was heated at 95°. The oily free aldehyde that formed was extracted into Et_2O. The Et_2O was evaporated and the residue was dissolved in a mixture of MeOH (30 ml), H_2O (5 ml), and KOH (2.8 g), and the solution was heated at 80° for 1 h. The solution was cooled and acidified to precipitate the product acid which was recrystallized from benzene to yield 2.9 g (35%) of **36**: mp 147–148°. Anal. ($C_{11}H_{10}Cl_2O_4$) C, H, Cl.

(*E*)-4-[2,3-Dichloro-4-(2-nitro-1-butenyl)phenoxy]butyric Acid (37). Compound **36** and 1-nitropropane were condensed (method B) to yield **37** (38%): mp 155–156.5° (from EtOH); NMR δ 8.02 (1 H, s, HC=). Anal. ($C_{14}H_{15}Cl_2NO_5$) C, H, N.

Methyl (*E*)-[2,3-Dichloro-4-(2-nitropropenyl)phenoxy]-acetate (38). A solution of **5** (1.0 g, 0.0033 mol) and H_2SO_4 (0.5 ml) in MeOH (20 ml) was stirred at 25° for 1 h. The solid that separated was recrystallized from MeOH to yield 0.6 g (57%) of **38**: mp 118–119°. Anal. ($C_{12}H_{11}Cl_2NO_5$) C, H, N.

(*E*)-[2,3-Dichloro-4-(2-nitropropenyl)phenoxy]acetamide (39). A solution of **5** (4.0 g, 0.013 mol) and $SOCl_2$ (4.0 g, 0.033 mol) in benzene (50 ml) was boiled under reflux for 2 h. Solvent and excess $SOCl_2$ were then distilled at reduced pressure. The residue was treated with concentrated NH_4OH (10 ml) to obtain the amide which was recrystallized repeatedly from benzene–hexane to yield 0.58 g (15%) of **39**: mp 161.5–162°. Anal. ($C_{11}H_{10}Cl_2N_2O_4$) C, H, Cl.

Acknowledgment. We wish to thank Mr. K. B. Streeter, Mr. Y. C. Lee, and their staff for elemental analyses and Mrs. J. D. Schneeberg and Dr. D. W. Cochran for NMR spectra.

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Cycloalkanoindoles. 1. Syntheses and Antiinflammatory Actions of Some Acidic Tetrahydrocarbazoles, Cyclopentindoles, and Cycloheptindoles

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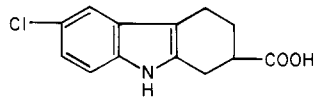
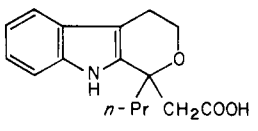
A novel series of acidic cycloalkanoindoles comprising tetrahydrocarbazole-, cyclopentindole-, and cycloheptindole-1-acetic acids has been synthesized via the Fischer indolization between a phenylhydrazine and a 1-alkyl-2-oxocycloalkaneacetic acid ester. These compounds were evaluated, orally, for their capacities to decrease established adjuvant arthritis in rats. The most active compound of the series was 1-ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid (AY-24 873), which had an ED_{50} of 1.1 ± 0.2 mg/kg. AY-24 873 was also studied orally in rats for its effect on the acute inflammatory response in the carrageenin paw edema test. It was found that AY-24 873 was about ten times more active against the chronic than against the acute models of inflammation used.

Several recent reports disclose diverse biological properties for acidic tetrahydrocarbazole derivatives. Antifungal,[1] antifertility,[1] hypocholesteremic,[2] and, particularly, antiinflammatory activity[1,3-6] have been reported in animals. In addition, one of these derivatives, 6-chloro-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (**1**),[4] has been shown to be clinically active in the treatment of acute gout.[5]



1



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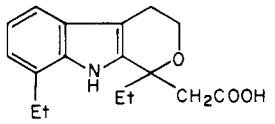


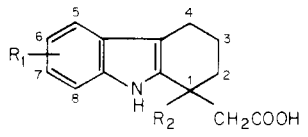
3

We have recently described the antiinflammatory activity of 1-*n*-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid (**2**, prodolic acid, USAN)[7,8] and of the closely related and more potent 1,8-diethyl analogue **3** (etodolic acid, USAN).[9] The tetrahydropyranoindole nucleus of prodolic and etodolic acids may be viewed as an oxygen analogue of a 1,2,3,4-tetrahydrocarbazole. The observation that the antiinflammatory activity of prodolic acid and its congeners is profoundly influenced by the presence of and the nature of alkyl substituents at positions 1 and 8 of the tetrahydropyrano indole-1-acetic acid moiety[7,9] has prompted an investigation of a series of similarly substituted cycloalkanoindoles, comprising tetrahydrocarbazole-, tetrahydrocyclopentindole-, and hexahydrocycloheptindole-1-acetic acid derivatives and related compounds. The results obtained form the basis of this report.

