Synthesis and Stereochemical Analysis of Isomeric *N*-Substituted 5- and 6-Propanilido-2-Azabicyclo[2.2.2]octanes

*Say-Jong Law, Daniel H. Lewis and Ronald F. Borne**

Department of Medicinal Chemistry, School of Pharmacy,
University of Mississippi, University, MS 38677

Received October 10, 1977

The synthesis and stereochemical analysis of *N*-methyl and *N*-phenethyl-substituted 5- and 6-propanilido derivatives of 2-azabicyclo[2.2.2]octane were investigated for potential evaluation as analgesics related to fentanyl. Stereochemical assignments for the eight isomers reported here were made on the basis of nmr studies employing europium chemical shift reagents and hydrogen bonding studies employing ir analysis of the anilino- and propanilido-derivatives.

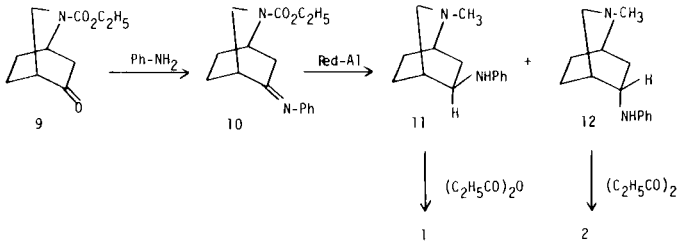
J. Heterocyclic Chem., 15, 273 (1978)

As part of our continuing studies regarding the importance of conformational factors in the actions of bio-active agents, we examined the potential contribution of boat conformations in the action of the 4-anilidopiperidine analgesics. The isomers of **1-8** represent analogs of this group of analgesics in which the piperidine ring is restricted in a semi-rigid fashion to a boat conformation.

1 and 5 R = CH_3; X = $N(Ph)COC_2H_5$; Y = H
2 and 6 R = CH_3; X = H; Y = $N(Ph)COC_2H_5$
3 and 7 R = CH_2CH_2Ph; X = $N(Ph)COC_2H_5$; Y = H
4 and 8 R = CH_2CH_2Ph; X = H; Y = $N(Ph)COC_2H_5$

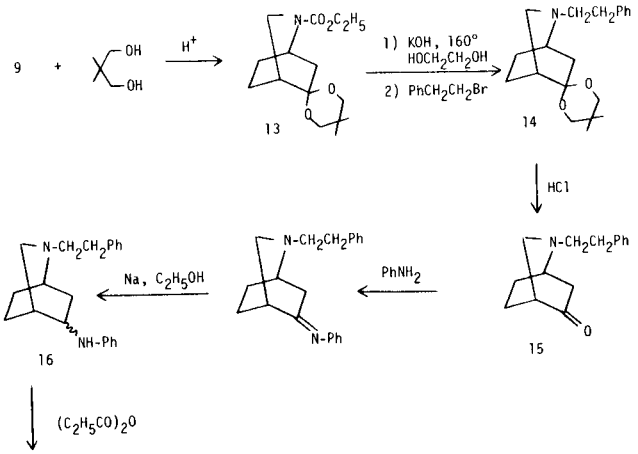
The synthesis of **1** and **2** is outlined in Scheme I. The starting ketone (**9**) was previously synthesized by Krow, *et al.*, (1). Intial attempts to prepare **10** through condensation of **9** with aniline in the presence of catalytic amount of *p*-toluenesulfonic acid failed, surprisingly, to produce appreciable quantities of the anil. Appreciable quantities of **10** were obtained (57% yield) when molecular sieves (2) were used as both a dehydrating agent and as a catalyst.

SCHEME I



Simultaneous reduction of the anil and the carbethoxy function of **10** with Red-Al gave **11** and **12** in a 47:53 ratio as determined by glc. Pure **11** and **12** were obtained through repetitive separation of the mixture on neutral alumina columns. Acylation of **11** and **12** with excess propionic anhydride gave the target compounds **1** and **2**, respectively. The *N*-phenethyl analogs **3** and **4** were prepared in an analogous manner (Scheme II) but required the protection of the ketone function during carbamate hydrolysis. Thus, treatment of **9** with 2,2-dimethyl-1,3-propanediol gave ketal **13**. Hydrolysis and decarboxylation of

SCHEME II



13 with potassium hydroxide in ethylene glycol at 160° gave the crude amine which was subsequently alkylated with phenethyl bromide to yield the pure hydrobromide salt of **14**. Hydrolysis of **14** with hydrochloric acid yielded the *N*-phenethyl ketone **15**. Condensation of **15** with aniline in the presence of molecular sieves and reduction of the anil with sodium and ethanol gave a mixture of the isomeric anilino compounds (**19**). Separation of the mixture by column chromatography was unsuccessful because of the close Rf values in various solvent systems. Thus, propionylation was carried out on the mixture and **3** and **4** separated by column chromatography.

The synthesis of **5-8** proceeded through the pathway outlined in Scheme III. Treating the epoxy ester **17** with methylamine (3) or phenethylamine yielded the amino alcohols (**18a** and **18b**) whose stereochemistry was defined by *trans*-diaxial opening of the epoxide. Cyclization of each amino alcohol at 130-170° yielded the lactam (**19a** or **19b**)

Table I

Spectral data for Isomeric *N*-Methyl-6-anilino-2-azabicyclo[2.2.2]octanes **23a** and **24a** and *N*-Methyl-6-propanilido-2-azabicyclo[2.2.2]-octanes **5** and **6**.

		11	**12**	**1**	**2**
Nmr (δ)	$N\text{-}CH_3$	s, 2.33	s, 2.37	s, 2.07	s, 2.33
	5-CH	m, 3.70	m, 3.80	t, 4.65	t, 4.80
Ir (cm^{-1})	N-H	3350 (a)	3320 (a)	-----	-----
		3430 (b)	3440 (b)	-----	-----
	C=O	-----	-----	1665 (a)	1665 (a)
		-----	-----	1667 (c)	1665 (c)

(a) Liquid film spectra of free bases. (b) Spectra of 8% solutions of free bases in carbon tetrachloride. (c) Spectra of 5% solutions of hydrochloride salts in chloroform.

Table II

Spectral data for Isomeric *N*-Methyl-6-Anilino-2-azabicyclo[2.2.2]octanes **23a** and **24a** and *N*-Methyl-6-Propanilido-2-azabicyclo[2.2.2]-octanes **5** and **6**.

