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

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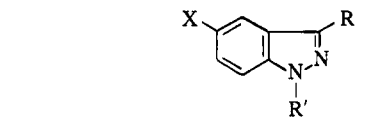
Various 1-substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles were prepared by alkylation of the 1-substituted-3-hydroxy-4,5-cycloalkylpyrazoles (**5**). The latter compounds were accessible by recently revealed procedures. The title compounds were prepared because of their relationship to Benzydamine (**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.

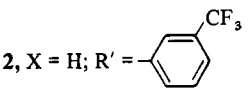
There is still clinical interest in the antiinflammatory properties of Benzydamine (**1**), 1-benzyl-3-[3-(dimethylamino)-propoxy]indazole, particularly as it is exceptionally well tolerated even in patients who already have a history of serious gastric disorders.[1] There is considerable interest generally 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 account[5] 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 = $C_6H_5CH_2$) 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).

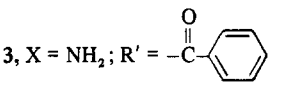
Pharmacology. The new compound **18** was devoid of



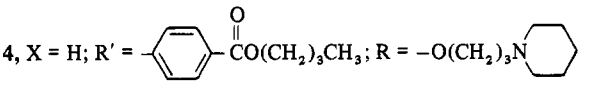
1, X = H; R′ = $-CH_2-C_6H_5$; R = $-O(CH_2)_3N(CH_3)_2$



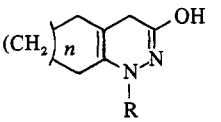
2, X = H; R′ = $3\text{-}CF_3C_6H_4$; R = OH



3, X = NH_2; R′ = $-CO-C_6H_5$; R = H



4, X = H; R′ = $4\text{-}CO(CH_2)_3CH_3C_6H_4$; R = $-O(CH_2)_3N$(morpholino)



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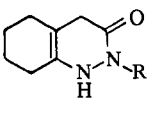

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significant antiinflammatory properties (*e.g.*, in the carrageenin paw test) and was inactive in our preliminary CNS screen. However, in order to explore the structure-activity possibilities of this new molecule, the *N*-phenyltetrahydroindazole **5a**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

Table I[a]

Compd	R	n	Yield, %	Mp, °C	Formula
5a	C_6H_5	2	53	207	$C_{13}H_{14}N_2O$
5b	$C_6H_5CH_2$	2	35	182	$C_{14}H_{16}N_2O$
5c	p-ClC_6H_4	2	36[b]	217	$C_{13}H_{13}ClN_2O$
5d	o-$OCH_3C_6H_4$	2	33[c]	210	$C_{14}H_{16}N_2O_2$
5e	p-$CH_3C_6H_4$	2	44	216	$C_{14}H_{16}N_2O$
5f	C_6H_5	1	11.4[b]	261	$C_{12}H_{12}N_2O$
5g	C_6H_5	3	23[d]	223	$C_{14}H_{16}N_2O$

[a] All compounds listed above were crystallized from ethanol. [b] Refluxing 10 mmoles of hydrazide of 2-chlorocyclohexene-1-carboxylic acid for 20 hr in 25 g of naphthalene and 2.5 ml of quinoline. [c] Refluxing 31 mmoles of 2-chlorocyclopentene-1-carboxylic acid phenylhydrazide for 2 hr in 26 ml of quinoline. [d] Refluxing 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 ±0.3% of the theoretical values.

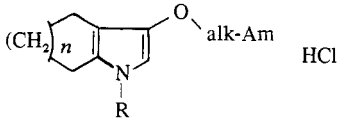
Biological Methods. In the studies described in Table II, mature male albino CF_1 mice were used. Drugs were administered in aqueous solutions or methyl cellulose suspensions at a fixed volume of 0.20 ml/20 g body weight. Concentration varied with the dose of drug to be administered.