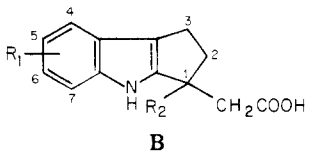
Chemistry. The novel cycloalkanoindole-1-acetic acid derivatives prepared are collected in Table I. They were synthesized via the Fischer indolization between the phenylhydrazines **4–9** and the 1-alkyl-2-oxocycloalkane-acetic acid esters **10–16**. The recently reported synthesis of **24**[10] could not be repeated, and this compound was also obtained via the Fischer condensation of phenylhydrazine and ethyl 2-oxocyclohexaneacetate. The 2-(2-propyl)-, 2-*n*-propyl-, and, 2-*n*-butylphenylhydrazines **6–8** are new compounds and their syntheses are described in the Experimental Section.

The required 1-alkyl-2-oxocyclohexane- and cyclopentaneacetic acid esters were obtained via the ruthenium dioxide–sodium metaperiodate oxidation[11] of the known 2-alkyl-2-allylcyclohexanones **17–19**, and the novel cy-

Table I. Chemical Data and Antiinflammatory Activities of Cycloalkanoindoleacetic and -carboxylic Acids



A



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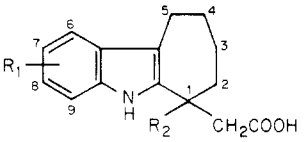
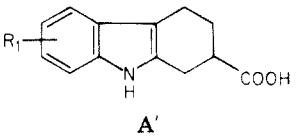


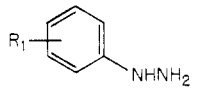
C



A'

No.	Nucleus	R_1	R_2	Mp, °C	Recrystn solvent[a]	% yield[b]	Formula[c]	"Therapeutic test" in arthritic rats, ED_{50}, mg/kg ± SE
24	A	H	H	134-136[d]	I	24.0	$C_{14}H_{15}NO_2$	Inactive[e]
25	A	H	Me	188-189	I, II	20.0	$C_{15}H_{17}NO_2$	Inactive[e]
26	A	H	Et	148-150	I, II	22.0	$C_{16}H_{19}NO_2$	3.3 ± 1.4
27	A	H	*n*-Pr	139-140	I, III	24.9	$C_{17}H_{21}NO_2$	20.0 ± 5.0
28	A	8-Et	Et	119-121	II, IV	17.0	$C_{18}H_{23}NO_2$	1.9 ± 0.5
29	A	8-*n*-Pr	Et	127-128	II, IV	19.4	$C_{19}H_{25}NO_2$	1.1 ± 0.2
30	A	8-(2-Pr)	Et	181-184	I, II	17.0	$C_{19}H_{25}NO_2$	5.4 ± 2.8
31	A	8-*n*-Bu	Et	131-134	II	19.2	$C_{20}H_{27}NO_2$	4.2 ± 1.2
32	A	6-OMe	Et	Oil		18.0	$C_{17}H_{21}NO_3$	Inactive[f]
33	B	H	Me	146-150	II, IV	4.8	$C_{14}H_{15}NO_2$	Inactive[f]
34	B	H	Et	138-139	I, II	17.8	$C_{15}H_{17}NO_2$	~100
35	B	7-Et	Me	124-129	II	5.1	$C_{16}H_{19}NO_2$	>50[g]
36	B	7-Et	Et	Oil		18.0	$C_{17}H_{21}NO_2$	6.2 ± 1.2
37	C	9-Et	Me	148-151	II, IV	7.0	$C_{18}H_{23}NO_2$	Inactive[h]
38	C	9-Et	Et	103-107	II, IV	22.7	$C_{19}H_{25}NO_2$	>50[g]
39	A'	H		239-241[i]	II, V		$C_{13}H_{13}NO_2$	Inactive[e]
40	A'	6-OMe		223-225[j]	VI, VII		$C_{14}H_{15}NO_3$	20.0 ± 8.3
1	A'	6-Cl		247-249[k]	VI, VII		$C_{13}H_{12}ClNO_2$	21.3 ± 9.3
41	Phenylbutazone							5.4 ± 1.2
42	Indomethacin							0.2 ± 0.05
49	Naproxen							2.1 ± 0.4