		23a	**24a**	**5**	**6**
Nmr (δ)	$N\text{-}CH_3$	s, 2.40	s, 2.57	s, 2.10	s, 2.62
	6-CH	m, 3.59	m, 3.97	t, 4.67	t, 5.07
Ir (cm^{-1})	N-H	3370 (a)	3420, 3340 (a)	-----	-----
		3380 (b)	3440 (c)	-----	-----
	C=O	-----	-----	1665 (a)	1665 (a)
				1660 (d)	1650 (d)
				1625, 1660 (e)	1650 (e)

(a) Liquid film spectra of free base. (b) Spectra of 0.04% solutions of free bases in carbon tetrachloride. (c) Spectra of 0.5% solutions of free bases in carbon tetrachloride. (d) Spectra of 5% solutions of free bases in chloroform. (e) Spectra of 5% solutions of hydrochloride salts in chloroform.

which was smoothly reduced with Red-Al to the amino alcohol (**20a** or **20b**). Oxidation of the amino alcohol with benzophenone/potassium *t*-butoxide, gave the requisite ketone **21a** as previously described (4) and **21b**. These reactions proceeded uneventfully with the exception of the oxidation of **20a**. If this reaction was carried out at reaction times exceeding 2 hours, small amounts (10%) of ketone **22**, obviously the product of the base-catalyzed condensation of **21a** with benzophenone, were obtained. Anil formation was conducted as described previously for the 5-ketones and reduction to the isomeric anilino derivatives (**23a**, **23b**, **24a**, **24b**) achieved with sodium and ethanol. These reduction conditions were favored to enhance formation of the *exo*-isomers **23a** and **23b**. For example, Red-Al reduction of the *N*-methyl anil derived from **21a** gave **23a** and **24a** in a ratio of 1:17 while catalytic hydrogenation enhanced the formation of **23a** by reducing this ratio to 1:9. Nearly equal amounts of these isomers (45:55) were obtained using sodium and ethanol. Isomer ratios of these mixtures were determined by glc. The mixture of amines obtained from this reduction was separable by column chromatography in both cases (R = CH_3 or CH_2-CH_2Ph) and subsequent propionylation conducted individually on each isomer.

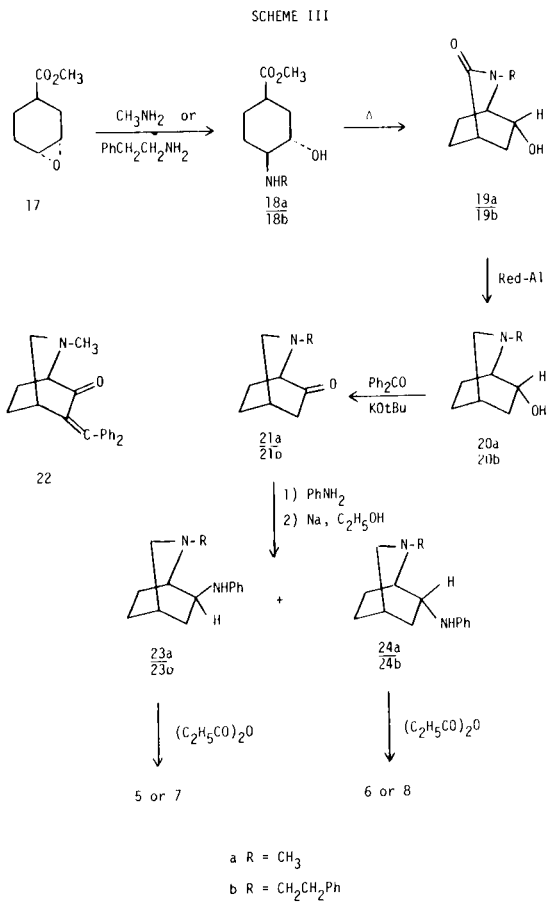
Table III

Spectral data for Isomeric *N*-phenethyl-5-propanilido-2-azabicyclo-[2.2.2]octanes **3** and **4**, *N*-phenethyl-6-anilino-2-azabicyclo[2.2.2]-octanes **23b** and **24b**, and *N*-phenethyl-6-propanilido-2-azabicyclo-[2.2.2]octanes **7** and **8**.

Compound	Nmr (δ)		Ir (cm^{-1})
	6-CH	5-CH	NH
3	-----	m, 4.27	-----
4	-----	m, 4.43	-----
23b	m, 3.51	-----	3360 (a)
			3370 (b)
24b	m, 3.90	-----	3420 (a)
			3440 (b)
7	t, 4.67	-----	-----
8	t, 5.01	-----	-----

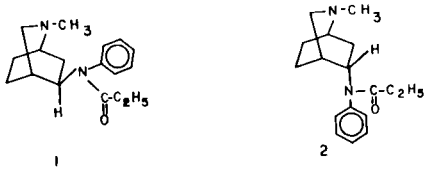
(a) Liquid film spectra of free base. (b) Spectra of 0.04% solution of free base in carbon tetrachloride.

SCHEME III



Stereochemical Assignments.

Spectral data for the *N*-methyl-5-propanilido analogs (**1** and **2**) and the anilino precursors (**11** and **12**) are summarized in Table I, while data for the *N*-methyl-6-propanilido analogs (**5** and **6**) and their anilino precursors (**23a** and **24a**) are found in Table II. Table III summarizes spectral data on the basis of which the orientations of the propanilido or anilino groups of *N*-phenethyl analogs were determined. It was initially anticipated that infrared dilution studies would be of value in determining the *exo* or *endo* relationships of the two nitrogen atoms for all anilino isomers; the persistence of N-H absorption in the range 3320-3380 cm^{-1} at high dilution (0.04%) should indicate a state of intramolecular hydrogen bonding due to an *exo*-relationship, while a shift of N-H absorption to 3420-3440 cm^{-1} on dilution would indicate free N-H absorption as anticipated for the *endo*-isomer. From the N-H stretching frequency data, the usefulness of infrared dilution studies is limited to the 6-anilino isomers. Apparently the distance between *N*-atoms in the 5-anilino isomers is too great to permit intramolecular hydrogen bonding. The liquid film spectra of both **11** and **12** (Table I) showed N-H absorption at 3320-3350 cm^{-1}. Upon dilution with carbon tetrachloride below 8% concentrations both spectra lost the hydrogen bonding peaks and showed a shift to free N-H absorption. Thus no intramolecular hydrogen bonding indicative of an *exo*-relationship was observed in either **11** or **12**. Spectra of the hydrochloride salts of **1** and **2** gave equally disappointing results. No effect due to the protonated nitrogen on the carbonyl frequency could be observed when 5% chloroform solution spectra were taken. On the other hand, the liquid film spectra of **24a** (Table II) showed both free and associated N-H absorption as a sharp peak and broad shoulder at two different frequencies. Upon dilution with carbon tetrachloride below 0.5% concentration only free N-H stretching was observed indicating an *endo*-relationship between the two nitrogen atoms. The N-H absorption of **23a**, as one may expect, remained at the lower frequency range at high dilution suggesting the presence of intramolecular hydrogen bonding. Hence, an *exo*-relationship of the two nitrogen atoms was indicated. Similar results were observed with the corresponding *N*-phenethyl derivatives, **23b** and **24b** (Table III). Their configurations were assigned accordingly. While no differences in carbonyl absorption for **1** and **2** were observed, comparison of spectra of the free bases and hydrochloride salts of **5** and **6** in this region indicated an interaction of the protonated nitrogen atom and carbonyl group in **5** (as indicated



