of crystalline **3**. The mass spectrum, vpc retention time, and infrared spectrum of this material were identical were those of 3-hydroxymethylacronycine.[3] *Anal.* ($C_{20}H_{19}O_4N$) C, H, O.

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4- (and 5-) (2-Thienyl)-1-naphthaleneacetic Acids as Antiinflammatory Agents

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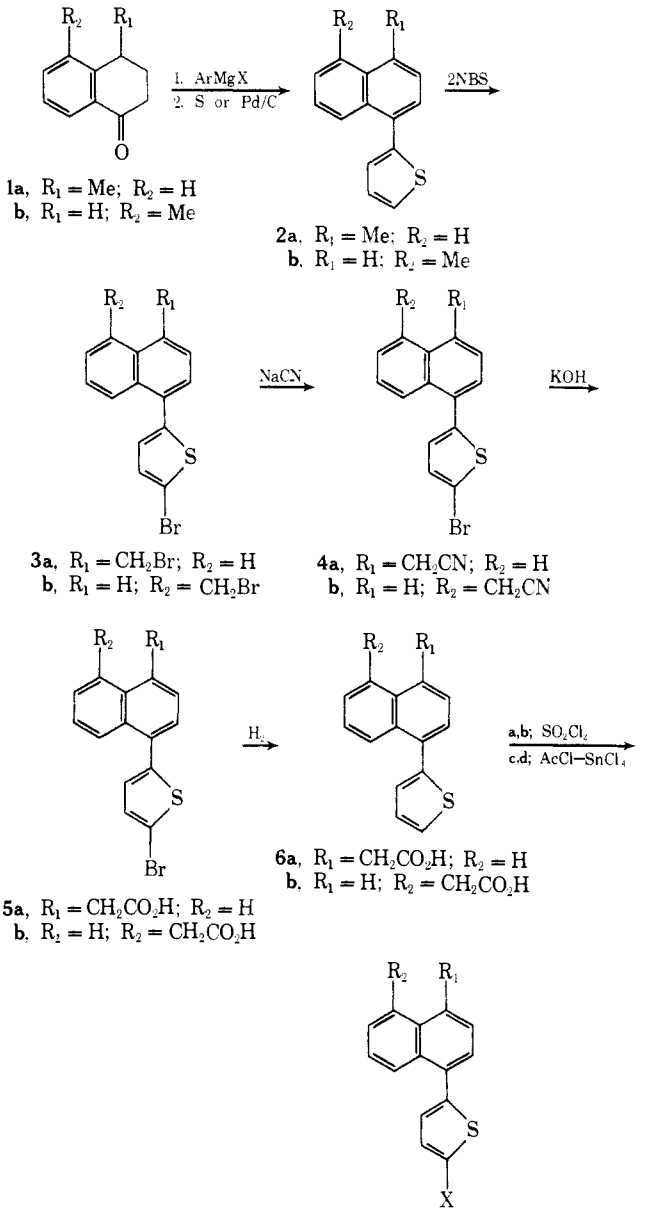
In an earlier paper[1] we described a series of substituted 4- and 5-phenyl-1-naphthaleneacetic acids which showed high potency as antiinflammatory agents. In the present paper we describe a series of 4- and 5-(2-thienyl)-1-naphthaleneacetic acids.[2] Measured by the anti-uv-erythema test in guinea pigs, several members of this series exhibit high potency as antiinflammatory agents.

Chemistry. The compounds were prepared as outlined in Scheme I starting with 3,4-dihydro-4- (or 5-) methyl-1(2*H*)-naphthalenone (**1**). In general, the intermediates **1–4** were not extensively purified but were carried through the sequence to the acetic acid stage where acidic product was easily separated. The crude acids were then purified by chromatography on silica gel. Most of the neutral material carried along in the reaction sequence arises from the fact that the side-chain bromination frequently does not go to completion, and the unreacted methyl derivative is thus carried along in subsequent reactions.