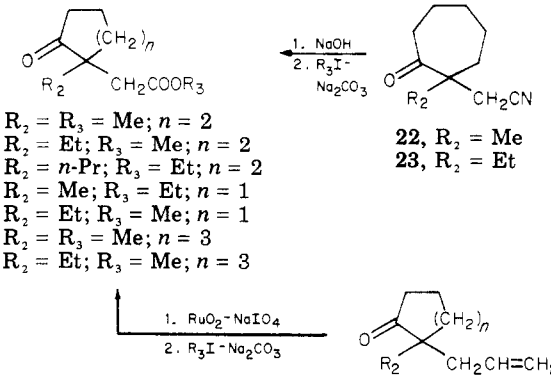
[a] I = benzene; II = hexane; III = petroleum ether, bp 60-90°; IV = ether; V = acetone; VI = ethanol; VII = water. [b] Yield refers to the overall yield of acid based on the amounts of phenylhydrazine and carbonyl component used in the Fischer indolization. [c] All new compounds were analyzed for C, H, and N except **38** which was analyzed only for N. The results were within ±0.4% of the calculated values. [d] Lit.[10] mp 137-138°. [e] Inactive at 100 mg/kg (highest dose tested). [f] Inactive at 25 mg/kg (highest dose tested). [g] The compound reduced the paw size by 0.5 ml in some rats but the ED_{50} was greater than 50 mg/kg. [h] Inactive at 10 mg/kg (highest dose tested). [i] Lit.[13] mp 233-235°. [j] Lit. mp 226-227°,[13] 223-227°.[6] [k] Lit.[4] mp 249-250°.



4, R_1 = H
5, R_1 = 2-Et
6, R_1 = 2-(2-Pr)
7, R_1 = 2-(*n*-Pr)
8, R_1 = 2-(*n*-Bu)
9, R_1 = 4-OMe

clopentanone derivatives **20** and **21**, to produce acetic acid derivatives which were esterified to afford **10–14** (see Scheme I). The 1-alkyl-2-oxocycloheptaneacetic acid esters were obtained by alkylation of 2-oxocycloheptaneacetonitrile[12] to give the nitriles **22** and **23** which

Scheme I

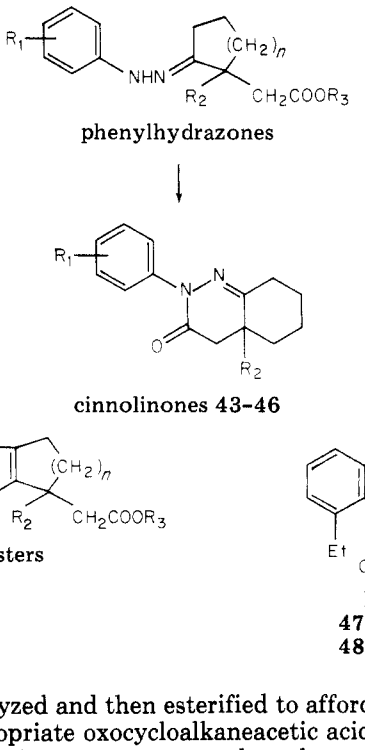


10, $R_2 = R_3$ = Me; n = 2
11, R_2 = Et; R_3 = Me; n = 2
12, R_2 = *n*-Pr; R_3 = Et; n = 2
13, R_2 = Me; R_3 = Et; n = 1
14, R_2 = Et; R_3 = Me; n = 1
15, $R_2 = R_3$ = Me; n = 3
16, R_2 = Et; R_3 = Me; n = 3

22, R_2 = Me
23, R_2 = Et

17, R_2 = Me; n = 2
18, R_2 = Et; n = 2
19, R_2 = *n*-Pr; n = 2
20, R_2 = Et; n = 1
21, R_2 = Me; n = 1

Scheme II



47, R_2 = Me
48, R_2 = Et

were hydrolyzed and then esterified to afford **15** and **16**.

