EtOH was slowly added to 1500 ml of a hot solution of *l*-dibenzoyltartaric acid (94.0 g, 0.25 mol) in 95% EtOH. Upon cooling overnight the *d*-amine *l*-dibenzoyl tartrate separated (due to its insolubility, specific rotation data were obtained by converting samples to the amine hydrochloride). Four successive recrystallizations from 1000 ml of 95% EtOH were required to obtain optically pure material.

The *d*-amine *l*-dibenzoyl tartrate (8 g, 0.014 mol) was partitioned between 2 *N* HCl and EtOAc. The aqueous layer was evaporated and the residue recrystallized from MeOH-EtOAc to yield 2.55 g of white crystals: mp 225-230°, $[\alpha]^{25}D$ +13.3° (H_2O) (α +0.272, *c* 1.024 g/100 ml, *l* = 2).

l-2,3-Dichloro-α-methylbenzylamine Hydrochloride. The filtrates from the first recrystallization of the *d*-amine *l*-dibenzoyl tartrate were evaporated to dryness, basified with NaOH, and extracted (Et_2O). The Et_2O layer was dried (K_2CO_3) and evaporated. The resultant free amine (18.7 g, 0.098 mol) in 250 ml of 95% EtOH was treated with *d*-dibenzoyltartaric acid (36.95 g, 0.098 mol) in 750 ml of 95% EtOH as for the *d*-amine *l*-dibenzoyl tartrate. The optically pure *l*-amine *d*-dibenzoyl tartrate (6 g, 0.011 mol) thus obtained was converted to the amine hydrochloride which was recrystallized (MeOH-EtOAc) to yield 1.94 g of white crystals: mp 227-231°, $[\alpha]^{25}D$ −12.4° (H_2O) (α −0.250, *c* 1.007 g/100 ml, *l* = 2).

Acknowledgments. We gratefully acknowledge the assistance of William A. Day in the synthesis of the benzylamines and of Mary Jo Brandt in some of the animal studies.

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Syntheses of Cisoid and Transoid Analogs of Phenethylamine

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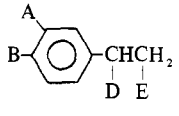
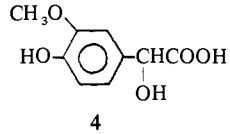
In an attempt to ascertain whether the cisoid or transoid phenethylamine moieties are responsible for the catatonic state produced by bulbocapnine (**5**), *trans*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**6**), *trans*-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (**7**), aza-1-methyl-1,2,3,7,8,8a-hexahydroacenaphthalene (**8**), and 1-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]-quinoline (**9**) were synthesized. Compounds **6** and **7**, both transoid analogs, produced catalepsy in rats. The symptoms produced by **7** in cats were similar to those observed with bulbocapnine (**5**).

Catecholamines along with some of their metabolites and derivatives have been implicated in various neuropsychiatric disorders.[1] Metanephrine (**1**), normetanephrine (**2**), and 3-methoxy-4-hydroxymandelic acid (**4**) have been reported to be excreted in abnormally high concentrations during psychotic episodes in patients with periodic catatonia. Furthermore, 3,4-dimethoxyphenethylamine (**3**, DMPEA) is capable of producing a catatonic state in animals. It has also been reported to be present in the urine of 92% of the schizophrenic population but was found to be absent from the urine of normal subjects.





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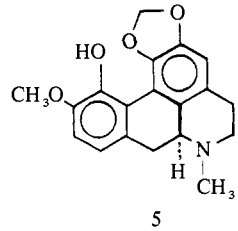
	A	B	D	E
1	CH_3O	OH	OH	$NHCH_3$
2	CH_3O	OH	OH	NH_2
3	CH_3O	CH_3O	H	NH_2

Bulbocapnine (**5**), one of the Corydalis alkaloids, has been widely used to produce experimental catatonia in various animal species.[2] In addition to its ability to produce catatonia, bulbocapnine has been shown to be an α-adrenergic blocking agent.

