amido-3′-deoxyisoguanosine (TLC) 60 mg. Evaporation of the water layer from the reaction mixture gave a solid residue which was triturated with methanol (2 × 25 ml). Evaporation of the methanol gave a solid which was chromatographed on a silica gel column using $CHCl_3$–MeOH (9:1) as eluent: yield of white solid 81 mg (17%); mp 248–250° dec; λ_{max} in nm ($\epsilon \times 10^{-3}$) 0.1 *N* HCl 262 (20.1), 268 sh; λ_{max} in nm ($\epsilon \times 10^{-3}$) pH 7 buffer and 0.1 *N* NaOH 262 (22.2), 268 sh; ^{1}H NMR (DMSO-d_6) δ 1.95 (s, Me of Ac), 3.65 (m, $H_{5'}$), 4.0 (m, $H_{4'}$), 4.45 (m, $H_{3'}$ and $H_{2'}$), 5.05 (t, OH at $C_{5'}$), 5.9 (d, $J_{1'2'}$ = 2.3 Hz, $H_{1'}$), 5.95 (d, OH at $C_{2'}$), 7.8 (br s, NH_2), 7.9 (d, NH), 8.4 ppm (s, H_8). *Anal.* ($C_{12}H_{15}FN_6O_4 \cdot 0.25\ H_2O$) C, H, N.

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2-Aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazines, a New Class of Antidepressants

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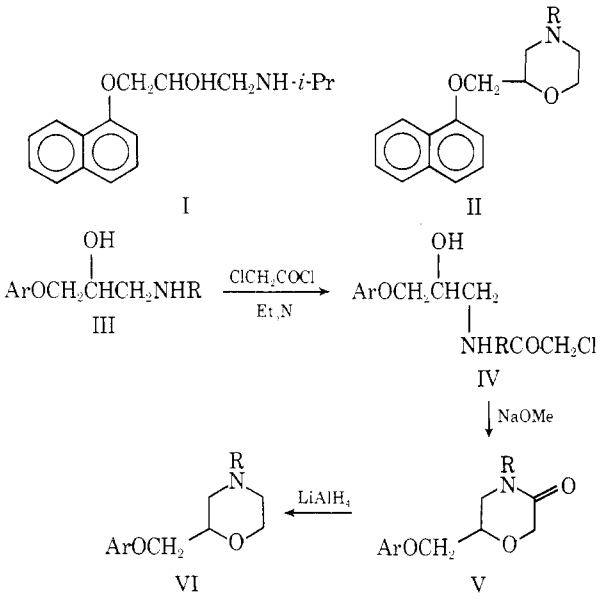
Some 2-aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazines have been shown to possess marked antidepressant activity. The 1,4-oxazines were synthesized by lithium aluminum hydride reduction of the readily available 6-aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazin-3-ones. High antidepressant activity was associated with ortho substitution of the 2-phenoxymethyl group and with 1,4-oxazines devoid of 4-substituents.

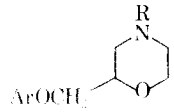
Effects on the central nervous system have been reported to be produced by the β-receptor blocking drug propranolol (I).[1,2] During a research program investigating the central nervous system properties of chemical structures related to the aryloxypropanolamines III, a number of 2-(naphthoxymethyl)-2,3,5,6-tetrahydro-1,4-oxazines II were synthesized and shown to possess potent antidepressant properties. This observation led us to synthesize a wide variety of 2-aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazines and evaluate more fully their biological activity.[3]

Syntheses. The tetrahydrooxazines (VI) were conveniently synthesized from the propanolamines III.[5-7] Treatment of III with chloroacetyl chloride under basic conditions gave the amides IV, which were readily cyclized utilizing sodium methoxide to produce the lactams V. The 1,4-oxazin-3-ones when crystalline were isolated and the compounds characterized are listed in Table II. The yields of the 1,4-oxazinones based on the propanolamines were in the 40–60% range. Lithium aluminum hydride reduction of these lactams gave the required tetrahydrooxazines in 30–60% yield. The chloroacetylation stage also produced some O-acylated product, but the ester was readily removed by acid treatment. The secondary amines VI (R = H) could also be prepared in this way starting with the primary amines III (R = H), but better yields (20% overall based on propanolamine) were obtained by preparing the N-benzylated compound VI (R = $PhCH_2$–) and then removing the benzyl group by hydrogenolysis. The N-benzylated propanolamines III (R = $PhCH_2$–) were conveniently prepared from benzylamine and 3-aryloxypropylene oxides. The