The appropriate oxocycloalkaneacetic acid esters and phenylhydrazines were converted to the corresponding phenylhydrazones in ethanol solution. In condensations involving the oxocyclopentane- and oxocycloheptaneacetic acid esters **13–16** phenylhydrazone formation proceeded

Table II. Acute and Chronic Antiinflammatory Activities and Ulcerogenic Effects of Selected Compounds

Compound	Inhibn of carrageenin paw edema, ED_{30}, mg/kg[a]	"Therapeutic test" in arthritic rats, ED_{50}, mg/kg ± SE	Ulcerogenic effect, ED_{50}, mg/kg ± SE	Ratio between ulcerogenic and therapeutic ED_{50}'s
29	10.5	1.1 ± 0.2	24 ± 7.9	24
40	12.7	20.0 ± 8.3		
1	10.2	21.3 ± 9.3		
2 (prodolic acid)	89.9	9.0 ± 2.8	678 ± 41	75
3 (etodolic acid)	10.2	0.7 ± 0.1	60 ± 7.8	85
41 (phenylbutazone)	11.7	5.4 ± 1.2	100 ± 18	18
49 (naproxen)		2.1 ± 0.4	28 ± 8.5	13

[a] ED_{30}'s were calculated graphically.

more conveniently in the presence of an acid catalyst, achieved by adding the phenylhydrazine as its hydrochloride salt.

The crude phenylhydrazones were cyclized with dilute sulfuric acid under conventional conditions (see the Experimental Section) and the neutral products were isolated. In the case of cyclizations of cyclohexanephenylhydrazones (Scheme II, $n = 2$), the neutral fractions consisted of esters and cinnolinones which were readily separated by chromatography on silica gel, the ester component being eluted first. Generally, the crude esters were hydrolyzed directly to the acids shown in Table I. The esters corresponding to the acids **24**, **26**, **27**, and **29** were obtained crystalline and were characterized. In a number of instances, the cinnolinones **43–46** obtained as by-products in the preparation of the acids **29**, **26**, **27**, and **25**, respectively, were isolated and characterized (see Experimental Section).

In cyclizations of cyclopentanephenylhydrazones (Scheme II, $n = 1$), only esters were isolated which were hydrolyzed directly to the acids **33–36**. "Cinnolinone-type" by-products were probably formed but were not isolated as the chromatographic workup was terminated after elution of the desired esters with benzene.

Two cycloheptanephenylhydrazones (Scheme II, $n = 3$) were cyclized. Thus the phenylhydrazone from **15** and **5**·HCl was cyclized with dilute sulfuric acid to afford a neutral fraction which gave, after chromatography, the methyl ester of **37** and the lactam **47** which were combined and hydrolyzed to afford the acid **37**. The phenylhydrazone from **16** and **5**·HCl was cyclized by pyrolysis. After chromatography, the only product isolated was the lactam **48**, which was hydrolyzed to the acid **38**.

Pharmacology and Structure–Activity Relationships. The 15 cycloalkanoindole-1-acetic acids **24–38** shown in Table I were tested orally for antiinflammatory activity in groups of six rats with established adjuvant arthritis ("therapeutic test") as described previously.[7,8,14] Treatment with compounds was started 14 days after adjuvant (*Mycobacterium butyricum* in mineral oil) injection in the foot pad of the left hind paw and continued until day 22 (nine po administrations). A decrease of the volume of the injected paw, of 0.5 ml (approximately 50% of the maximum possible decrease) or more, as a result of drug treatment was considered to be a "therapeutic effect". Smaller changes were considered to be negative. Paw volume was measured by mercury displacement. From the number of rats showing a "therapeutic effect", the therapeutic ED_{50} was calculated by probit analysis.[15] Compounds which failed to decrease the injected paw size by 0.5 ml in any of the rats at the arbitrarily chosen maximum screening dose of 100 mg/kg were considered inactive. Table I also contains the results obtained from a comparison of the activities of **24–38** in the "therapeutic test", with the structurally related 1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (**39**) and the 6-methoxy analogue **40**, two compounds which are reported to be active in the rat paw edema test, and in the uv erythema test,[6] and with the 6-chloro analogue **1** which is reported to be active in an adjuvant arthritis model[4,5] and in the treatment of acute gout in man.[5] Comparisons in the "therapeutic test" were also made between the above compounds and phenylbutazone (**41**), indomethacin (**42**), and naproxen (**49**). Selected compounds were also tested orally in the carrageenin paw edema model according to the method of Winter et al.[16] and for their gastrointestinal effects 18 h after administration of a single oral dose in 24-h starved male Charles River rats. The animals were sacrificed with ether inhalation and their stomachs were examined for the presence of lesions. The presence of a lesion (erosion, ulcer) was considered an ulcerogenic effect. The UD_{50} (dose which produced lesions in 50% of the rats) was calculated by probit analysis.[15] These results are compared in Table II with the results obtained in the "therapeutic test".