It can be seen that within the bulbocapnine molecule there are two tricyclic components which embody the catecholamine moiety fixed in rigid conformations (**5a** and **5b**). In structure **5a** the catecholamine amine portion is held in a transoid form and in structure **5b** the catecholamine moiety is embodied in a cisoid manner. The possibility exists that one of these rigidly held phenethylamines is responsible for the production of catatonia while the other may be responsible for the α-adrenergic blockade. The purpose of this research was to prepare cisoid and transoid structure of the type shown below (**6-9**) to de-



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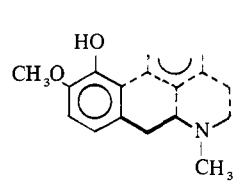
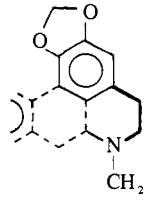


a

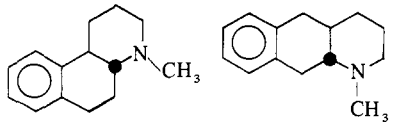


b

†Presented in part by S. E-A. before the Midwest Regional Meeting of the American Chemical Society, Lincoln, Neb., Oct 28-30, 1970.

‡Taken in part from the dissertation presented by L. W. H., Oct 1968, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

termine which steric features are responsible for the observed pharmacological effect.



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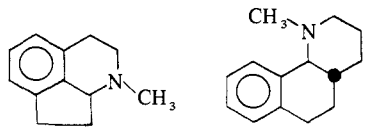

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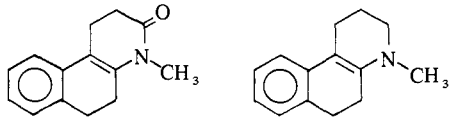
The synthesis of *trans*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**6**) was initiated utilizing β-tetralone and methyl 3-(*N*-methylamino)propionate[3] to afford 4-methyl-3-keto-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (**10**).[4] Compound **10** was treated with $LiAlH_4$ to yield 4-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (**11**) which was converted to the desired compound **6** by reduction with Li in liquid NH_3 by the method of Horii, *et al.*[5]

trans-1-Methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]-



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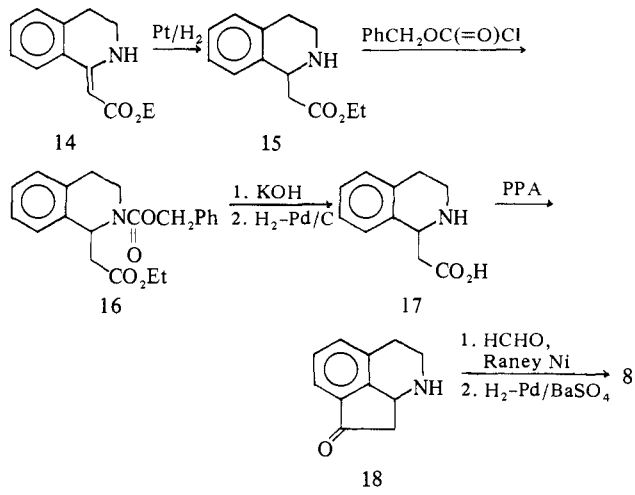
quinoline perchlorate (**7**) was prepared *via* the cyclization of 2-benzyl-3-piperidinecarboxylic acid (**12**). The acid **12** was cyclized utilizing polyphosphoric acid to give the amino ketone which underwent reductive methylation in the presence of formaldehyde to give the amino alcohol **13**. On hydrogenolysis the *N*-methylbenzoquinoline **7** was obtained. The route to starting acid is depicted below.

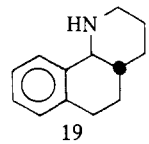
1-Aza-1-methyl-1,2,3,7,8,8a-hexahydroacenaphthalene hydrochloride (**8**) was prepared *via* a seven-step sequence utilizing ethyl 3,4-dihydroisoquinoline-1-acetate (**14**) as the starting material.[6,7] Ethyl 1,2,3,4-tetrahydroisoquinoline-1-acetate (**15**) was obtained by hydrogenation of **14** followed by treatment with benzyl chloroformate to yield the ester **16**. Hydrolysis of **16** followed by hydrogenolysis produced **17**. Cyclization of **17** to give 1-aza-7-keto-1,2,3,7,8,8a-hexahydroacenaphthylene (**18**) was accomplished by heating with polyphosphoric acid. Reductive methylation of the amino ketone **18** with formaldehyde afforded the amino alcohol which underwent hydrogenolysis to give the desired compound 8.