amines when crystalline were characterized and are listed in Table III. As an alternative to hydrogenolysis the benzyl group could be removed by treatment with ethyl chloroformate followed by alkaline hydrolysis of the *N*-ethoxycarbonyl derivative.[4] The *o*-allylphenoxymethyl compound VI (Ar = *o*-allylphenyl; R = H) was prepared via the N-benzylated derivative using the ethyl chloroformate–alkali fis-

Table I



Compd	Ar	R	Salt	Mp, °C	Empirical formula	Analyses[a]	Reserpine antag, ED_{10}, mg/kg po	Redn in locomotive act., min effective dose, mg/kg po	Anticonvulsant act., ED_{50}, mg/kg po
1	1-Naphthyl	*i*-Pr	Hydrogen oxalate[a]	143–145	$C_{18}H_{23}NO_2 \cdot C_2H_2O_4$	C, H, N	10–30	10	100
2	5-Tetralinyl	*i*-Pr	Hydrogen oxalate[c]	166–168	$C_{18}H_{27}O_2N \cdot C_2H_2O_4$	C, H, N	10	30	
3	4-Indanyl	*i*-Pr	Hydrogen oxalate[d]	134–138	$C_{17}H_{25}O_2N \cdot C_2H_2O_4$	C, H, N	30–100	100	
4	Phenyl	*i*-Pr	Hydrogen oxalate[c]	141–142	$C_{14}H_{21}O_2N \cdot C_2H_2O_4$	C, H, N	10		
5	2-Ethoxyphenyl	*i*-Pr	Hydrochloride[a]	158–160	$C_{16}H_{25}O_3N \cdot HCl$	C, H, N, Cl	10		
6	2-Allyloxyphenyl	*i*-Pr	Hydrogen oxalate[c]	132–134	$C_{17}H_{25}O_3N \cdot C_2H_2O_4$	C, H, N	3	3–10	100
7	2-Chlorophenyl	*i*-Pr	Hydrogen oxalate[c]	117–118	$C_{14}H_{20}O_2NCl \cdot C_2H_2O_4$	C, H, N, Cl	1–3	10	
8	3,4-Methylenedioxyphenyl	*i*-Pr	Hydrogen oxalate[c]	157–159	$C_{18}H_{21}O_4N \cdot C_2H_2O_4$	C, H, N	30		
9	3-Trifluoromethylphenyl	*i*-Pr	Hydrogen oxalate[c]	134–136	$C_{15}H_{20}O_2NF_3 \cdot C_2H_2O_4$	C, H, N, F	30–100	30	75
10	3-Tolyl	*i*-Pr	Hydrochloride[a]	174–175	$C_{15}H_{23}NO_2 \cdot HCl$	C, H, N, Cl	Inactive, 100	3	100
11	4-Biphenyl	*i*-Pr	Hydrogen oxalate[c]	180–181	$C_{20}H_{25}O_2N \cdot C_2H_2O_4$	C, H, N	10		
12	1-Naphthyl	Benzyl	Hydrochloride[b]	230	$C_{22}H_{23}O_2N \cdot HCl$	C, H, N	Inactive, 100		Inactive, 100
13	1-Naphthyl	Allyl	Hydrogen oxalate[b]	210–212	$C_{18}H_{21}O_2N \cdot C_2H_2O_4$	C, H, N	30–100		
14	1-Naphthyl	Cyclopentyl	Hydrogen oxalate[c]	163–165	$C_{20}H_{25}O_2N \cdot C_2H_2O_4$	C, H, N	10–30	100	
15	1-Naphthyl	CH_3	Hydrogen oxalate[c]	180–182	$C_{16}H_{19}O_2N \cdot C_2H_2O_4$	C, H, N	10–30		
16	1-Naphthyl	H	Hydrogen oxalate[c]	160–162	$C_{15}H_{17}O_2N \cdot C_2H_2O_4$	C, H, N	10		
17	2-Methoxyphenyl	H	Oxalate[d]	192–194	$(C_{12}H_{17}O_3N)_2 \cdot C_2H_2O_4$	C, H, N	1–3	3	100
18	2-Ethoxyphenyl	H	Hydrogen oxalate[c]	106–108	$C_{13}H_{19}O_3N \cdot C_2H_2O_4$	C, H, N	0.3	3	30
19	2-*n*-Propoxyphenyl	H	Hydrogen oxalate[d]	133–135	$C_{14}H_{21}O_3N \cdot C_2H_2O_4$	C, H, N	0.3	3	30–100
20	2-Isopropoxyphenyl	H	Hydrogen oxalate[c]	98–103	$C_{14}H_{21}O_3N \cdot C_2H_2O_4$	C, H, N	3	10	