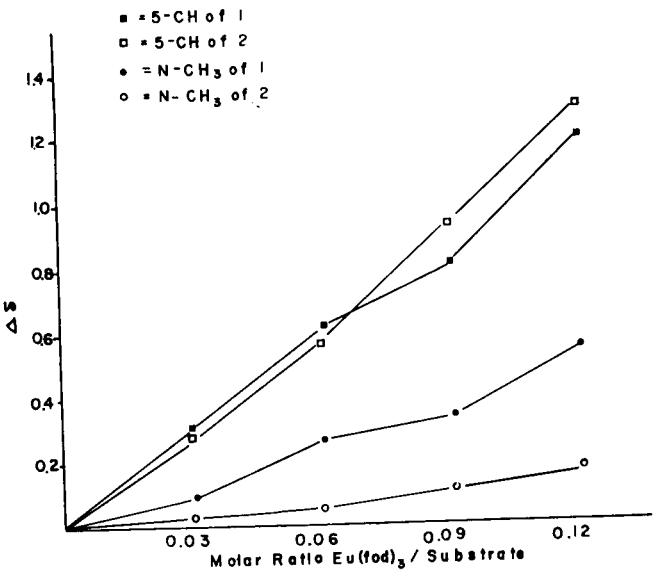


Fig. 1. Effect of europium shift reagent on chemical shifts of 5-methine and *N*-methyl protons of 5-*exo* (**1**)- and 5-*endo* (**2**)-propanilido derivatives.

by the shift in carbonyl absorption to 1625 cm^{-1}) but not in **6** (Table II). This observation supports the assignment of *exo*-orientation of the propanilido and ring nitrogen atoms of **5** and thus an *endo*-orientation of **6**.

In the nuclear magnetic resonance studies, comparison of the chemical shifts of the N-CH_3 and 5-CH or 6-CH protons of isomeric pairs was found to be of value in configurational assignments. An unusual upfield shift of the *N*-methyl peak in propanilido **1** and **5** relative to the position of the *N*-methyl signal of the corresponding anilino derivatives was observed. The reason for this upfield shift can be rationalized upon construction and examination of Dreiding models of all *N*-methyl anilino and propanilido isomers. In the models of *exo*-isomers, **11** and **23a** the phenyl ring tends to occupy space relatively far removed from the bicyclic ring to reduce steric interactions. Thus, no obvious effect due to the phenyl ring is observed on the chemical shift of the *N*-methyl groups. After the introduction of the propionyl group (**1** and **5**) the phenyl ring is forced to assume a conformation directly above the *N*-methyl group so that a shielding anisotropic effects results. Acylation of the *endo*-isomers **12** and **24a** would have no expected effect on the *N*-methyl group. It then logically follows that propanilido analogs **2** and **6** possess the *endo*-configuration. The chemical shifts of the methine protons at the 5 or 6 position were also of value in assignment of stereochemistry since the signal for the *exo*-proton in the *endo*-isomers (**12**, **24a**, **24b**, **2**, **6** and **8**) appears consistently downfield from that of the *endo*-proton in the *exo*-isomers (**11**, **23a**, **23b**, **1**, **2** and **7**). This observation is consistent with results reported in both the 2-azabicyclo[2.2.2]octane (5) and bicyclo[2.2.2]heptane (6) ring systems. This observation permitted the assignment of the *N*-phenethyl-5-propanilido derivatives **3** and **4** (Table III).

Additional support for the assignments of the *N*-methyl propanilides (**1**, **2**, **5** and **6**) was obtained from europium shift reagent studies shown in Figures 1, 2 and 3. Figure 1 indicates that the chemical shifts of the 5-CH protons of **1** and **2** were affected by the shift reagent to a much greater extent than were the signals for the *N*-methyl protons suggesting that the shift reagent binds perferentially to the amide oxygen rather than to the basic nitrogen atom. Similar binding preferences have been previously reported for other systems (7). While Figure 1 indicates that the shift

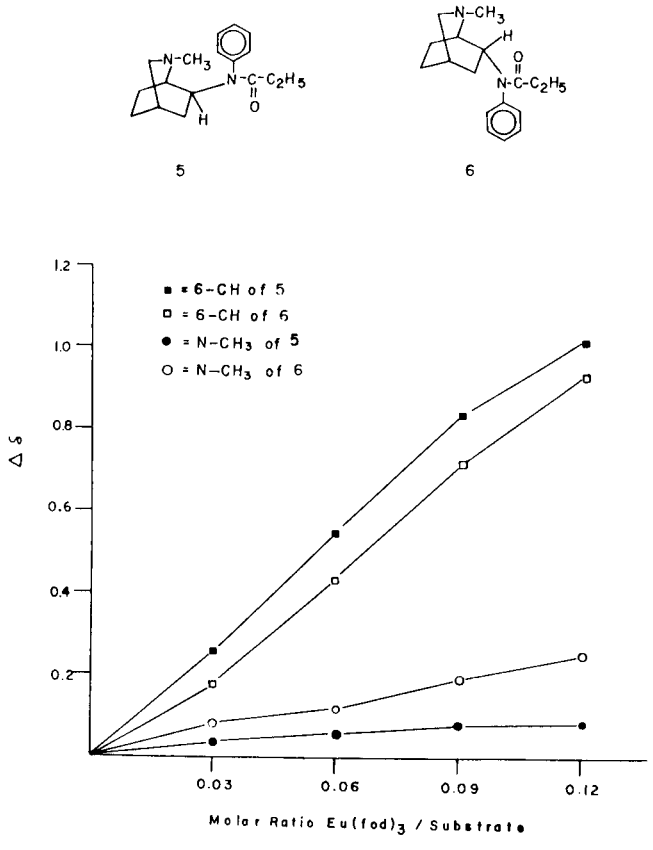


Fig. 2. Effect of europium shift reagent on chemical shifts of 6-methine and *N*-methyl protons of 6-*exo* (**5**)- and 6-*endo* (**6**)-propanilido derivatives.