To determine if the rigid transoid or cisoid phenethylamine could be replaced by a rigid benzylamine system, 1-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinoline



14 15 16 17 18

(**9**) was prepared. A modification of the method of Parcell and Hauk[8] produced **19** which under Escheweiler-Clark conditions gave the desired compound **9**.



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Biological Results. Methods. Catalepsy. Female Holtzman rats weighing 200-300 g were utilized. The investigation was based on constant observation during an experiment period of approximately 2 hr. The agents were injected intraperitoneally and the rats were placed with their forelegs on a rod (15-cm height). If catalepsy was present, this position was maintained for a period greater than 20 sec. Along with catalepsy, the rigidity of body muscles was also observed.

Two cats were injected with the agents and the behavioral effects observed.

Isolated Rat Vas Deferens Preparation. Rat vas deferens was suspended in a 10-ml bath of Tyrode's solution. The temperature of the bath was 35-36° and a gas mixture of 95% oxygen plus 5% carbon dioxide was bubbled through the bath. The magnification of the level was four. Cumulative dose-response curves to norepinephrine and dopamine were obtained using the method of van Rossum.[9]

Blood Pressure Recordings. Cats weighing from 2.5 to 4.25 kg were anesthetized with sodium pentobarbital (30 mg/kg ip). Arterial blood pressure was measured with a Statham transducer coupled to the carotid artery. Drug injections were made into cannulae inserted into the femoral vein. After suitable responses had been obtained to the agonist at three dose levels, the drug was administered intravenously. Subsequently the agonist was readministered at the same dose levels and in the case of the blockade the doses of the agonist were doubled until the antagonism had been surmounted.

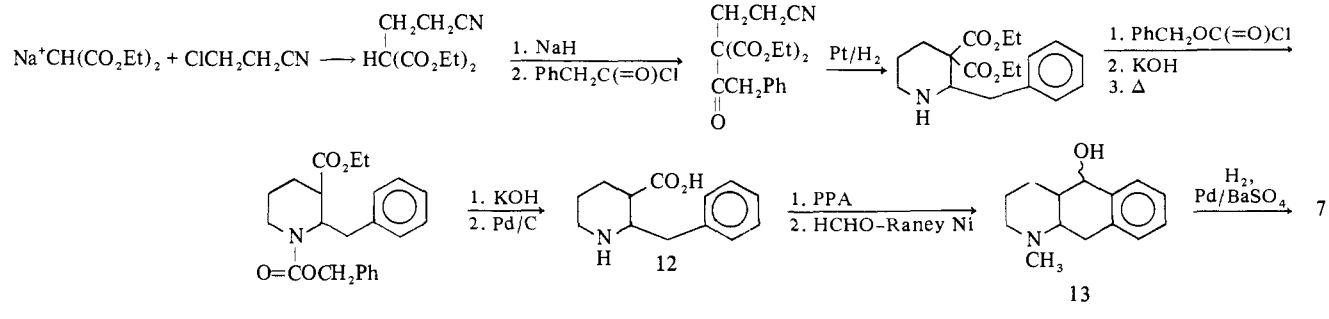

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Table I. Antagonist Effect on the Cumulative Contractile Response of the Rat Vas Deferens to Norepinephrine and Dopamine