21	2-Allyloxyphenyl	H	Hydrogen oxalate[d]	115–118	$C_{14}H_{19}O_3N \cdot C_2H_2O_4$	C, H, N	0.3	10	30
22	2-Phenoxyphenyl	H	Oxalate[c]	159–161	$(C_{17}H_{19}O_3N)_2 \cdot C_2H_2O_4$	C, H, N	0.3	3	100
23	2-*n*-Heptoxyphenyl	H	Hydrogen oxalate[c]	97–99	$C_{18}H_{29}O_3N \cdot C_2H_2O_4$	C, H, N	10	10	
24	2-Tolyl	H	Hydrogen oxalate[c]	117–120	$C_{12}H_{17}O_2N \cdot C_2H_2O_4$	C, H, N	1–3	3	
25	2-Allylphenyl	H	Hydrogen oxalate[d]	87–94	$C_{14}H_{19}O_2N \cdot C_2H_2O_4$	C, H, N	1	3	30–100
26	2-Chlorophenyl	H	Hydrogen oxalate[d]	144–147	$C_{11}H_{14}O_2NCl \cdot C_2H_2O_4$	C, H, N, Cl	3	10	
27	4-Methoxyphenyl	H	Hydrogen oxalate[c]	146–149	$C_{12}H_{17}O_3N \cdot C_2H_2O_4$	C, H, N	10–30	10	100
28	3-Methoxyphenyl	H	Hydrogen oxalate[c]	159–161	$C_{12}H_{17}O_3N \cdot C_2H_2O_4$	C, H, N	Inactive, 100	10	
29	2,6-Dimethoxyphenyl	H	Hydrogen oxalate[c]	153–156	$C_{13}H_{19}O_4N \cdot C_2H_2O_4$	C, H, N	10		
30	2-Hydroxyphenyl	H	Free base[c]	157–158	$C_{11}H_{15}O_3N$	C, H, N	10–30		
31	4-Acetamidophenyl	*i*-Pr	Hydrochloride[c]	210–214	$C_{16}H_{24}O_3N_2 \cdot HCl$	C, H, N	30–100		

[a] Recrystallized from butyl acetate. [b] Recrystallized from methanol. [c] Recrystallized from methanol–ethyl acetate. [d] Recrystallized from methanol–diethyl ether. [e] All compounds analyzed within ±0.4% of theory.

sion method, hydrogenolysis giving the *n*-propyl derivative. The *o*-chlorophenyl compound VI (Ar = *o*-chlorophenyl; R = H) was also prepared using this route, hydrogenolysis in this case removing the *o*-chloro group.

The *p*-acetamidophenoxymethyl derivative VI (R = *i*-Pr; Ar = *p*-acetamidophenyl) was prepared from the *p*-nitrophenoxypropanolamine III (R = *i*-Pr; Ar = *p*-nitrophenyl) by chloroacetylation and cyclization to the lactam by the general procedure, followed by reduction of the nitro group to amino by hydrogenation, reduction of the lactam to the tetrahydrooxazine with lithium aluminum hydride, and finally acetylation of the aromatic amino group with acetic anhydride.