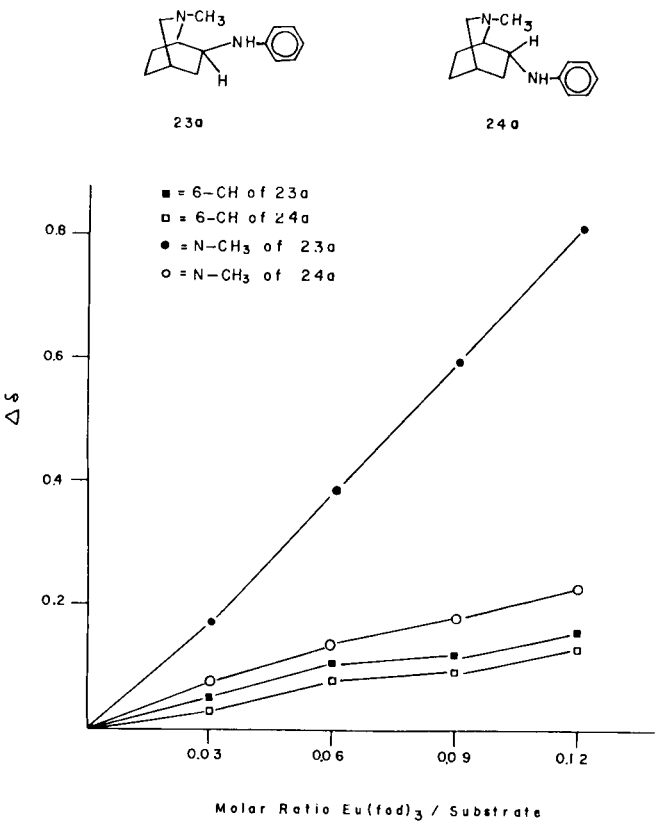


Fig. 3. Effect of europium shift reagent on chemical shifts of 6-methine and *N*-methyl protons of 6-*exo* (**23a**)- and 6-*endo* (**24a**)-anilino derivatives.

reagent affected the 5-CH protons of **1** and **2** to the same extent, the *N*-methyl signal of the *exo*-isomer was shifted significantly further downfield than the *N*-methyl signal of the *endo*-isomer indicating the proximity of the complexed shift reagent to the *N*-methyl function in the *exo*-isomer. Since the extent of the induced shift is inversely proportional to the third order of the distance between the target protons and the site of complexation (7), the observations from the shift reagent study confirms our assignment of stereochemistry of **1** and **2** and hence the two aniline precursors (**11** and **12**). Figure 2 indicates that the chemical shifts of the 6-CH protons of **5** and **6** were also affected to a far greater extent than those of the *N*-methyl protons indicating the same preferential binding of the shift reagent to the amide oxygen. But contrary to what one may expect the *N*-methyl signal of the *endo*-isomer was shifted much greater than the *N*-methyl signal of the *exo*-isomer. The most plausible explanation for this observation can be gleaned from examination of Dreiding models of **5** and **6**. In the case of the *exo*-isomer (**5**), once the shift reagent complexes with the oxygen atom the carbonyl group is forced to assume a conformation in which the oxygen is maximally disposed from the *N*-methyl group to reduce steric interactions, while in the *endo*-isomer (**6**) the carbonyl group after complexation is still free to assume a conformation in which the oxygen atom is in close proximity to the *N*-methyl group and thus affects its chemical shift. To further resolve this anomaly, shift reagent studies were conducted on the anilino precursors (**23a** and **24a**) and these results are presented in Figure 3. The large difference in induced chemical shifts of the *N*-methyl protons of the two isomers suggests that the shift reagent complexes with the anilino nitrogen atoms despite the expected differences in basicity indicating that steric, rather than electronic factors determine the site of complexation (7). One would then anticipate that the *N*-methyl group closest to the site of complexation, *i.e.*, the *exo*-isomer, would be affected to a greater extent than the *N*-methyl group in the *endo*-isomer. Thus, the isomer in which the *N*-methyl group was shifted four-fold downfield from the other was assigned the *exo*-configuration. Assignment of the *exo*-configuration to the anilino derivative **23a** confirms the stereochemical assignment of the propanilido derivative **5**. Because of the complex pattern observed for the methylene protons of the *N*-phenethyl derivatives, shift reagent studies were of little value in confirming the previous assignments.

EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus and were corrected. The ir spectra were obtained with a Beckman IR-33 or a Perkin-Elmer 257 spectrophotometer. The nmr spectra were measured in deuterochloroform on a Jeolco C-60-HL spectrometer and chemical shifts are reported in ppm (δ) downfield from tetramethylsilane as internal standard. Mass spectral data were obtained on a Dupont Model 21-492 spectrometer. Gas chromatographic analyses were conducted on a Perkin-Elmer 900 gas chromatograph. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Red-Al [sodium bis (2-methoxyethoxy)-aluminum hydride] was purchased from Aldrich Chemical Company.

2-Carbethoxy-2-azabicyclo[2.2.2]octan-5-one Anil (**10**).

A mixture of **9** (**1**) (14.0 g., 0.07 mole), aniline (7.4 g., 0.08 mole), and molecular sieves (4A, 30 g.) in 200 ml. of benzene was refluxed under nitrogen for 24 hours. The reaction mixture was filtered and the filtrate evaporated. The residue was distilled to give excess aniline followed by **10** as a viscous liquid (11.0 g., 57%) b.p. 166°/0.06 mm; nmr: δ 1.1-1.4 (t, 3H, CH_3), 1.6-2.1 (broad, 4H, H at C-7 and C-8), 2.2-2.9 (broad, 3H, H at C-4 and C-6), 3.37-3.73 (broad d, 2H, H at C-3), 3.9-4.5 (m, 3H, H at C-1 and O-CH_2), 6.6-7.4 (m, 5H, aromatic); ms: m/e 272 (M^+, base).

2-Methyl-5-*exo*- and *endo*-anilino-2-azabicyclo[2.2.2]octane (**11** and **12**).

