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1-Substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles with Central Nervous System Depressant Activity

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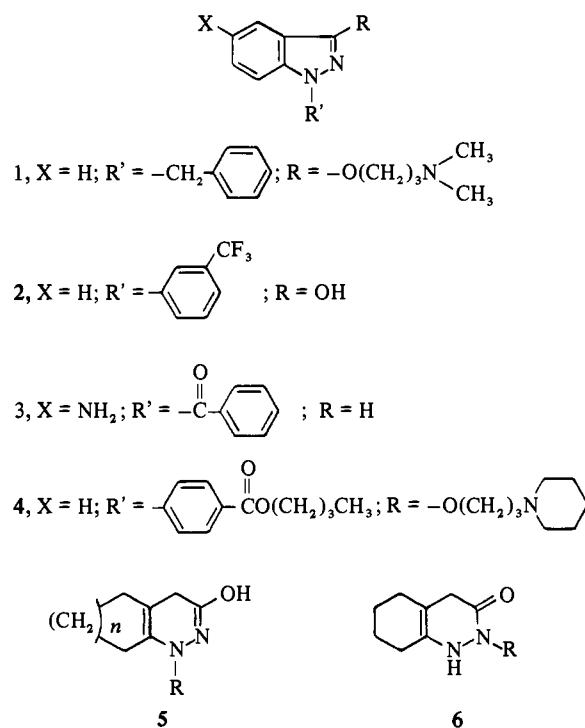
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Various 1-substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles were prepared by alkylation of the 1-substituted-3-hydroxy-4,5-cycloalkylpyrazoles (5). The latter compounds were accessible by recently revealed procedures. The title compounds were prepared because of their relationship to Benzydamine (1), which has interesting antiinflammatory properties. The 1-aryl compounds, however, showed CNS depressant profiles, while the 1-benzyl compounds more analogous to 1 were devoid of both CNS and antiinflammatory activity. Thus, of the 1-aryl compounds, 8 and 14 showed marked depressant effects in the jiggle cage test at doses well separated from those that caused neurological deficit.

There is still clinical interest in the antiinflammatory properties of Benzydamine (1), 1-benzyl-3-[3-(dimethylamino)propoxy]indazole, particularly as it is exceptionally well tolerated even in patients who already have a history of serious gastric disorders.¹ There is considerable interest generally in indazoles as potential antiinflammatory drugs, e.g., 2,² 3,³ 4.⁴ Therefore, as the related tetrahydroindazoles, i.e., 1-substituted-3-alkoxytetrahydroindazoles, were undescribed, we chose to investigate them in the hope of encountering a new type of antiinflammatory compound. A recent account⁵ of work on the tetrahydrocyclopentapyrazole system was based on somewhat similar reasoning, and this effort was, like ours, unsuccessful in the search for a novel antiinflammatory compound. We did, however, encounter quite a good level of selective CNS depression in the compounds which we now report.

Chemistry. Prior to our work,⁶ a specific synthesis of 1-aryl(or alkyl)-3-hydroxy tetrahydroindazoles (5, $n = 2$) had not been described. However, an alternate route to these long-neglected isomers 5 of the well-investigated 2-aryl(or alkyl)pyrazolones 6 has recently been published.^{7,8} All the 1-substituted-3-hydroxy-4,5-cycloalkylpyrazoles (5, $n = 1, 2$, and 3; R = aryl, benzyl) used in this investigation were generally prepared as described previously,⁶ i.e., by cyclization of appropriate *N*-substituted-2-chlorocycloalkene-1-carboxylic acid hydrazides (see Table I). O-Alkylation of 5b ($n = 2$; R = C₆H₅CH₂) with 3-chloro-*N,N*-dimethylpropylamine to prepare the tetrahydro analog 18 of Benzydamine (1) proceeded well and without evidence of any competitive *N*-alkylation (see Table II).