Biological Assay Results. Each compound was tested in mice (males, 18–21 g of the Alderley Park, No. 1, specific pathogen free strain) for potential antidepressant, sedative, and anticonvulsant activity. Compounds were administered orally in logarithmically increasing doses in 0.5 ml of an aqueous solution or, in the case of less soluble compounds, as a ball-milled dispersion in an inert suspending agent. Throughout, control animals received 0.5 ml of the respective vehicle alone.

Antidepressant activity was assessed by the ability to reverse reserpine-induced hypothermia.[8] Groups of six mice were pretreated with reserpine (2 mg of base/kg subcutaneously) and 17 hr later with the test compound. Gastric temperatures were recorded immediately before dosing with the test compound (t0) and at intervals of 2, 4, and 6 hr thereafter (t2, t4, and t6). The cumulative temperature rise (T) was then calculated according to the formula: T = (t2 + t4 + t6) − 3 t0. For convenience in comparing the calorigenic activity of the different compounds, the minimum dose of each which produced a cumulative temperature difference of 10° greater than the controls has been defined as the ED_{10}.

Sedative activity was measured in groups of ten mice housed singly in photobeam cages. The number of beam interruptions occurring during the 60-min periods immediately prior to and after dosing was recorded and the expression log (counts after dosing/counts before dosing) calculated for both treated and control groups. The significance of any observed difference in locomotor activity as measured by this technique was assessed by means of the Student's t test.

Anticonvulsant activity was determined in groups of ten mice 2 hr after administration of the test compound. Each animal was subjected to a constant current of 20 mA for 0.33 sec and ED_{50}'s were calculated by log–probit analysis from the number of mice which were protected.

Structure–Activity Relationships. The compound derived from propranolol (1) in Table III showed antireserpine activity at 10–30 mg/kg compared with a score of 5–10 mg/kg exhibited by the widely used antidepressant drug, amitriptyline. The 1-tetralin and phenyl derivatives (**2** and **4**) had increased activity whereas the indan **3** had reduced activity. Very high activity was shown by the ortho-substituted phenyl compounds, the *o*-chlorophenyl derivative **7** displaying activity at 1–3 mg/kg. Replacement of the 4-isopropyl group in **1** by other alkyl groups and hydrogen demonstrated that the highest activity in the series of compounds **12–16** was found in the secondary amine **16.**

Synthesis of ortho-substituted phenyl derivatives with no N-substituent produced the extremely active compounds **17–26,** some of which showed activity at 0.3 mg/kg. The activity enhancement produced by an ortho substituent in the phenyl ring was demonstrated by comparing the activities of the ortho, meta, and para isomers, **17, 27,** and **28.** Surprisingly, the 2,6-dimethoxyphenyl compound **29** possessed lower activity (10 mg/kg) than **17,** indicating that

further ortho substitution is detrimental to activity.

The *o*-ethoxyphenyl derivative **18** which displayed antireserpine activity at 0.3 mg/kg has been processed for clinical trial evaluation. This compound in common with other active compounds in this series also reduced locomotor activity at 3 mg/kg and possessed anticonvulsant action at 30 mg/kg against convulsions induced electrically in mice.[9] Initial clinical trial results with **18**, trademark Vivalan, have been encouraging.[10,11]

Experimental Section

All melting points are uncorrected. The NMR spectra were taken on a Varian HA-100D and the mass spectra analyses were performed on a Hitachi Perkin-Elmer RMU-6E machine. All spectra for compounds listed in Table I were consistent with the assigned structure.

2-Aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazines (VI, R = alkyl, H). The same general route, which is exemplified for the case of compound **1** in Table I, was used for the tertiary amines 1–15 and the secondary amines **20** and **21**. The starting materials, the 3-aryloxy-2-hydroxypropylamines, were prepared from the phenols and epichlorohydrin followed by treatment of the resultant epoxide with an amine.[5-7] The 1,4-oxazinones which were characterized are listed in Table II.