A solution of **10** (6.0 g., 0.022 mole) in 80 ml. of benzene was added to Red-Al (26 ml., 0.09 mole) over a period of 1 hour and the resulting mixture refluxed an additional 8 hours. The reaction mixture was cooled, treated with ethanol and water to destroy excess hydride and filtered. The organic phase of the filtrate was separated and the aqueous layer extracted with chloroform (2 x 30 ml.). The organic phases were combined, dried over sodium sulfate and evaporated to give a residue which was distilled to give 3.7 g. (78%) of a mixture of **11** and **12**, b.p. 117-120°/0.1 mm. in a 47:53 ratio as determined by glc (8). Pure **11** (0.42 g.) and **12** (0.56 g.) were obtained from this mixture by two successive separations on neutral alumina columns (Woelm, 80-200 mesh, 30:1 ratio) packed and eluted with ether-hexane (1:5). While **12** possessed a longer glc retenion time than **11**, it was eluted first from the alumina column: Compound **11** appeared as an oil but **12** solidified on standing and was recrystallized from ether-petroleum ether (m.p. 76-78°). Compound **12** had ir (carbon tetrachloride): 3440 cm^{-1} (NH); nmr: δ 0.9-2.1 (broad 7H, H at C-4, C-6, C-7, C-8), 2.37 (s, 3H, N-CH_3), 2.43-2.9 (broad, 3H, H at C-1 and C-3), 3.33-3.9 (broad 2H, H at NH and C-5), 6.43-7.37 (m, 5H, aromatic); ms: m/e 216 (M^+), 124 (base).

Anal. Calcd. for $C_{14}H_{20}N_2 \cdot H_2O$: C, 71.75; H, 9.46; N, 11.95. Found: C, 71.91; H, 9.49; N, 11.98.

Compound **11**.

This compound had ir (carbon tetrachloride) 3430 cm^{-1} (NH); nmr: δ 1.12-2.1 (broad, 7H, H at C-4, C-6, C-7 and C-8), 2.33 (s, 3H, N-CH_3), 2.4-2.6 (broad, 2H, H at C-3), 2.8-3.1 (broad, 1H, H at C-1), 3.23-4.07 (broad, 2H, H at C-5 and NH), 6.40-7.27 (m, 5H, aromatic); ms: m/e 216 (M^+), 124 (base).

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.73; H, 9.47; N, 13.17.

2-Methyl-5-*endo*-propanilido-2-azabicyclo[2.2.2]octane (**2**).

A mixture of **12** (0.42 g., 0.002 mole) and propionic anhydride (2.8 g., 0.02 mole) was refluxed for 6 hours and concentrated. The residue was stirred with a saturated sodium carbonate solution for 15 minutes and extracted with chloroform (2 x 50 ml.). The extract was dried (sodium sulfate) and evaporated to give a crude oil which was dissolved in petroleum ether and placed on a neutral alumina column (Woelm, 80-200 mesh, 20 g.). Elution was carried out with ether-petroleum ether (1:6) and monitored with glc. The fractions that were free of any impurities were combined and evaporated to give a clear oil (0.35 g., 70%) ir (liquid film): 1665 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_3), 1.17-1.5 (broad 4H, H at C-7 and C-8), 1.57-2.2 (broad, 4H, H at $COCH_2$ and C-6), 2.33 (s,

3H, N-CH_3), 2.4-2.6 (m, 2H, H at C-3), 2.9-3.03 (broad d, 1H, H at C-4), 3.07-3.30 (broad, 1H, H at C-1), 4.6-5.03 (broad t, 1H, H at C-5), 7.0-7.5 (broad, 5H, aromatic); ms: m/e 272 (M^+), 124 (base).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.82; H, 8.97; N, 10.13.

2-Methyl-5-*exo*-propanilido-2-azabicyclo[2.2.2]octane (**1**).

A mixture of **11** (0.56 g., 0.003 mole) and propionic anhydride (3.7 g., 0.03 mole) was refluxed and worked up in the same manner as in the preparation of **2**. Purification of the crude material on a neutral alumina column yielded a clear oil (0.47 g., 66%); ir (liquid film): 1667 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_2CH_3), 1.2-2.4 (broad, 12H, H at C-7, C-8, C-6, $COCH_2$, N-CH_3 and C-4), 2.6-3.2 (broad, 3H, H at C-3 and C-1), 4.4-4.9 (broad t, 1H, H at C-5), 7.07-7.7 (broad, 5H, aromatic); ms: m/e 272 (M^+), 124 (base).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.93; H, 9.00; N, 10.40.

2-Carbethoxy-2-azabicyclo[2.2.2]octan-5-one-2,2-dimethylpropylene Ketal (**13**).

A mixture of **9** (19.8 g., 0.10 mole) 2,2 dimethyl-1,3-propanediol (20.8 g., 0.20 mole) and 1.0 g. of *p*-toluenesulfonic acid in 300 ml. of dry benzene was refluxed for 4 hours until the water collected in the Dean-Stark apparatus became constant. The reaction mixture was cooled, washed with 10% potassium carbonate (2 x 100 ml.), dried and evaporated to give a clear oil (28.0 g., 99%), ir (liquid film) 1690 cm^{-1} (C=O, carbamate); nmr: δ 1.0 (s, 6H, C-CH_3), 1.27 (t, 3H, CH_2CH_3), 1.4-2.6 (broad, 7H, H at C-7, C-8, C-6 and C-4), 3.1-3.9 (broad, 6H, H at C-3 and OCH_2C), 3.93-4.37 (q over a broad signal, 3H, H at C-1 and OCH_2CH_3).

2-Phenethyl-2-azabicyclo[2.2.2]octan-5-one-2,2-dimethylpropylene Ketal Hydrobromide (**14**).

A solution of **13** (40.0 g., 0.14 mole) and 40.0 g. of potassium hydroxide in 300 ml. of ethylene glycol was heated at 160° under nitrogen for 12 hours. The reaction mixture was cooled, diluted with 600 ml. of water, and extracted with chloroform (3 x 200 ml.). The combined extracts were washed with water (2 x 150 ml.), dried (magnesium sulfate) and evaporated to give a brown oil (29.7 g., 99%). The oil (19.3 g., 0.09 mole) was dissolved in 300 ml. of acetonitrile, added to phenethyl bromide (21.0 g., 0.11 mole) and refluxed for 10 hours. The reaction mixture was cooled and filtered to give a white solid (18.6 g., 52%) m.p. 219-220°. The filtrate was evaporated to give a residue which was triturated with ether and filtered to give a second crop of crystals (7.0 g., 20.0%), m.p. 219-220°; ms: m/e 315 (M^+), 225 (base); nmr: δ 1.0 (d, 6H, C-CH_3), 1.5-2.8 (broad, 7H, H at C-7, C-8, C-6 and C-4), 3.10-3.90 (broad, 12H, H at N-CH_2CH_2Ph, C-3, C-1, OCH_2C and N H), 7.27 (s, 5H, aromatic).