Compd	Antagonist concn, *M*	Concn 1	3	10	30	100
			Norepinephrine ($\times 10^{-6}$ *M*)			
(*N* = 2)[a]	Control	0.8	13.4 ± 5.7	68.3 ± 15.8	90.5 ± 9.5	100
6	3×10^{-5}	0	0	17.2 ± 1.8	115.5 ± 15.5	256.0 ± 23.0
6	1×10^{-4}	0	0	8.6 ± 0.9	113.0 ± 13.0	277.0 ± 15.0
(*N* = 4)	Control	4.5 ± 2.1	18.7 ± 6.0	48.2 ± 11.1	78.5 ± 8.5	100
7	1×10^{-5}	0	5.5 ± 1.5	34.8 ± 9.7	100 ± 10.8	165 ± 24.9
7	3×10^{-5}	0	0.9 ± 0.9	42.4 ± 10.8	168.7 ± 3.9	291.7 ± 55.6
7	1×10^{-4}	0	3.1 ± 1.7	29.6 ± 7.6	126.3 ± 25.2	327.5 ± 115.6
(*N* = 7)	Control	7.5 ± 1.7	20.1 ± 3.1	54.4 ± 4.2	86.1 ± 3.8	100
8	1×10^{-5}	2.5 ± 0.9	11.9 ± 2.2	47.8 ± 4.3	85.8 ± 7.9	113.5 ± 5.1
8	3×10^{-5}	1.7 ± 0.8	9.0 ± 1.8	54.4 ± 8.8	92.8 ± 9.3	127.7 ± 10.4
8	1×10^{-4}	0.8 ± 0.6	9.1 ± 1.3	45.7 ± 7.6	110.7 ± 9.9	159.3 ± 10.1
			Dopamine ($\times 10^{-5}$ *M*)			
(*N* = 5)	Control		16.7 ± 2.0	86.5 ± 7.0	98.3 ± 1.7	
6	3×10^{-6}	0	0	12.8 ± 4.1	65.7 ± 11.3	71.8 ± 11.9
6	1×10^{-5}	0	0	4.3 ± 1.1	17.2 ± 3.1	59.4 ± 10.7
(*N* = 4)	Control	1.0 ± 0.6	34.4 ± 1.7	93.9 ± 2.4	99.1 ± 1.0	
7	3×10^{-6}	0	4.0 ± 2.1	45.0 ± 4.1	77.7 ± 3.1	71.5 ± 9.0
7	1×10^{-5}	0	0.6 ± 0.6	6.3 ± 2.4	43.1 ± 4.0	68.7 ± 6.1
(*N* = 4)	Control	2.0 ± 1.1	33.6 ± 10.4	93.9 ± 3.9	97.5 ± 1.5	
8	1×10^{-5}	0	4.7 ± 1.3	64.5 ± 10.8	90.7 ± 6.1	
8	3×10^{-5}	0	1.9 ± 1.3	31.3 ± 7.5	61.6 ± 10.1	47.4 ± 12.1

[a] *N* = number of experiments at each concentration of antagonist.

Results

Catalepsy. Experiments in Rats. After the injection of 10 mg/kg of **6**, rats decreased the locomotor activity in 2-5 min (two rats). A catelepsy was induced 5-10 min after injection. There was a rigidity of skeletal muscle. However, the animal could walk several steps after giving an external stimulation. Increasing the dose to 20 mg/kg, rats produced a strong catalepsy, but catalepsy was interrupted by chronic convulsion (two rats). The duration of catatonia lasted for 2-3 hr. A dose of 50-100 mg/kg of **6** proved lethal. The rats died in convulsion within 5-20 min after the injection.

The symptoms observed after the injection of **7** were similar to that after the injection of **6**. After injection of 40 or 50 mg/kg of **6**, the rats decreased locomotor activity and a catalepsy followed.

After the injection of **8** (50 mg/kg) the rats decreased exploratory activity and tremor occurred but no catalepsy was observed. A dose of 100 mg/kg of this drug was lethal. The rats died in convulsion.

Experiment in Cats. The cats (2.5 kg) were injected with 30 mg/kg of **7**. The cats produced a rage and fear behavior and hissed when touched. There were autonomic syndromes, such as piloerection and urination. A cataleptic state was produced about 1 hr after injection and lasted 1-2 hr. The symptoms produced by **7** were similar to that of bulbocapnine.

Another cat was injected with 30 mg/kg of **8**. No apparent changes of behavior were observed after the injection.