4-Isopropyl-6-(naphth-1-yloxymethyl)-2,3,5,6-tetrahydro-1,4-oxazin-3-one. A solution of 1-isopropylamino-3-(naphth-1-yloxy)propan-2-ol (7.5 g, 0.03 mol) in ethylene chloride (150 ml) was added to a solution of sodium hydroxide (12 g) in water (60 ml). The mixture was cooled to −5° and was vigorously stirred. Chloroacetyl chloride (2.5 ml, 0.03 mol) was added dropwise over a period of 30 min, the temperature being kept below 0°, and then the mixture was stirred at room temperature for 3 hr. The organic phase was separated, washed with 10% aqueous hydrochloric acid and then with water, and evaporated. The resultant oil (8.6 g) in anhydrous methanol (100 ml) was added to a solution of sodium (0.6 g) in anhydrous methanol (100 ml) and the mixture was refluxed for 6 hr. The mixture was evaporated and partitioned between 10% aqueous hydrochloric acid and ether. Evaporation of the ether furnished 3.5 g (40%) of the oxazin-3-one, colorless prisms (from petroleum ether, bp 80–100°).

4-Isopropyl-2-(naphth-1-yloxymethyl)-2,3,5,6-tetrahydro-1,4-oxazine (1). A mixture of 4-isopropyl-6-(naphth-1-yloxymethyl)-2,3,5,6-tetrahydro-1,4-oxazin-3-one (2.0 g, 0.007 mol), lithium aluminum hydride (0.5 g, 0.014 mol), and dry ether (100 ml) was refluxed for 6 hr. Ethyl acetate (100 ml) was added and the mixture was refluxed for 10 min. Water was added and the organic phase separated and dried. A 1% ethereal solution of oxalic acid was added to the crude oxazine which was isolated as the hydrogen oxalate (1.6 g, 65%): colorless prisms (*n*-butyl acetate); mp 143–145°.

2-Aryloxymethyl-2,3,5,6-tetrahydro-1,4-oxazines (VI, R = H). Compounds **16–19, 22–24,** and **27–30** were conveniently prepared from the N-benzylated 1,4-oxazines by hydrogenolysis as exemplified for compound **16.** Compounds **25** and **26** were synthesized from the N-benzylated 1,4-oxazines by the ethyl chloroformate–alkali fission method[4] as exemplified for compound **26.** The N-benzylated 1,4-oxazines were prepared by the method described for compound **1.** In general, the intermediate N-benzylated 1,4-oxazin-3-ones V (R = $PhCH_2$–) and the N-benzylated 1,4-oxazines were not isolated and characterized. The N-benzylated propanolamines which were characterized are listed in Table III.

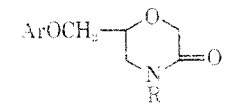
2-(Naphth-1-yloxymethyl)-2,3,5,6-tetrahydro-1,4-oxazine (16). A solution of **12** free base (1.75 g) in concentrated hydrochloric acid (0.5 ml) and ethanol (40 ml) was hydrogenated at atmospheric pressure using a 5% palladium–charcoal catalyst (0.75 g). Filtration and evaporation gave the hydrochloride, which was converted to the hydrogen oxalate (1.1 g, 60%): mp 160–162° (from methanol–ethyl acetate).

2-(2-Chlorophenoxymethyl)-2,3,5,6-tetrahydro-1,4-oxazine (26). 4-Benzyl-2-(2-chlorophenoxymethyl)-2,3,5,6-tetrahydro-1,4-oxazine (6.5 g, 0.02 mol) and ethyl chloroformate (2.0 ml, 0.02 mol) in benzene solution (100 ml) were refluxed for 5 hr. The solvent was removed and the residue was refluxed 2 days with 10% methanolic potassium hydroxide solution (100 ml). The methanol was removed and the residue was partitioned between ether and water. The ether phase was extracted with 2 *N* hydrochloric acid and the acid extract after basification and ether extraction gave the *oxazine*, which was converted to the hydrogen oxalate (4.0 g, 60%): colorless prisms; mp 144–147° (from ethanol–ether).