Pharmacology. The new compound 18 was devoid of



significant antiinflammatory properties (e.g., in the carrageenin paw test) and was inactive in our preliminary CNS screen. However, in order to explore the structure-activity possibilities of this new molecule, the *N*-phenyltetrahydroindazole 5a was prepared and O-alkylated with 3-chloro-

Table I^a

Compd	R	n	Yield, %	Mp, °C	Formula
5a	C ₆ H ₅	2	53	207	C ₁₃ H ₁₄ N ₂ O
5b	C ₆ H ₅ CH ₂	2	35	182	C ₁₄ H ₁₆ N ₂ O
5c	<i>p</i> -ClC ₆ H ₄	2	36 ^b	217	C ₁₃ H ₁₃ ClN ₂ O
5d	<i>o</i> -OCH ₂ C ₆ H ₄	2	33 ^c	210	C ₁₄ H ₁₆ N ₂ O ₂
5e	<i>p</i> -CH ₃ C ₆ H ₄	2	44	216	C ₁₄ H ₁₆ N ₂ O
5f	C ₆ H ₅	1	11.4 ^b	261	C ₁₂ H ₁₂ N ₂ O
5g	C ₆ H ₅	3	23 ^d	223	C ₁₄ H ₁₆ N ₂ O

^aAll compounds listed above were crystallized from ethanol. ^bRefluxing 10 mmoles of hydrazide of 2-chlorocyclohexene-1-carboxylic acid for 20 hr in 25 g of naphthalene and 2.5 ml of quinoline. ^cRefluxing 31 mmoles of 2-chlorocyclopentene-1-carboxylic acid phenylhydrazide for 2 hr in 26 ml of quinoline. ^dRefluxing 67 mmoles of crude phenylhydrazide of 2-chlorocycloheptene-1-carboxylic acid in 90 ml of quinoline for 2.5 hr.

N,N-dimethylpropylamine. The product 19 from the above alkylation process showed a marked depressant effect in mice, in the jiggle cage, after subcutaneous administration of 75 mg/kg. This observation was deserving of follow-up (see Tables II and III). Shortening the side chain by alkylation of 5a with 2-chloro-*N,N*-dimethylethylamine yielded compound 9 which now showed marked depression after oral administration (see Table III). A branched ethyl chain, as in compound 10, gave a less interesting compound. Preparation of compounds with basic side chains containing amines other than dimethylamino, *e.g.*, compounds 11, 12, and 13, was also unrewarding. For while compound 13 showed marked effects orally at 75 mg/kg there was evidence of neurotoxicity in the mice at a dose of only 300 mg/kg po. Substitution of the *N*-aryl group by *p*-chloro, as in compound 14, yielded one of the most interesting compounds of the series. The other compound of interest was the monoethylamino compound 8. Both compounds 14 and 8 were selected for further investigation in neuro-

and psychopharmacological testing procedures. Details of these results will be published elsewhere.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated in Tables I and II and the following text by the symbols of the elements, analytical results obtained for these elements were within $\pm 0.3\%$ of the theoretical values.




Biological Methods. In the studies described in Table II, mature male albino CF₁ mice were used. Drugs were administered in aqueous solutions or methyl cellulose suspensions at a fixed volume of 0.20 ml/20 g body weight. Concentration varied with the dose of drug to be administered.

Spontaneous motor activity of mice was recorded utilizing a modification of the jiggle-cage apparatus first described by Schulte, *et al.*⁹ A spring-suspended, circular, wire-mesh cage (10-cm diameter, 9-cm height) was attached to a Grass FT-03 force-displacement transducer. The electrical impulses generated by the animals' movements were transmitted *via* a Grass Model 7P1A low-level DC pre-amplifier and a Grass Model 7DAB DC driver amplifier to a Grass Model 7 polygraph. Chart speed was 0.25 mm/sec. Most consistent results were obtained when three animals were placed in each cage and allowed 1 hr to adapt to this environment before injection. Activity was monitored for 2 hr and the record obtained was visually compared with that of control animals tested concurrently in another cage.