Anal. Calcd. for $C_{20}H_{30}BrNO_2$: C, 60.60; H, 7.63; N, 3.54. Found: C, 60.81; H, 7.90; N, 3.31.

2-Phenethyl-2-azabicyclo[2.2.2]octan-5-one (**15**).

A mixture of **14** (11.9 g., 0.03 mole) and 200 ml. of 10% hydrochloric acid was heated at 70° for 1 hour. The reaction mixture was cooled, washed with chloroform (3 x 50 ml.), neutralized with potassium carbonate, and extracted with chloroform (3 x 100 ml.). The combined extracts were dried (magnesium sulfate) and evaporated to give an oil (6.8 g., 98%). An analytically pure sample was obtained by passing the oil through a silica gel column packed and eluted with ether-petroleum ether (1:1); ir (liquid film): 1740 cm^{-1} (C=O, ketone); nmr: δ 1.40-2.13 (broad, 4H, H at C-7 and C-8), 2.17-2.57 (broad, 3H, H at C-6 and C-4), 2.70 (s, 4H, NCH_2-CH_2Ph), 2.8-3.2 (broad, 3H, H at C-3 and C-1), 7.10 (s, 5H, aromatic); ms: m/e 229 (M^+), 138 (base).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.43; H, 8.46; N, 5.98.

2-Phenethyl-5-*exo*- and *endo*-propanilido-2-azabicyclo[2.2.2]octane (**3** and **4**).

A mixture of **15** (10.6 g., 0.046 mole), aniline (11.5 g., 0.123 mole) and molecular sieves (4A, 20 g.) in 150 ml. of dry benzene was refluxed under nitrogen for 24 hours. The reaction mixture was cooled, filtered, and evaporated to give a residue which was distilled to remove the excess of aniline. The pot residue was then taken up in 150 ml. of absolute ethanol. Sodium metal (8.0 g.) was added at a rate to maintain mild reflux. The resulting mixture was refluxed under nitrogen for 40 hours, cooled, treated slowly with 100 ml. of water, evaporated to remove most of the ethanol and extracted with ether (4 x 75 ml.). The combined ether extracts were dried and evaporated to give a residue which was chromatographed on silica gel column (MN, 70-270 mesh, 30:1 ratio) packed and eluted with ether-petroleum ether (1:3), to give a mixture of anilino isomers (1.3 g., 9%) as determined by glc (9). A solution of this mixture (0.79 g., 0.0026 mole) in propionic anhydride (6.0 g., 0.046 mole) was refluxed under nitrogen for 10 hours. The reaction mixture was cooled, stirred with saturated potassium carbonate (30 ml.) for 3 hours at room temperature, then diluted with 30 ml. of water and extracted with ether (3 x 25 ml.). The combined extracts were extracted with 10% hydrochloric acid (3 x 15 ml.). The acidic solution was neutralized with potassium carbonate and extracted with ether (3 x 25 ml.). The extracts were dried and evaporated. The residue was chromatographed on silica gel column (MN, 70-270 mesh, 30:1 ratio), packed and eluted with ether-petroleum ether (1:2). Pure **3** (0.22 g., 23%) and **4** (0.48 g., 51%) were obtained from this mixture with **3** being eluted first. Compound **3** had ir (liquid film): 1650 cm^{-1} (C=O, amide); nmr: δ 1.0-1.30 (t, 3H, CH_2CH_3), 1.50-2.57 [broad, 9H, H at C-7, C-8, C-6, C-4, and CH_2CH_3 (q, 2.13-2.57)], 2.60-4.0 (broad, 7H, H at NCH_2CH_2Ph, C-3 and C-1), 4.03-4.5 (broad, 1H, H at C-5), 6.37-7.33 (m, 10H, NPh and CPh); ms: m/e 362 (M^+, base).

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.41; H, 8.46; N, 7.68.

Compound **4** had m.p. 107-108.5°; ir (liquid film): 1650 cm^{-1} (C=O, amide); nmr: δ 1.0-133 (t, 3H, CH_2CH_3), 1.50-2.53 [broad, 9H, H at C-7, C-8, C-6 and CH_2CH_3 (q, 2.13-2.53)], 2.53-4.0 (broad, 7H, H at NCH_2CH_2Ph, C-3 and C-1), 4.03-4.90 (broad, 1H, H at C-5), 6.33-7.33 (m, 10H, aromatic); ms: m/e 362 (M^+, base).

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.69; H, 8.42; N, 7.68.

6-*endo*-Hydroxy-2-phenethyl-2-azabicyclo[2.2.2]octan-3-one (**19b**).

A solution of **17** (60.0 g., 0.38 mole) and phenethylamine (48.5 g., 0.40 mole) in 160 ml. of ethanol was refluxed for 12 hours and evaporated. The residue was heated under nitrogen at 170° for 5 hours, cooled, taken up in 150 ml. of methanol and added to 150 ml. of 10% sodium hydroxide. The mixture was refluxed for 1 hour, evaporated to remove most of the methanol and extracted with dichloromethane (4 x 100 ml.). The combined extracts were dried and evaporated to give a yellow oil (63.2 g., 68%). An analytical sample was obtained by passing the oil through a silica gel column packed and eluted with ether; ir (liquid film) 3400 cm^{-1} (O-H), 1650 cm^{-1} (C=O, amide); nmr: δ 1.10-2.50 (broad, 7H, H at C-7, C-8, C-5 and C-4), 2.60-2.97 (t, 2H, CH_2Ph), 3.17-4.13 (broad, 5H, H at NCH_2, C-1, C-6 and O-H), 7.08 (s, 5H, aromatic); ms: m/e 245 (M^+), 154 (base).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71.

Found: C, 73.53; H, 7.96; N, 5.67.

6-*endo*-Hydroxy-2-phenethyl-2-azabicyclo[2.2.2]octane (**20b**).