2-(4-Aminophenoxymethyl)-4-isopropyl-2,3,5,6-tetrahydro-1,4-oxazine. 4-Isopropyl-6-(4-nitrophenoxymethyl)-2,3,5,6-tetrahydrooxazin-3-one was prepared as an oil in the usual manner from 1-isopropylamino-3-(4-nitrophenoxy)propan-2-ol. The oxazin-3-one (3.0 g) was hydrogenated at atmospheric pressure in absolute ethanol (150 ml) over 5% Pd/C (1.5 g) for 3.5 hr. The catalyst was filtered off and washed with 20% triethylamine in ethanol (50 ml). The total filtrate was evaporated and the residue, dissolved in ethyl acetate (100 ml), was extracted with 2 *N* HCl. The aqueous layer was made alkaline and extraction with ethyl acetate furnished the 6-(4-aminophenoxymethyl)-2,3,5-6-tetrahydrooxazin-3-one (2.24 g, 80%) as a crude solid. This oxazinone in dry ether (200 ml) was added to lithium aluminum hydride (0.9 g, 0.024 mol) in ether (30 ml) and the mixture refluxed for 24 hr. The cooled mixture was treated with 20% Rochelle salt solution (50 ml) and the ether layer separated. The aqueous layer was further extracted with ethyl acetate and the combined organic extracts were evaporated to give the *oxazine* (1.2 g, 51%) as a colorless oil.

2-(4-Acetamidophenoxymethyl)-4-isopropyl-2,3,5,6-tetrahydro-1,4-oxazine (31). The 4-aminophenoxymethyl-2,3,5,6-tetrahydrooxazine (4.98 g, 0.02 mol) in dry ethanol (50 ml) was treated dropwise with acetic anhydride (2.5 ml, 0.025 mol) at room temperature over a period of 10 min. After stirring for 30 min, the solvent was removed in vacuo and the residue partitioned between ethyl acetate and 2 *N* HCl. The aqueous layer was made alkaline and extracted with ethyl acetate. The resultant crude base was converted to its hydrochloride (1.08 g, 17%): mp 210–214° (methanol–ethyl acetate–hexane).

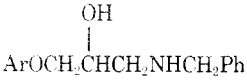
Table II



Ar	R	Mp, °C[a]	Empirical formula	Analyses
1-Naphthyl	*i*-Pr	110.5–111.5	$C_{18}H_{21}O_3N$	C, H, N
1-Naphthyl	Benzyl	86–89	$C_{22}H_{21}O_3N$	C, H, N
1-Naphthyl	Allyl	113–114	$C_{18}H_{19}O_3N$	C, H, N
1-Naphthyl	Me	105–107	$C_{16}H_{17}O_3N$	C, H, N
3-Tolyl	*i*-Pr	75–77	$C_{15}H_{21}O_3N$	C, H, N

[a] Compounds recrystallized from petroleum ether, bp 100–120°.

Table III



Ar	Mp, °C[a]	Empirical formula	Analyses
2-Ethoxyphenyl	77–79	$C_{18}H_{23}O_3N$	C, H, N
2-Allyloxyphenyl	87–90	$C_{19}H_{23}O_3N$	C, H, N
2-Methoxyphenyl	89–92	$C_{17}H_{21}O_3N$	C, H, N
4-Methoxyphenyl	97–99	$C_{17}H_{21}O_3N$	C, H, N
2-Tolyl	80–82	$C_{17}H_{21}O_2N$	C, H, N

[a] Compounds recrystallized from benzene–petroleum ether, bp 60–80° mixtures.

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3,4-Dihydro-1*H*-1,4-oxazino[4,3-*a*]indoles as Potential Antidepressants

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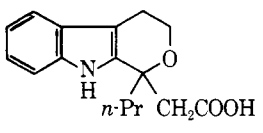
A series of 3,4-dihydro-1*H*-1,4-oxazino[4,3-*a*]indoles bearing basic side chains has been synthesized by a novel chemical process. These compounds have been screened for potential antidepressant activity. One of these derivatives, 3,4-dihydro-1,10-dimethyl-1-(3-methylaminopropyl)-1*H*-1,4-oxazino[4,3-*a*]indole (AY-23,673), was particularly potent in the prevention of reserpine ptosis test in mice, with an ED_{50} of 0.5 mg/kg ip.