The results show that with compounds containing the 1,2,3,4-tetrahydrocarbazole-1-acetic acid grouping (**24–32**), the presence of an alkyl substituent at position 1 is essential for activity and that the optimal 1-substituent is an ethyl group. Thus, the 1-unsubstituted derivative **24**, as well as the 1-methyl analogue **25**, is devoid of activity at the 100 mg/kg dose, while the 1-ethyl analogue **26** is more potent than phenylbutazone (**41**), having an ED_{50} of 3.3 mg/kg.

In the previously described 1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic acid series,[7] a similar relationship was observed between activity and the nature of the 1-substituent, with the 1-ethyl analogue and the 1-*n*-propyl analogue (prodolic acid, **2**) exhibiting maximum activities.

We have shown recently[9] that the introduction of an ethyl group at the 8 position of 1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid, to generate etodolic acid (**3**), results in a tenfold increase in antiinflammatory activity, and this finding has been the stimulus for the synthesis and testing of **28–31**, which are 8-alkyl derivatives of 1-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid (**26**). Compounds **28–31** show a high level of activity with the 8-ethyl and 8-*n*-propyl analogues **28** and **29** being the most potent having ED_{50}'s of 1.9 and 1.1 mg/kg, respectively.

We have also studied the similar analogues in the cyclopentindole and cycloheptindole series. Of the six compounds tested, **33–38**, only 1,7-diethyl-1,2,3,8-tetrahydrocyclopentindole-1-acetic acid (**36**) had a pronounced activity, with an ED_{50} of 6.2 mg/kg. In an accompanying report[17] we have compared the antiinflammatory activities of the 1-acetic acid derivatives of the tetrahydrocarbazole, cyclopentindole, and cycloheptindole nuclei described herein and the similarly substituted derivatives of the related pyrano[3,4-*b*]indole and thiopyrano[3,4-*b*]indole nuclei, with the antidepressant properties of 1-ethanamine derivatives of these five nuclei. The comparison reveals

that while representatives of all five nuclei possess high antidepressant activity, the presence of high antiinflammatory activity is restricted to only certain of the nuclei.

We have also examined three 1,2,3,4-tetrahydrocarbazole-2-carboxylic acids (**1**, **39**, and **40**) which have been described in the literature (vide supra) as being active antiinflammatory agents. **39** was found to be inactive, while **1** and **40** had weaker activities than phenylbutazone in our adjuvant arthritis model. However, when **1** and **40** were tested for inhibition of acute inflammation by the carrageenin paw edema method, they were found to have a potency comparable to that of **29**, phenylbutazone (**41**), and etodolic acid (**3**), while prodolic acid (**2**) was considerably less active (Table II).

It was reported previously that prodolic acid was markedly less active in models of acute inflammation than in chronic models,[8] and in the present study a similar profile is observed with **29** and with etodolic acid (**3**).[18] In contrast, **1** and **40** appear to be more active in models of acute inflammation.

A comparison of the results obtained in the ulcerogenic test, coupled with those for the therapeutic test, reveals that the ratio between the ulcerogenic and therapeutic ED_{50}'s for **29** is 24, compared to ratios of 18 and 13 for phenylbutazone and naproxen, respectively. In contrast, the ratios for the pyrano[3,4-*b*]indole analogues, prodolic acid (**2**) and etodolic acid (**3**), are 75 and 85, respectively.

In conclusion, this study has identified **29**, 1-ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid,[19] as a novel antiinflammatory agent which is very potent in rats in a model of chronic inflammation (ED_{50} 1.1 mg/kg) while being less active against acute inflammatory responses. Compound **29** has a wider safety margin with respect to ulcerogenic potential than either phenylbutazone or naproxen, but the margin with **29** is much less than with the structurally related prodolic and etodolic acids.

Experimental Section

All compounds had NMR and ir spectra consistent with their respective structures and were homogeneous by TLC. NMR spectra were determined in $CDCl_3$ using a Varian A-60A spectrometer and the chemical shifts are reported as parts per million downfield from Me_4Si. Melting points were taken on a Thomas-Hoover apparatus and need no correction.