A solution of **19b** (63.2 g., 0.258 mole) in 150 ml. of dry benzene was added dropwise to Red-Al (60%, 260 ml., 0.772 mole) and refluxed for 4 hours. The reaction mixture was treated with ethanol-water to decompose the excess Red-Al and filtered. The organic phase of the filtrate was kept and the aqueous layer extracted with chloroform (3 x 75 ml.). The organic phases were combined, dried and evaporated. The residue was fractionally distilled to give a clear oil (42.4 g., 71%, b.p. 158-160°/0.45 mm.) which solidified on standing; m.p. 76-78°; ir (carbon tetrachloride): 3650 cm^{-1} (O-H); nmr: δ 1.20-2.50 [broad, 8H, H at C-7, C-8, C-5, O-H (s, 1.88) and C-4], 2.50-3.17 (broad, 7H, H at NCH_2-CH_2Ph, C-3 and C-1), 4.01-4.41 (m, 1H, H at C-6), 7.25 (s, 5H, aromatic); ms: m/e 231 (M^+), 140 (base).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.89; H, 9.15; N, 6.06. Found: C, 77.89; H, 9.17; N, 5.98.

2-Methyl-2-azabicyclo[2.2.2]octan-6-one (**21a**) and 2-Methyl-5-diphenylmethylidene-2-azabicyclo[2.2.2]octan-6-one (**22**).

A solution of **20a** (10.0 g., 0.071 mole) in 30 ml. of benzene was added dropwise to a mixture of benzophenone (52.0 g., 0.284 mole) and potassium *t*-butoxide (12.0 g., 0.107 mole) in 500 ml. of benzene and the resulting mixture heated at 40° for 2 hours, washed with water (2 x 150 ml.) and extracted with 10% hydrochloric acid (3 x 100 ml.). The acidic solution was neutralized with potassium carbonate and extracted with chloroform (4 x 75 ml.). The combined extracts were dried and evaporated to give a residue which was chromatographed on an alumina column (Woelm, neutral, 80-200 mesh, 30:1 ratio) packed and eluted with ether-petroleum ether (2:3) to give the desired ketone **21a** (7.7 g., 78%) followed by the side product **22** (2.2 g., 10%), m.p. 145-147°.

Compound **21a** had ir: (liquid film) 1740 cm^{-1} (C=O, ketone); nmr: δ 1.0-2.56 [broad, 10H, H at C-7, C-8, C-6, C-4 and N-CH_3 (s, 2.43)], 2.57-2.97 (broad, 2H, H at C-3), 3.17-3.50 (broad, 1H, H at C-1).

Compound **22** had ir (potassium bromide): 1705 cm^{-1} (C=O, ketone); nmr: δ 1.50-2.70 [broad, 8H, H at C-7, C-8, N-CH_3 (s, 2.49) and C-4], 2.70-3.37 (broad, 3H, H at C-3 and C-1), 7.0-7.50 (broad, 10H, aromatic); ms: m/e 303 (M^+), 247 (base).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.64. Found: C, 82.94; H, 6.89; N, 4.49.

2-Phenethyl-2-azabicyclo[2.2.2]octan-6-one (**21b**).

A solution of **20b** (26.6 g., 0.115 mole) in 200 ml. of benzene was added dropwise to a mixture of benzophenone (83.8 g., 0.46 mole) and potassium *t*-butoxide (14.9 g., 0.172 mole) in 600 ml. of dry benzene and heated at 45° for 30 minutes. The reaction mixture was worked up in the same manner as in the preparation of **21a** to give an oil (19.1 g., 72%). An analytical sample was obtained by passing the oil through a silica gel column (30:1 ratio) packed and eluted with ether-petroleum ether (2:1); ir (liquid film): 1740 cm^{-1} (C=O, ketone); nmr: δ 1.30-2.33 (broad, 7H, H at C-7, C-8, C-5 and C-4), 2.33-2.90 (broad, 6H, H at NCH_2CH_2-Ph, C-3), 3.0-3.27 (broad d, 1H, H at C-1), 7.03 (s, 5H, aromatic); ms: m/e 229 (M^+), 110 (base).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.36; H, 8.53; N, 5.98.

2-Methyl-6-*exo*- and 6-*endo*-anilino-2-azabicyclo[2.2.2]octane (**23a** and **24a**).

A mixture of **21a** (3.08 g., 0.022 mole), aniline (5.0 g., 0.054 mole), and molecular sieves (4A, 15.0 g.) in 75 ml. of benzene was refluxed for 48 hours. The reaction mixture was cooled, filtered and evaporated to give a residue which was distilled under reduced pressure to remove unreacted aniline and the residue dissolved in 100 ml. of absolute ethanol. Sodium metal (8.0 g., 0.348 g.-atom) was added in small portions at such a rate as to maintain mild refluxing. After addition was complete the resulting mixture was refluxed for 48 hours, under nitrogen, and cooled. Water (100 ml.) was slowly added, the mixture concentrated to remove most of the ethanol, and the concentrate extracted with ether (4 x 75 ml.). The combined ethereal extracts were dried, evaporated, and the residue chromatographed on a neutral alumina column (Woelm) packed and eluted with ether-petroleum ether (1:5) to give first **23a** (0.7 g., 14%); ir (carbon tetrachloride): 3380 cm^{-1} (N-H); nmr: δ 1.17-2.73 (broad, 12H, H at C-7, C-8, C-5, C-4, N-CH_3 and C-3), 3.0-3.33 (m, 1H, H at C-1), 3.33-3.83 (broad, 1H, H at C-6), 4.30-4.83 (broad, 1H, NH), 6.53-7.40 (m, 5H, aromatic); ms: m/e 216 (M^+), 97 (base).

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.61; H, 9.18; N, 13.06.

Following elution of a mixture of **23a** and **24a** (0.85 g.), pure **24a** eluted (1.1 g., 23%) ir (carbon tetrachloride): 3440cm^{-1} (N-H); nmr: δ 1.0-2.47 (broad, 7H, H at C-7, C-8, C-5 and C-4), 2.47-3.07 (broad, 6H, N-CH_3, C-3 and C-1), 3.47-4.20 (broad, 2H, H at NH and C-6), 6.50-7.40 (m, 5H, aromatic); ms: m/e 216 (M^+), 97 (base).

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.62; N, 9.29; N, 12.75.

2-Phenethyl-6-*exo*- and 6-*endo*-anilino-2-azabicyclo[2.2.2]octane (**23b** and **24b**).