Recent reports from this laboratory have described novel synthetic routes to pyrano- and thiopyrano-fused indolic systems which have led to the development of prodolic acid† (**1**), an antiinflammatory agent,[1] and tandamine hydrochloride† (**2**), a potential antidepressant.[2] This report describes the synthesis and antidepressant properties of a series of compounds containing the 3,4-dihydro-1*H*-1,4-oxazino[4,3-*a*]indole system **3** and bearing basic side chains attached at position 1.



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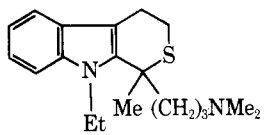

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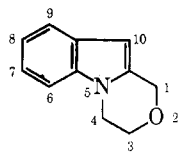

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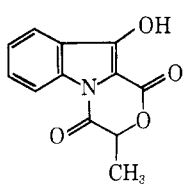
Chemistry. The only reported syntheses of oxazino[4,3-*a*]indoles are the preparation of **4** in 1949[3] and of **5** in 1952.[4] The synthetic routes used in those studies are not suitable for the synthesis of the types of derivatives described in this report. In the present investigation we have utilized a reaction whose potential for the formation of α,α-disubstituted pyrano rings was first recognized in our laboratory.[5] It involves the acid-catalyzed intramolecular



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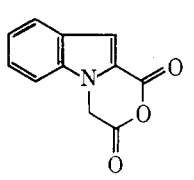

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alkylation of an aryl ring by a hemiketal formed in situ from an arylethanol and a carbonyl component. Its application to the synthesis of 1,1-disubstituted 3,4-dihydro-1*H*-1,4-oxazino[4,3-*a*]indoles is illustrated in Scheme I. The 3-methyl- and 3-ethylindole-1-ethanols (**6** and **7**, respectively) were allowed to react with the appropriate keto ester in benzene with *p*-toluenesulfonic acid as catalyst, followed directly by hydrolysis, to afford the 1,10-dialkyl-1-alkanoic acids **8–12** which are described in detail in Table I. The required indole-1-ethanol **6** was obtained from the readily available 3-methylindole and ethylene oxide, while **7** was prepared from the reaction of 3-ethylindole[6] with ethyl bromoacetate, followed by reduction of the resulting 1-acetic acid derivative with lithium aluminum hydride (see Experimental Section).

The five alkanoic acids **8–12** were ultimately transformed to the 23 basic derivatives **38–60** collected in Table III. Thus, the amides **13–30** were prepared from the corresponding alkanoic acids by conversion to the mixed anhydrides with ethyl chloroformate followed by reaction with the appropriate amine. The amides were reduced, either directly with lithium aluminum hydride (path A) or, in one case, via sodium borohydride reduction[7] of the ethoxyiminium salt **31** derived from amide **23** with triethyloxonium fluoroborate. Some of the basic compounds were best prepared from the acids via the intermediate alcohols **32** and **33**, tosylates **34** and **35**, and iodides **36** and **37** (path B). The intermediates **32–37** were characterized by spectroscopy and, with the exception of **37**, were obtained as oils. Reaction of these iodides with the appropriate amines afforded the required basic compounds.

Chemical data on the compounds referred to in Scheme I as well as definitions of the range of the variables R_1–R_4 and n are collected in Tables I–III and some detailed reaction conditions are given in the Experimental Section.

Pharmacology. The 23 compounds listed in Table III were investigated as antidepressant agents. The results are shown in Table III along with the activities of two standard antidepressants, amitriptyline (**61**) and imipramine (**62**). Acute toxicity was investigated ip in albino mice. Graded doses of the compounds were administered to groups of five animals each. The approximate LD_{50} was determined from the 5-day mortality data. Prevention of reserpine-induced ptosis was estimated by an adaptation of the method of Petersen et al.[8] The percentage of mice in which ptosis was prevented was recorded. The ED_{50} was determined according to the method of Finney.[9]

† Nonproprietary names adopted by the USAN Council.