Scheme I



1a, $R_1 = Me$; $R_2 = H$
b, $R_1 = H$; $R_2 = Me$

2a, $R_1 = Me$; $R_2 = H$
b, $R_1 = H$; $R_2 = Me$

3a, $R_1 = CH_2Br$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2Br$

4a, $R_1 = CH_2CN$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2CN$

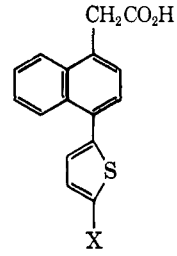
5a, $R_1 = CH_2CO_2H$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2CO_2H$

6a, $R_1 = CH_2CO_2H$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2CO_2H$

7a, $R_1 = CH_2CO_2H$; $R_2 = H$; X = Cl
b, $R_1 = H$; $R_2 = CH_2CO_2H$; X = Cl
c, $R_1 = CH_2CO_2H$; $R_2 = H$; X = C(=O)CH_3
d, $R_1 = H$; $R_2 = CH_2CO_2H$; X = C(=O)CH_3
e, $R_1 = H$; $R_2 = CH_2CO_2H$; X = C_2H_5

Aromatization of the intermediate dihydro derivative to give **2** can be accomplished by heating with sulfur or, less conveniently, by heating with Pd/C in the presence of nitrobenzene. In the case of **2a**, this aromatization is easily followed with nmr by the disappearance of the aliphatic methyl doublet centered at 1.3 ppm in the dihydro derivative and the appearance of the aromatic methyl singlet at 2.7 ppm. With **2b**, the methyl group in the dihydro compound is on a phenyl ring and shows a singlet at 2.18 ppm. The completely aromatized molecule has the methyl

Table I. 4-(2-Thienyl)-1-naphthaleneacetic Acids



Compd no.	X	Rel potency[a] (95% confidence limits)	Mp, °C[b]	Recrystn solvent[c]	Formula	Analyses[d]
Phenylbutazone		1.0				
6a	H	6.8 (4.0–13)	166–168	A	$C_{16}H_{12}O_2S$	C, H, S
5a	Br	6.0 (3.6–10)	138.5–140.5	B	$C_{16}H_{11}BrO_2S$	C, H, S, Br
7a	Cl	15 (8.4–26)	127–128	C	$C_{16}H_{11}ClO_2S$	C, H, S, Cl
7c	C(=O)CH3	<0.1	177–178	D	$C_{18}H_{14}O_3S$	C, H, S

[a]Values are obtained in guinea pigs from formal quantitative bioassays except for compounds **7c**, **7d**, and **7e** which are preliminary screening estimates. [b]Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. [c]A = acetonitrile, B = C_6H_6–cyclohexane, C = EtOH–H_2O, D = C_6H_6–EtOAc, E = C_6H_6–hexane, F = cyclohexane. [d]Analyses of the elements indicated were within ±0.3% of the calculated values.

on a naphthalene nucleus and gives a methyl singlet at 2.62 ppm.

The first exposure to NBS gave bromination in the 5 position of the thiophene ring. That the aromatic methyl group was not attacked is attested to by the unaltered position of the methyl singlet at approximately 2.7 ppm in the nmr. In addition to side-chain bromination, NBS is known to attack thiophene derivatives at unsubstituted α positions.[3] After partial purification, the second exposure to NBS gave side-chain bromination. The degree of side-chain bromination is easily estimated by integrating the nmr signals for the methyl singlet at approximately 2.7 ppm and the bromomethyl singlet at approximately 4.85 ppm. In one case, this double bromination was performed in one step utilizing 2 mol of NBS, with comparable results.

Reaction with NaCN gave the cyanomethyl derivatives **4a,b** which retain the nuclear bromine. Hydrolysis with KOH gave the nuclear brominated acetic acids **5a,b**. This bromine is readily removed catalytically giving **6a,b.**

With the exception of nitration and certain alkylations, electrophilic substitution of thiophenes is known[4] to give substitution almost exclusively in the α position, in this case the unsubstituted 5 position. Thus, SO_2Cl_2 chlorination of **6a,b** gave **7a,b**, while AcCl–$SnCl_4$ on the corresponding ethyl esters and subsequent hydrolysis gave **7c,d.** The position of the acetyl group is confirmed by the infrared spectra (in $CHCl_3$) which show the acetyl carbonyl at 1660 cm^{-1} in **7c,d**. Both α- and β-acetylnaphthalene have their carbonyl frequencies at approximately 1680 cm^{-1}, while 2-acetylthiophene shows a carbonyl frequency at 1663 cm^{-1}. Reduction of the acetyl group of **7d** using hydrazine gave the ethyl derivative **7e.**