In a manner similar to that described for the preparation of **23a** and **24a**, the anil derived from treating **21b** (9.6 g., 0.042 mole), aniline (11.5 g., 0.124 mole) and molecular sieves (4A, 30.0 g.) was reacted with sodium metal (12.5 g.) in 150 ml. of absolute ethanol. Chromatography of the residue obtained on work-up on silica gel (MN, 70-270 mesh) packed and eluted with ether-petroleum ether (1:5) eluted first pure **23b** (1.2 g., 9%); ir (carbon tetrachloride): 3370 cm^{-1} (N-H); nmr: δ 1.10-2.70 (broad, 9H, H at C-7, C-8, C-5, C-4 and CH_2Ph), 2.80 (s, 4H, H at NCH_2 and C-3), 3.10-3.70 (broad, 2H, H at C-1 and C-6), 4.30-4.73 (broad, 1H, N*H*), 6.40-7.60 (m, 10H, aromatic); ms: m/e 306 (M^+), 215 (base).

Anal. Calcd. for $C_{21}H_{26}N_2$: C, 82.30; H, 8.33; N, 9.14. Found: C, 82.32; H, 8.60; N, 9.02.

Following elution of a mixture of **23b** and **24b** (0.5 g.), pure **24b** eluted (1.3 g., 10%); ir (carbon tetrachloride): 3440 cm^{-1} (N-H); nmr: δ 1.0-2.60 (broad, 7H, H at C-7, C-8, C-5 and C-4), 2.80-3.13 (m, 7H, H at NCH_2CH_2Ph, C-3 and C-1), 3.40-4.17 (broad, 2H, H at NH and C-6), 6.50-7.47 (m, 10H, aromatic); ms: m/e 306 (M^+), 215 (base).

Anal. Calcd. for $C_{21}H_{26}N_2$: C, 82.30; H, 8.55; N, 9.14. Found: C, 82.44; H, 8.63; N, 9.03.

2-Methyl-6-*exo*-propanilido-2-azabicyclo[2.2.2]octane (**5**).

A solution of **23a** (400 mg., 1.9 mmole) in propionic anhydride (4.9 g.) was refluxed under nitrogen for 10 hours and distilled under reduced pressure to remove excess propionic anhydride. The residue was chromatographed on silica gel (NM, 70-270 mesh) packed and eluted with ether-petroleum ether (1:1) to give **5** as clear oil (340 mg., 65%), ir (liquid film): 1665 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_2CH_3), 1.20-2.0 (broad, 9H, H at C-7, C-8, C-5, $COCH_2$ and C-4), 2.0-2.30 (broad, 4H, NCH_3 and 1H of C-3), 2.63-2.93 (broad, 2H, H at one of C-3 and C-1), 4.67 (t, 1H, H at C-6), 7.0-7.50 (broad, 5H, aromatic); ms: m/e 272 (M^+, base).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.10; H, 9.00; N, 10.40.

2-Methyl-6-*endo*-propanilido-2-azabicyclo[2.2.2]octane (**6**).

In a manner similar to that described for the preparation of **5**, the residue obtained from treatment of 1.55 g. (7.0 moles) of **24a** with 9.1 g. of propionic anhydride was chromatographed on silica gel to give 1.3 g. (68%) of **6**, m.p. 78-80°; ir (liquid film): 1665 cm^{-1} or (nujol): 1655 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_2CH_3), 1.7-2.20 (broad, 9H, H at C-7, C-8, C-5, $COCH_2$ and C-4), 2.33-3.17 (broad, 6H, H at C-3, N-CH_3 and C-1), 5.07 (t, 1H, H at C-6), 7.0-7.60 (broad, 5H, aromatic); ms: m/e 272 (M^+, base).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.89; H, 8.91; N, 10.17.

2-Phenethyl-6-*exo*-propanilido-2-azabicyclo[2.2.2]octane (**7**).

In a manner similar to that described for the preparation of **5**, the residue obtained from treatment of 430 mg. (1.4 mmoles) of **23b** with 4.0 g. of propionic anhydride was chromatographed on silica gel to give 406 mg. (80%) of **7**, m.p. 95-97°; ir (nujol): 1640 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_2CH_3), 1.23-2.30 (broad, 9H, H at C-7, C-8, C-5, $COCH_2$ and C-4), 2.43-3.10 (broad, 7H, H at NCH_2CH_2Ph, C-3 and C-1), 4.67 (t, 1H, H at C-6), 7.0-7.60 (broad, 10H, aromatic); ms: m/e 362 (M^+), 271 (base).

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.62; H, 8.33; N, 7.65.

2-Phenethyl-6-*endo*-propanilido-2-azabicyclo[2.2.2]octane (**8**).

In a manner similar to that described for the preparation of **5**, the residue obtained from treatment of 478 mg. (1.5 mmoles) of **24b** with 4.0 g. of propionic anhydride was chromatographed on silica gel to give 300 mg. (55%) of **8** as an oil; ir (liquid film): 1665 cm^{-1} (C=O, amide); nmr: δ 1.0 (t, 3H, CH_2CH_3), 1.14-2.20 (broad, 9H, H at C-7, C-8, C-5, $COCH_2$ and C-4), 2.37-3.27 (broad, 7H, H at NCH_2CH_2Ph, C-3 and C-1), 5.01 (t, 1H, H at C-6), 6.90-7.53 (broad, 10H, aromatic); ms: m/e 362 (M^+), 271 (base).

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.46; H, 8.45; N, 7.53.

Acknowledgment.

The authors gratefully express appreciation to Dr. John K. Baker for his consultation regarding the nmr data and Dr. Stephen Billets for supplying mass spectral data. This research was supported in part by grant 1 ROI NSO9188 from the National Institute of Neurological Diseases and Stroke and in part by the Research Institute of Pharmaceutal Sciences, School of Pharmacy, University of Mississippi.

REFERENCES AND NOTES

(1) G. Krow, R. Rodebaugh, M. Grippi and R. Carmosin, *Syn. Commun.*, **2**, 211 (1972).

(2) K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1970 (1971).

(3) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).

(4) R. F. Borne, C. R. Clark and R. L. Peden, *J. Heterocyclic Chem.*, **10**, 241 (1973).

(5) R. F. Borne, C. R. Clark and J. M. Holbrook, *J. Med. Chem.*, **16**, 853 (1973).

(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Pergamon Press, New York, N. Y., 1969, p. 231.

(7) A. F. Cockerrill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.*, **73**, 533 (1973).

(8) Carbowax column, 20M, 4%; column temperature 175°, retention times: **11** = 12.2 minutes; **12** = 14.6 minutes.

(9) OV-17 column, 3%; column temperature 230°; retention times: isomer A = 21.0 minutes; isomer B = 25.0 minutes.