Effect on the Cumulative Contractile Response of the Rat Vas Deferens to Norepinephrine and Dopamine (Table I). By using *l*-norepinephrine and dopamine as agonists, cumulative dose-response curves were ascertained on the vas deferens in the presence and in the absence of various concentrations of drugs. In control responses, the cumulative dose-response curves induced by *l*-norepinephrine and dopamine had a similar shape and about equal maximum height. The responses to *l*-norepinephrine were depressed by all three drugs when smaller doses of norepinephrine were used. All three drugs produced a dose-related increase in the maximum response to cumulative dose of *l*-norepinephrine. All three drugs in dose 3×10^{-6}-1×10^{-4} *M* caused a shift of dose-response curves of dopamine to the right. Compounds **6** and **7** appeared to be more potent in antagonizing the contractile response to dopamine.

Effect on the Pressor Response to Norepinephrine and Epinephrine in Cats. All three drugs (10 mg/kg) depressed the pressor response to norepinephrine and reversed the pressor response to epinephrine. The depressor response to isoproterenol was unaffected.

Effect on the Depressor Response to Dopamine in Cats. After the injection of phenoxybenzamine (3 mg/kg) and propranolol (1 mg/kg), a characteristic depressor response to dopamine was induced. Compounds **6** and **7** in doses of 3-10 mg/kg reduced the depressor response to dopamine. The depressor response to dopamine was not affected by **8** (10 mg/kg).

Conclusions

The pharmacological effects of compound **9** in the assays utilized were insignificant. Since this compound is a substituted benzylamine rather than phenethylamine, the lack of adrenergic effect is to be expected.

As stated earlier, the purpose of this work was to attempt to determine if the cisoid phenethylamine or the transoid phenethylamine structure of bulbocapnine is responsible for α-adrenergic blockade and if the cisoid or transoid moiety is responsible for catatonia. From the preliminary results it appears that the transoid compounds **6** and **7** are more effective α-adrenergic blocking agents than the cisoid compound **8** when norepinephrine was used as the agonist in low concentrations.

Both the cisoid and transoid compound were effective in blocking dopamine; however, the transoid compounds were effective at lower doses than the cisoid compound.

It must be remembered that in smooth muscle preparation the antagonism seen is primarily due to α-adrenergic receptors and not dopamine receptors. The dopamine receptor can be specifically demonstrated with blood pressure effect only in situations where all other receptors are excluded.

The preliminary work reported in this paper indicates that there is a steric preference at the α-adrenergic and dopamine receptors. Currently the compounds having various oxygen-containing substituents on the aromatic ring are being prepared and tested.

Experimental Section

Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data (μ) were recorded on Beckman IR8 and IR10 spectrophotometers. Nmr data (ppm, δ) were recorded on Varian Associates Model A-60, A-60A, and HA-100 spectrophotometers (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, The University of Kansas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Unless otherwise stated, the spectral data were consistent with the assigned structures.

3-Keto-4-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (10). This compound was prepared according to the method of Nelson, *et al.*,[4] by refluxing a toluene solution of β-tetralone (25.0 g, 0.17 mol) and methyl β-methylaminopropionate[3] (20.0 g, 0.17 mol) under N_2 for 6 hr. The curde enamine was heated with ethylene glycol to obtain 11.7 g (32.1%) of pale yellow crystals, mp 103–104° (lit.[4] 106–107°).

4-Methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (11). This compound was prepared according to Nelson, *et al.*,[4] from 9.80 g (0.045 mol) of 10 by $LiAlH_4$ reduction. An 85% yield (8.0 g) of a pale yellow oil was obtained.

trans-4-Methyl-1,2,3,4,4a,5,6,10b-octahydro[*f*]quinoline (6). Utilizing the method of Horii, *et al.*,[5] 1.59 g (0.008 mol) of the enamine was reduced with Li/NH_3. The crude oil was distilled [104–108° (0.4 mm)] to afford 1.4 g (87.5%) of a colorless oil. *Anal.* ($C_{14}H_{19}N$) C, H, N.

Diethyl 2-Benzyl-2,3-piperidenedicarboxylate. The process of Michne and Albertson[10] was modified to produce the desired compound. A solution of diethyl 2-cyanoethylphenylacetylmalonate (1.5 g, 4.4 mmol) in 20 ml of HOAc was hydrogenated over PtO_2 at 25° under 60 psi. The catalyst was removed and the solvent removed. The residue was dissolved in 20% HCl, washed with Et_2O, made basic with NH_4OH, and extracted with Et_2O. The extract was washed with H_2O and dried (Na_2SO_4) and the solvent removed to give 1.1 g (68.7%) of an oil which was converted to the HCl salt by treatment with ethereal HCl, mp 178–180° (lit.[10] 179°).