A profile of the drug effect was determined by the method introduced by Irwin¹⁰ and modified as previously reported.¹¹ At least three doses of the drug, three animals per dose, were tested. Animals were housed in individual 10-cm cube cages. Numerous neurological and behavioral evaluations were made at 15-min intervals during the 2-hr test period. Grading scales were incorporated to allow quantitation of the drug effects.

Chemical Procedures. Procedure A. A solution of 3 g of 1-benzyl-3-hydroxytetrahydroindazole (5, R = CH₂C₆H₅) in 40 ml of DMF was treated with 650 mg of NaH (55% washed three times with ether) in 10 ml of DMF. After 1 hr stirring at room temperature, the enolate salt formation was complete. Then a solution of 2.1 g of 3-chloro-*N,N*-dimethylpropylamine in 25 ml of toluene was added, and the reaction mixture was stirred for 20 hr at 60°. The reaction mixture was diluted with ether and washed twice with ice-cold water. After drying (Na₂SO₄) and evaporating the solvent, the

Table II

Compd	n	R	Alk	Am	Mp, °C	Procedure	Yield, %	Formula	Analysis	Uv, $\bar{m}\mu$ (ϵ)
7	2	C ₆ H ₅	CH ₂ CH ₂	NH ₂	199	A ^a	23	C ₁₅ H ₁₉ N ₃ O	C, H, N	263 (16,170)
8	2	C ₆ H ₅	CH ₂ CH ₂	NHCH ₃	197	B	63.5	C ₁₆ H ₂₁ N ₃ O	C, H, N	263 (16,140)
9	2	C ₆ H ₅	CH ₂ CH ₂	N(CH ₃) ₂	160	A	82	C ₁₇ H ₂₃ N ₃ O	C, H, N	264 (16,190)
10	2	C ₆ H ₅	CH ₂ CH(CH ₃)	N(CH ₃) ₂	95	A	69	C ₁₈ H ₂₅ N ₃ O	C, H, N	264 (16,710)
11	2	C ₆ H ₅	CH ₂ CH ₂		164	B	60	C ₁₉ H ₂₅ N ₃ O	C, H, N	263 (15,950)
12	2	C ₆ H ₅	CH ₂ CH ₂		174	B	36	C ₂₀ H ₂₇ N ₃ O	C, H, N	263 (15,700)
13	2	C ₆ H ₅	CH ₂ CH ₂		134	B	62	C ₂₁ H ₂₉ N ₃ O	C, H, N	262 (13,000)
14	2	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₂	N(CH ₃) ₂	183	A	75	C ₁₇ H ₂₂ ClN ₃ O	C, H, N	269 (20,800)
15	2	<i>o</i> -OCH ₂ C ₆ H ₄	CH ₂ CH ₂	N(CH ₃) ₂	168	A	49	C ₁₈ H ₂₅ N ₃ O ₂	C, H, N	279 (4900) 250 (17,120)
16	2	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ CH ₂	N(CH ₃) ₂	170	A	77	C ₁₈ H ₂₅ N ₃ O	C, H, N	263 (17,290)
17	2	CH ₂ C ₆ H ₅	CH ₂ CH ₂	N(CH ₃) ₂	167	A	70	C ₁₈ H ₂₅ N ₃ O	C, H, N	231 (8140)
18	2	CH ₂ C ₆ H ₅	CH ₂ CH ₂ CH ₂	N(CH ₃) ₂	143	A	79	C ₁₉ H ₂₇ N ₃ O	C, H, N	232 (8900)
19	2	C ₆ H ₅	CH ₂ CH ₂ CH ₂	N(CH ₃) ₂	157	A	77	C ₁₈ H ₂₅ N ₃ O	C, H, N	265 (15,640)
20	1	C ₆ H ₅	CH ₂ CH ₂	N(CH ₃) ₂	207	A	29	C ₁₆ H ₂₁ N ₃ O	C, H, N	268 (19,930)
21	3	C ₆ H ₅	CH ₂ CH ₂	N(CH ₃) ₂	159	A	50	C ₁₈ H ₂₅ N ₃ O	C, H, N	258 (12,450)

^a2-Bromoethylphthalimide was used as alkylating agent. The phthalimide-protecting group was removed with NH₂NH₂-CH₃OH.