Pharmacology. Using a method described earlier,[1] all compounds were screened for their ability to suppress the erythema developing in albino guinea pig skin 2 hr after a standard exposure to ultraviolet irradiation using Winder's modification[5] of Wilhelmi's method.[6] All agents were administered by gavage to depilated guinea pigs. The more potent compounds were then assessed in guinea pigs by the anti-uv-erythema method in a formal quantitative bioassay employing overall randomization of treatment. Proportions of animals failing to develop erythema, as related to dosage, were subjected to standard probit analysis[7] with appropriate consideration of erythema failures with vehicle. This quantitative assay employed 40 animals per dose level of test compound, 40 animals per dose level of phenylbutazone, and 120 animals receiving vehicle.

Discussion

Inspection of Tables I and II shows that high potency is exhibited by the unsubstituted thienyl compounds **6a,b** and by those bearing a bromine or chlorine in the 5 position (**5a,b and 7a,b**). When the group in this position is acetyl (**7c,d**) or ethyl (**7e**), the potency is greatly reduced.

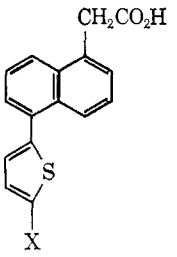
In a previous paper[1] from these laboratories describing a series of substituted 4- and 5-phenyl-1-naphthaleneacetic acids, the unsubstituted phenylnaphthaleneacetic acids showed higher potency than the compounds reported here. However, the fluoro- and chloro-substituted phenyl derivatives are comparable in potency to the more potent compounds reported here. It is interesting that while the 5-bromo compounds **5a,b** maintained high potency, the potency of the *m*-bromophenyl derivative described in the previous series fell below that of phenylbutazone. The other substitution common to both series, namely ethyl, caused a fall in potency in both cases.

Experimental Section

Infrared spectra were measured on a Beckman IR-7 and IR-9 or on a Digilab FTS-14. The nmr spectra were recorded on a Varian A-60 with tetramethylsilane as an internal standard and are in CCl_4 unless otherwise stated. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values.

2-(3,4-Dihydro-4-methyl-1-naphthalenyl)thiophene. To the Grignard solution prepared from 28.8 g (1.2 g-atoms) of Mg and 195 g (1.2 mol) of 2-bromothiophene in 400 ml of Et_2O was added dropwise a solution of 160 g (1.0 mol) of 3,4-dihydro-4-methyl-1(2*H*)-naphthalenone (**1a**) in 300 ml of Et_2O. After refluxing for 1 hr, the solution was decomposed with dilute HCl and worked up in the usual fashion. The crude product was then taken up in 300 ml of Ac_2O and heated at reflux for 1 hr. The reaction mixture was poured onto ice and neutralized with NaOH. The crude product was extracted into Et_2O and processed in the usual fashion giving 215.8 g of the crude product as a dark oil. This was dissolved in 500 ml of absolute EtOH and 60 g of Girard's T reagent added, together with 60 ml of AcOH. After refluxing 0.5 hr, 500 ml of ethylene glycol was added and the EtOH removed under reduced pressure. The ethylene glycol solution was extracted twice with Et_2O and the Et_2O washed with saturated $NaHCO_3$. Concentration of the Et_2O solution left the crude dihydronaphthalene.