3-Carbethoxy-1-benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylic Acid. A mixture of the above diester (4.5 g, 0.01 mol) and KOH (2.25 g, 0.04 mol) in 25 ml of EtOH was refluxed 4 hr, the EtOH removed, and the residue dissolved in H_2O. The aqueous solution was washed with Et_2O, acidified with HCl, and extracted with Et_2O. The extract was washed with H_2O and dried (Na_2SO_4) and the solvent removed to give a pale yellow solid which crystallized from aqueous MeOH to give 3.3 g (77.6%) of white needles, mp 173–175°. *Anal.* ($C_{24}H_{27}NO_6$) C, H, N.

Ethyl 1-Benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylate. The above half-acid ester (0.5 g, 1.1 mmol) was heated at 170–190° under N_2 for 6 hr, cooled, dissolved in Et_2O, washed with H_2O, and washed with dilute NaOH. The Et_2O solution was dried (Na_2SO_4) and the solvent removed to give 0.35 g of a brown semisolid material which did not crystallize from any of a variety of solvents. This compound was carried forth to the next reaction.

1-Benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylic Acid. Ethyl 1-benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylate (0.5 g, 1.1 mmol), prepared by the method of Michne and Albertson,[10] was refluxed in 20 ml of EtOH containing 1 g of KOH for 3 hr. The EtOH was removed and the residue dissolved in H_2O. The aqueous solution was washed with Et_2O, acidified with HCl, and extracted with Et_2O. The extract was washed with H_2O and dried (Na_2SO_4) and the solvent removed to give a pale yellow solid. Recrystallization (aqueous MeOH) produced white crystals (0.3 g, 96.7%), mp 175–177°. *Anal.* ($C_{21}H_{23}NO_4$) C, H, N.

trans-5-Keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride. The amino acid, 1-benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylic acid (0.57 g, 2.6 mmol), and PPA (8.2 g) were stirred as the temperature was allowed to rise from 25 to 120° during a period of 20 min. The mixture was allowed to stand at 120° for an additional 30 min. After cooling to 80° the mixture was diluted with 13 ml of ice H_2O, made basic with K_2CO_3 solution, and extracted with Et_2O. The extract was washed with H_2O and dried (Na_2SO_4) and the Et_2O removed to give pale brown crystals. The HCl salt was obtained by treatmet with EtOH–HCl and, after removal of the solvent, was recrystallized (Me_2CO) and the crystal washed with Et_2O to give colorless plates (0.27 g, 90%), mp 204–205° dec. *Anal.* ($C_{13}H_{16}NOCl$) C, H, N.

trans-1-Methyl-5-hydroxy-1,2,3,4,4a,5,10,10a-octahydrobenzo-[*g*]quinoline (13). The above ketone, as the free base (0.4 g, 0.2 mmol), in 30 ml of MeOH was allowed to stand with 1.8 ml of 37% HCHO for 4 hr at 25°. One-half teaspoonful of W-2 Raney Ni was added and the mixture agitated in a Parr apparatus at 18 psi of H_2 for 8 hr. The catalyst and the solvent were removed to give a residue which was dissolved in MeOH. Treatment with ethereal HCl produced the HCl salt. Recrystallization (MeOH–Et_2O) gave 0.4 g (80%) of prisms, mp 248–250° dec. *Anal.* ($C_{14}H_{20}NOCl$) C, H, N.

trans-1-Methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Perchlorate (7). A solution of 13 (1.2 g, 4.7 mmol) in 100 ml of glacial HOAc and 5 ml of 70% $HClO_4$ was hydrogenated in a Parr apparatus (60 psi) over 2.4 g of 5% $Pd/BaSO_4$ for 12 hr. The catalyst and solvent were removed and the residue was treated with 10 ml of H_2O. The $HClO_4$ salt separated, was filtered, and dried *in vacuo* to yield 1.3 g (92.8%) of a white solid, mp 175–176°. *Anal.* ($C_{14}H_{20}NClO_4$) C, H, N.