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 preamplifier 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 Irwin[10] 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 = $CH_2C_6H_5$) 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 (Na_2SO_4) and evaporating the solvent, the

Table II



HCl

Compd	n	R	Alk	Am	Mp, °C	Procedure	Yield, %	Formula	Analysis	Uv, mμ (ε)
7	2	C_6H_5	CH_2CH_2	NH_2	199	A[a]	23	$C_{15}H_{19}N_3O$	C, H, N	263 (16,170)
8	2	C_6H_5	CH_2CH_2	$NHCH_3$	197	B	63.5	$C_{16}H_{21}N_3O$	C, H, N	263 (16,140)
9	2	C_6H_5	CH_2CH_2	$N(CH_3)_2$	160	A	82	$C_{17}H_{23}N_3O$	C, H, N	264 (16,190)
10	2	C_6H_5	$CH_2CH(CH_3)$	$N(CH_3)_2$	95	A	69	$C_{18}H_{25}N_3O$	C, H, N	264 (16,710)
11	2	C_6H_5	CH_2CH_2		164	B	60	$C_{19}H_{25}N_3O$	C, H, N	263 (15,950)
12	2	C_6H_5	CH_2CH_2		174	B	36	$C_{20}H_{27}N_3O$	C, H, N	263 (15,700)
13	2	C_6H_5	CH_2CH_2		134	B	62	$C_{21}H_{29}N_3O$	C, H, N	262 (13,000)
14	2	p-ClC_6H_4	CH_2CH_2	$N(CH_3)_2$	183	A	75	$C_{17}H_{22}ClN_3O$	C, H, N	269 (20,800)
15	2	o-$OCH_3C_6H_4$	CH_2CH_2	$N(CH_3)_2$	168	A	49	$C_{18}H_{25}N_3O_2$	C, H, N	279 (4900) 250 (17,120)
16	2	p-$CH_3C_6H_4$	CH_2CH_2	$N(CH_3)_2$	170	A	77	$C_{18}H_{25}N_3O$	C, H, N	263 (17,290)
17	2	$CH_2C_6H_5$	CH_2CH_2	$N(CH_3)_2$	167	A	70	$C_{18}H_{25}N_3O$	C, H, N	231 (8140)
18	2	$CH_2C_6H_5$	$CH_2CH_2CH_2$	$N(CH_3)_2$	143	A	79	$C_{19}H_{27}N_3O$	C, H, N	232 (8900)
19	2	C_6H_5	$CH_2CH_2CH_2$	$N(CH_3)_2$	157	A	77	$C_{18}H_{25}N_3O$	C, H, N	265 (15,640)
20	1	C_6H_5	CH_2CH_2	$N(CH_3)_2$	207	A	29	$C_{16}H_{21}N_3O$	C, H, N	268 (19,930)
21	3	C_6H_5	CH_2CH_2	$N(CH_3)_2$	159	A	50	$C_{18}H_{25}N_3O$	C, H, N	258 (12,450)

[a] 2-Bromoethylphthalimide was used as alkylating agent. The phthalimide-protecting group was removed with NH_2NH_2–CH_3OH. 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	T, 200	
	−2, 25	−2, 50	
8	−3, 75	−3, 150	T, 600
	−2, 18.75	−2, 38	+1, 150
9	−3, 75	−3, 150	
	−2, 18.75	0, 60	
10	−2, 75		
11	−3, 50		
	0, 12.5		
12	−3, 150	−2, 300	
	−2, 37.5		
13	−3, 150	T, 300	
	−2, 37.5	−3, 75	
		−2, 38	
19	−3, 75		
	0, 19		
16	T, 62		
	−2, 15		
14	−3, 100	−3, 200	T, 800
	−2, 25	−2, 50	−1, 200
15	T, 75		
	0, 19		
20	−3, 100		
	0, 25		
21	−3, 100	−2, 200	
	−2, 25		

[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 CH_2Cl_2, dried over Na_2SO_4, 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.*