Table II. 5-(2-Thienyl)-1-naphthaleneacetic Acids



Compd no.	X	Rel potency[a] (95% confidence limits)	Mp, °C[b]	Recrystn solvent[c]	Formula	Analyses[d]
Phenylbutazone		1.0				
6b	H	21 (14–31)	151.5–152.5	E	$C_{16}H_{12}O_2S$	C, H, S
5b	Br	4.4 (2.6–7.1)	148–149.5	B	$C_{16}H_{11}BrO_2S$	C, H, S, Br
7b	Cl	13 (7.3–22)	138–140	F	$C_{16}H_{11}ClO_2S$	C, H, S, Cl
7d	C(=O)CH$_3$	<0.1	168–169.5	C	$C_{18}H_{14}O_3S$	C, H, S
7e	C_2H_5	0.2	124.5–125.5	E	$C_{18}H_{16}O_2S$	C, H, S

[a–d] See footnotes in Table I.

2-(5,6-Dihydro-5-methyl-1-naphthalenyl)thiophene. The same procedure as above was followed using 3,4-dihydro-5-methyl-1(2*H*)-naphthalenone (**1b**). On neutralizing the Ac_2O solution, a solid separated and was collected and dried. Two recrystallizations from hexane gave pure product, mp 67.5–69.5°.

2-[4- (or 5-) Methyl-1-naphthalenyl]thiophene (2a,b). A mixture of 65.5 g (0.29 mol) of the dihydronaphthalene was mixed with 9.27 g (0.29 g-atom) of sulfur and heated at 212–220° for 1 hr. The mixture was then diluted with C_6H_6 and passed through a column of Woelm basic alumina. Removal of the C_6H_6 gave the crude product which was purified by distillation.

Alternatively, the dihydronaphthalene could be aromatized by heating the compound in xylene in the presence of 20% Pd/C and nitrobenzene and removing the water formed in a Dean-Stark trap. This process required up to 4 days at reflux and was more efficient if the reaction mixture was worked up and distilled after 2 days, and the partially aromatized dihydronaphthalene was resubmitted to the aromatization conditions.

5-Bromo-2-[4- (or 5-) methyl-1-naphthalenyl]thiophene. A solution of 161.7 g (0.722 mol) of **2a,b** in 1.5 l. of CCl_4 was treated with 148 g (0.831 mol) of NBS and 1 g of dibenzoyl peroxide and heated at reflux while irradiating with a flood light for 2.5 hr. The succinimide was then filtered off and the filtrate extracted twice with 5% NaOH and then with H_2O. Concentration of the CCl_4 solution left the crude product. The unaltered methyl singlet at δ ~2.7 ppm in the nmr showed that the bromine had entered the thiophene nucleus.

5-Bromo-2-[4- (or 5-) bromomethyl-1-naphthalenyl]thiophene (3a,b). A solution of 210.8 g (0.696 mol) of the 5-bromo-2-[4- (or 5-) methyl-1-naphthalenyl]thiophene in 1.5 l. of CCl_4 was treated with 135 g (0.756 mol) of NBS and 1 g of dibenzoyl peroxide and heated at reflux while irradiating with a floodlight. The reaction was initiated with a few drops of concentrated HBr and the refluxing continued overnight. The succinimide was filtered off and the filtrate extracted twice with 5% NaOH and then with H_2O. Concentration of the CCl_4 solution left crude **3a,b**. The nmr shows the bromomethyl singlet at δ ~4.85 ppm.

4- (or 5-) (5-Bromo-2-thienyl)-1-naphthaleneacetonitrile (4a,b). A solution of 138.2 g (0.362 mol) of **3a,b** in 500 ml of acetone and 300 ml of EtOH was treated with a solution of 19.6 g (0.4 mol) of NaCN in 150 ml of H_2O and heated at reflux for 4 hr. Work-up in the usual manner gave crude **4a,b** which were used directly in the alkaline hydrolysis. In one instance where pure **4a,b** were required for other purposes, 4a was purified by chromatography on Woelm neutral alumina (eluted with C_6H_6–Et_2O, 1:1). Recrystallization from C_6H_6–hexane gave pure **4a**, mp 85–87.5°. *Anal.* ($C_{16}H_{10}BrNS$) C, H, Br, N, S.

Utilizing material derived from a run where the side-chain bromination was substantially complete, crystalline **4b** could be isolated by direct crystallization from C_6H_6–hexane, mp 95.5–97° *Anal.* ($C_{16}H_{10}BrNS$) C, H, N, S; Br: calcd, 24.35; found, 24.83.