1,2,3,4-Tetrahydroisoquinoline-1-acetic Acid (17). 2-Carbobenzoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (5.5 g, 0.016 mol) in 100 ml of EtOH was hydrogenated over 2.2 g of 5% Pd/C in a Parr apparatus at 18 psi for 8 hr. The catalyst and solvent were removed and the residue was washed with Et_2O to give a colorless solid, 2.5 g (83.3%). Recrystallization (MeOH) gave colorless needles, mp 239–241° dec. *Anal.* ($C_{22}H_{23}NO_2$) C, H, N.

1-Aza-7-keto-1,2,3,7,8,8a-hexahydroacenaphthylene (18). A mixture of 17 (0.5 g, 2.6 mmol) and 8.2 g of PPA was stirred and heated to 150°. The mixture was allowed to stand for 20 min at 150° and allowed to cool to 80°, and 25 ml of ice H_2O was added. The solution was made basic with K_2CO_3 solution and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4) and the solvent removed to give a brown oil which crystallized on standing to give 0.37 g (82.2%) of long needles. The needles were dissolved in Me_2CO and treated with alcoholic HCl. The solvent was removed and the residue dissolved in hot methanol, treated with charcoal, filtered, and crystallized to give white needles, mp 243–245° dec. Although the ir and nmr spectra were consistent with this structure, it was impossible to obtain an acceptable elemental analysis for this compound.

1-Aza-7-hydroxy-1-methyl-1,2,3,7,8,8a-hexahydroacenaphthylene. A mixture of the ketone 18 (0.34 g, 2.0 mmol) and 1.8 ml of 37% HCHO in 30 ml of MeOH was allowed to stand at 25° for 4 hr. One-half teaspoonful of W-2 Raney Ni was added and the mixture agitated on a Parr apparatus under H_2 at 18 psi for 12 hr. The catalyst and solvent were removed to give 0.23 g (62%) of white crystals. Recrystallization (MeOH) gave mp 200–201°. *Anal.* ($C_{12}H_{15}NO$) C, H, N.

1-Aza-1-methyl-1,2,3,7,8,8a-hexahydroacenaphthylene Hydrochloride (8). A solution of the above alcohol (0.88 g, 4.7 mmol) in 100 ml of glacial HOAc and 5 ml of 70% $HClO_4$ was hydrogenated over 5% $Pd/BaSO_4$ in a Parr apparatus at 60 psi for 12 hr. The catalyst and solvent were removed and the residue was dissolved in H_2O, made basic with NH_4OH, and extracted with Et_2O. The ethereal extract was washed with H_2O and dried (Na_2SO_4) and the Et_2O removed to give an oil which crystallized on standing to give 0.6 g (75%) of white crystals. The crystals were dissolved in Et_2O and treated with ethereal HCl. Recrystallization (MeOH) gave white needles, mp 262–266° dec. *Anal.* ($C_{12}H_{16}NCl$) C, H, N.

1-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinoline (9). A mixture of 1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]quinoline[8] (6.00 g, 0.032 mol), 3.0 ml of 37% HCHO, and 7.5 ml of 98% HCO_2H was refluxed for 4.5 hr. On cooling, the solution was diluted with 125 ml of H_2O, made basic with 50% aqueous NaOH, and extracted with Et_2O. The extract was dried (Na_2SO_4) and the solvent removed to yield 6.38 g of pale yellow liquid. Distillation afforded 4.09 g (64%) of a colorless product, bp 88–91° (0.35 mm). *Anal.* ($C_{14}H_{19}N$) C, H, N.