Procedure A. Alkylation of the sodio derivative in DMF with the appropriate chloroalkylamine. Procedure B. Alkylation of the sodio derivative in DMF with the appropriate α -chloroacetic acid amide and reduction of the product with diborane in THF.

Table III

Compd	Jiggle-cage effect, ^a dose, mg/kg sc	Jiggle-cage effect, ^a dose, mg/kg po	Dosage range effect, ^a dose, mg/kg po
7	-3, 100 -2, 25	T, 200 -2, 50	
8	-3, 75 -2, 18.75	-3, 150 -2, 38	T, 600 +1, 150
9	-3, 75 -2, 18.75	-3, 150 0, 60	
10	-2, 75		
11	-3, 50 0, 12.5		
12	-3, 150 -2, 37.5	-2, 300	
13	-3, 150 -2, 37.5	T, 300 -3, 75 -2, 38	
19	-3, 75 0, 19		
16	T, 62 -2, 15		
14	-3, 100 -2, 25	-3, 200 -2, 50	T, 800 -1, 200
15	T, 75 0, 19		
20	-3, 100 0, 25		
21	-3, 100 -2, 25	-2, 200	

^a- = depression; 3 = marked; 2 = moderate; 1 = minimal; T = toxic; + = stimulation.

residue (4.2 g) was dissolved in ethanol and neutralized with anhydrous HCl to give 3.65 g of hydrochloride (mp 143°).

Procedure B. A solution of 3.5 g of 3-hydroxy-1-phenyltetrahydroindazole (16.3 mmoles) in 35 ml of DMF was treated for 1 hr with a suspension of 810 mg of NaH (55% washed with ether) in 15 ml of DMF. Then a solution of α -chloro-*N*-methylacetamide (1.2 equiv) was added with stirring, and the solution kept at 60° for 20 hr. After cooling, the mixture was diluted with ether, washed with water, and dried. Residue after evaporation of solvent was 4.2 g of solid amide.

The crude amide was dissolved in 60 ml of THF and added to a cold solution of borane (2.5 equiv) in THF. After refluxing for 3 hr, the solution was cooled, an excess of aqueous 5 *N* HCl was added, and the THF was distilled off at atmospheric pressure. The aqueous acidic layer was made basic, the product extracted into CH₂Cl₂, dried over Na₂SO₄, and evaporated. The residue was taken up in ethanol and neutralized with ethereal HCl to give 3.1 g of crystalline HCl salt (8), mp 197–99°; yield, 63.5% over 2 steps.

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Synthesis and Antiinflammatory Activities of α -Methylfluorene-2-acetic Acid and Related Compounds

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In a search for new nonsteroidal antiinflammatory agents, a series of fluoreneacetic acid derivatives was synthesized and evaluated in the carrageenin-induced edema assay. Fluorene-2-acetic acid (4) and α -methylfluorene-2-acetic acid (9) emerged as compounds with potent antiinflammatory activity. Structure-activity relationships within this series are discussed.

Recently, several reports concerning the synthesis and antiinflammatory activities of non-N-containing aryl acetic acids have appeared in the literature.¹⁻⁸ Our own efforts in this area have culminated in the synthesis of several compounds containing a fluorene ring as the aryl portion and possessing antiinflammatory activities. In fact, we first observed antiinflammatory activity in the carrageenin-induced

edema assay† with the known fluorene-2-acetic acid (4). This observation led us to prepare a series of monosubstituted fluorene derivatives in which the position of the acid side chain and the nature of the alkyl group on the benzylic side-chain carbon atom were varied. In addition, several

†Modification of the method described by Winters, *et al.*