4- (or 5-) (5-Bromo-2-thienyl)-1-naphthaleneacetic Acid (5a,b). A solution of 109.8 g (0.334 mol) of **4a,b** in 750 ml of EtOH and 250 ml of dioxane was treated with 100 g (1.78 mol) of KOH in 200 ml of H_2O and heated at reflux with stirring overnight. The solvent was removed under reduced pressure and the residue taken up in H_2O and washed with Et_2O. Acidification with dilute HCl gave an oil which was extracted into Et_2O. Removal of the Et_2O gave the crude acid. Chromatography on silica gel (eluted with C_6H_6–Et_2O, 3:1) and recrystallization gave pure **5a,b**.

4- (or 5-) (2-Thienyl)-1-naphthaleneacetic Acid (6a,b). A solution of 38.3 g (0.11 mol) of **5a,b** in 250 ml of EtOH was treated with 9.5 g (0.116 mol) of NaOAc and 3 g of 20% Pd/C and shaken at 34° (51 psi) until the required amount of H_2 had been taken up. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. Dilution with H_2O precipitated the crude acid which could be purified by recrystallization.

4- (or 5-) (5-Chloro-2-thienyl)-1-naphthaleneacetic Acid (7a,b). A solution of 6.5 g (0.0249 mol) of **6a,b** in 70 ml of AcOH was treated with 2.0 ml (0.0249 mol) of SO_2Cl_2 and heated at reflux while irradiating with a floodlight for 2 hr. Dilution with H_2O gave the crude product which was purified by recrystallization.

Ethyl 4- (or 5-) (2-Thienyl)-1-naphthaleneacetate. A solution of 6.0 g (0.0224 mol) of **6a,b** in 60 ml of absolute EtOH was treated with 6 ml of concentrated HCl and heated at reflux overnight. Work-up in the usual fashion gave 4.3 g of the crude ester as an oil.

4- (or 5-) (5-Acetyl-2-thienyl)-1-naphthaleneacetic Acid (7c,d). A solution of 1.4 g (4.73 mmol) of the ester in 10 ml of C_6H_6 was treated with 0.35 ml (4.9 mmol) of AcCl and cooled in ice while 0.58 ml (4.9 mmol) of $SnCl_4$ was added dropwise rapidly. After stirring at ice bath temperature for 15 min, the mixture was allowed to warm to room temperature over 0.5 hr. The reaction mixture was decomposed with dilute HCl and extracted into Et_2O. Processing in the usual fashion gave the crude acetyl ester. This was hydrolyzed with KOH in EtOH–H_2O at reflux for 1 hr. Work-up in the usual fashion gave the crude product which was purified by recrystallization.

5-(5-Ethyl-2-thienyl)-1-naphthaleneacetic Acid (7e). A mixture of 1.62 g (5.23 mmol) of **7d** with 8.5 ml of diethylene glycol and 0.82 ml of 85% hydrazine hydrate was treated with 1.15 g of KOH and heated while allowing H_2O to distill off. On heating, the reaction mixture became homogeneous and after 1 hr the temperature had risen to 202°. The reaction mixture was kept at this temperature for 4 hr, then poured into H_2O, and acidified with dilute HCl. The crude product was extracted into Et_2O and the Et_2O washed several times with H_2O. Concentration of the Et_2O solution gave the crude acid as a brown solid. Chromatography on silica gel (product eluted with C_6H_6–Et_2O, 19:1) and recrystallization gave pure **7e**.

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the microanalyses. Thanks are also due Dr. Frank Short for helpful discussions during the progress of this work.