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Synthesis and Antifertility Activity of Some Oximinoandrostenes

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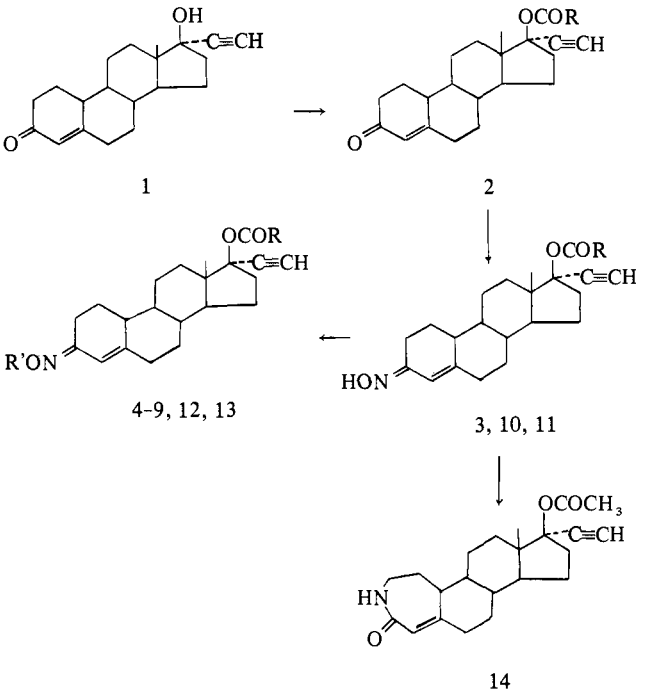
A number of oximino and 3-aza-*A*-homoandrostenes were synthesized from 17α-ethynyl-19-nortestosterone and evaluated for antifertility activity. Based on relative potency and Clauberg responses, 17β-acetoxy-19-norandrost-4-en-3-one oxime was selected for mechanism of action studies and human trials.

As part of a continuing program directed toward the development of new and novel progestational agents, 3-aza-*A*-homo steroids have been the object of considerable interest in our laboratory.[1-4] The rationale for this work and probable mode of action of the specific compounds have been described earlier.[3]

We chose 17α-ethynyl-19-nortestosterone (norethindrone) for our molecular modifications because it had exhibited antifertility activity in both animals and humans. The 17β-hydroxyl group was acylated by the known procedures[5-7] and converted to the oximino compounds (Table I) by the method described in the Experimental Section. Beckmann rearrangement of the free oxime gave the desired 3-aza-17α-ethynyl-17β-acetoxy-19-nor-*A*-homoandrost-4a-en-4-one (Scheme I).

Scheme I



The progestational response of these compounds was determined by the Clauberg test[8] after oral administration and the endometrial response was scored according to the index of McPhail.[9] Table II presents the response obtained with all the compounds. Norethindrone **1** and its acetate **2** are included for comparative purposes. On a milligram basis it appears that **2** is about 2.5 times as potent as the parent compound **1**. However, when **2** is converted to an oxime the activity drops 2.5-fold and is comparable to **1**. Most of the other oximino steroids do not increase progestational potency probably due to the fact that bulky substitutions at C-3 and C-17 prevent adsorption to the receptor. An exception to this is **8**. The THP ether group probably undergoes spontaneous hydrolysis to **3** which, in fact, is responsible for the observed activity.

A strikingly dissimilar activity of a ketone and its oximino derivative was observed when the compounds were tested for their antilittering activity. In this test the compound is administered in the diet or by gavage for 7 days to both male and female rats with sexes segregated. The treatment is continued for 15 days during which time the rats are permitted to cohabit freely. The sexes are once again segregated and are observed for 21 days with no treatment. A control group is similarly treated except that the compound is not administered. The females from both the control and the treated groups are observed for pregnancies and the size of litters. A minimum effective dose (MED) is then computed and is defined as the amount of compound in milligrams per kilogram per day which completely suppresses the production of litters.

The data thus obtained on compounds **1-14** are tabulated in Table III. The relative potency of the steroids is expressed in terms of the standard, norethindrone **1**. As observed earlier in the Clauberg test, an introduction of an acetate group at the C-17 position increases the activity by eightfold (compound **2**). However, contrary to the progestational data the conversion of the ketone to an oximino derivative (**3-13**) markedly enhances the antifertility activity. A 137-fold increase over norethindrone suggests that the mechanism of action of these compounds is vastly different. The data in Table III also suggest that there may be a different receptor involved and that the sterochemical requirements of a steroid to bind are different from those required to elicit progestational response. The oximino steroids may be acting postcoitally.