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6-Phenyl-6-propionoxyperhydrobenzo[c]quinolizines as Potential Analgetics†

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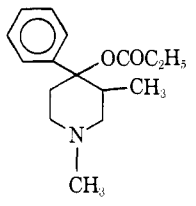
Much effort has been expended to prepare 4-phenylpiperidine analgetics related to prodine (1). Investigators hoped not only to separate analgetic activity from undesirable side effects but also to shed light on the stereochemical requirements of the analgetic receptor. Some examples are shown in Chart I. Smissman and Steinman[1,2] prepared 2 and 3; 2 is one-third as active as meperidine while 3 is inactive. In both 2 and 3 the piperidine ring is held in the chair conformation by an adjacent ring. The extra rings also provide bulk which preclude their conforming to the "two carbon fit" at the analgetic receptor. Sam, England, and Temple[3] prepared 4 which is twice as active as meperidine. In 4 boat forms are possible and evidence for one was given.

Chart I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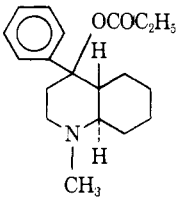
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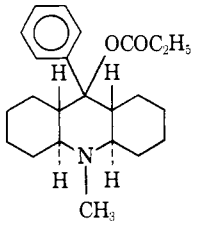
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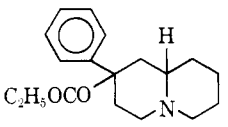
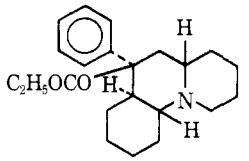
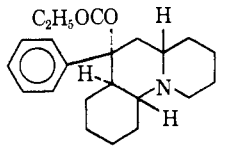

4

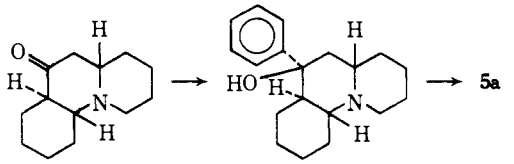
In a continuation of studies involving potential analgetics the related tricyclic compounds 5 were investigated. In 5, the piperidine ring is held in a chair conformation which, judging from the results with 2 and 3, would decrease activity. It was of interest, however, to see if the tetramethylene chain between the N and α carbon in 5 would increase the activity as it did in 4.

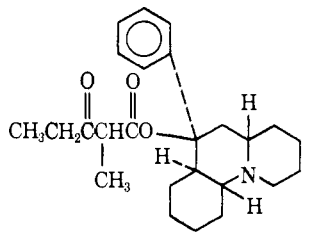

5a


5b

Procedures of Meyers and coworkers[4] and Horii, Morikawa, and Ninomiya[5] were utilized to prepare the starting ketone 6 for the synthesis of 5 as shown in Scheme I.

Scheme I


6 7 5a


8

Treatment of the trans-transoid-trans ketone 6 with phenylmagnesium bromide afforded only the equatorial phenyl isomer 7. The stereochemistry at C-6 is assumed since only one isomer was obtained (for supportive evidence from analogous systems see ref 1 and 3). The esterification of 7 proved more difficult than anticipated. Attempts using propionic anhydride in pyridine,[2] propionyl chloride in benzene,[6] propionyl chloride and triethylamine in toluene,[7] and propionic acid and *N,N*-carbonyldiimidazole in benzene[8] were unsuccessful. The use of propionyl chloride and triethylamine in toluene gave the β-keto ester 8. Others have noted that refluxing acyl chlorides in high boiling solvents in the presence of triethylamine produces ketene dimers which react with alcohols to give β-keto esters.[9] Ester **5a** eventually was prepared by the reaction of 7·HCl with propionyl chloride in acetonitrile.

The corresponding cis-transoid-trans-fused isomer 12 was investigated according to the method shown in Scheme II. The reaction of 9 with phenylmagnesium bromide gave a 50% yield of the 1,2-addition product **10**. The hydrogenation of 10 over Pd/C produced one isomer with an R_f (tlc) four times that of 7; Bohlmann bands in the ir spectra also exist indicating the formation of the cis-transoid-trans-fused isomer **11**. The cis-cisoid-trans-fused isomer would have isomerized to the more stable cis-cisoid-cis-fused isomer.[10] The esterification of 11 according to the method utilized for the preparation of **5a** gave 13 and 14 in a 2:1 ratio and a trace of 12.

Compounds **5a** and 8 were examined for analgetic activity *via* the hot-plate method[11,12] at sc doses up to 100 mg/kg and were found to be essentially inactive.

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