Preparation of Substituted Phenylhydrazines. The general procedure of Carlin and Carlson[20] was used to prepare the following new phenylhydrazines.

2-(2-Propyl)phenylhydrazine (6). A solution of $NaNO_2$ (14 g, 0.2 mol) in H_2O (140 ml) was added at 0° during 20 min to a stirred mixture of 2-(2-propyl)aniline[21] (27 g, 0.2 mol), concentrated HCl (150 ml), and H_2O (160 ml). After stirring for 60 min at 0° a solution of $SnCl_2 \cdot 2H_2O$ (112 g, 0.49 mol) in concentrated HCl (90 ml) was added during 30 min at −10°. The mixture was kept at −10° for 90 min; then the HCl salt of the product was isolated by filtration (8.5 g, 22%). It had mp 206–210° ($EtOH-Et_2O$). The free base was an oil: NMR δ 1.2 [6, d, J = 6.5 Hz, $CH(CH_3)_2$], 2.82 (1, m, CH), 3.95 (3, m, NH and NH_2), 7.1 (4, m, aromatic H's).

2-*n*-Propylphenylhydrazine (7) was prepared from 2-*n*-propylaniline[22] using the method described above. The HCl salt was obtained in 43% yield and had mp 188–190° dec ($MeOH-Et_2O$). The free base was an oil: NMR δ 0.92 (3, t, J = 7 Hz, CH_3), 1.6 (2, m, CH_2CH_3), 2.4 (2, m, $C_6H_4CH_2$), 3.9 (3, m, NH and NH_2), 7.0 (4, m, aromatic H's).

2-*n*-Butylphenylhydrazine (8) was prepared from 2-*n*-butylaniline[23] as described above. The HCl salt was obtained in 55% yield and had mp 193–196° ($MeOH-Et_2O$). Anal. ($C_{10}H_{17}ClN_2$) C, H, N. The free base was an oil: NMR δ 0.92 (3, t, J = 6.5 Hz, CH_3), 1.5 [4, m, $(CH_2)_2CH_3$], 2.5 (2, t, J = 7.5 Hz, $C_6H_4CH_2$), 3.85 (3, m, NH and NH_2), 7.1 (4, m, aromatic H's).

Preparation of 1-Alkyl-2-oxocyclohexaneacetic Acids and Esters. (a) Via Oxidative Cleavage of 2-Alkyl-2-allylcycloalkanones. Methyl 1-Methyl-2-oxocyclohexaneacetate (10). To a stirred solution of ruthenium dioxide (1.6 g, 0.012 mol) in CCl_4 (200 ml) at 0° under a N_2 atmosphere was added a solution of $NaIO_4$ (12.5 g, 0.058 mol) in H_2O (100 ml). After stirring for 30 min, the yellow CCl_4 layer containing ruthenium tetraoxide was separated and to it was added under N_2, during 1.5 h, a solution of 2-allyl-2-methylcyclohexanone[24] (**17**, 17.3 g, 0.114 mol) in Me_2CO (200 ml). As the addition proceeded, the mixture became brown, then black, as ruthenium dioxide precipitated. Reoxidation of the dioxide to the tetraoxide was achieved by the intermittent addition of $NaIO_4$ (125 g in 1.5 l. of H_2O and 300 ml of Me_2CO). During the reaction period (2 h) the temperature was maintained at 30°. 2-Propanol (30 ml) was added to destroy excess ruthenium tetraoxide, the solids were removed by filtration through Celite, and organic solvents were removed from the filtrate by evaporation under reduced pressure. The remaining aqueous solution was saturated with NaCl and extracted with Et_2O. The Et_2O phase was extracted three times with saturated aqueous $NaHCO_3$ and the basic solution was acidified with concentrated HCl, saturated with NaCl, and extracted with Et_2O. The Et_2O extracts were washed with concentrated aqueous NaCl, dried, and evaporated to afford **1-methyl-2-oxocyclohexaneacetic acid (10a,** 17.5 g, 91%), mp 76–78° (Et_2O–hexane) (lit.[25] mp 77–78°). The acetic acid **10a** (15.3 g, 0.09 mol) in Me_2CO (225 ml) was refluxed with K_2CO_3 (17.2 g, 0.125 mol) and excess MeI (50 ml) for 4 h. Removal of solids and fractionation of the filtrate afforded the methyl ester **10** (14.9 g, 90%): bp 105° (7 mm): NMR δ 1.23 [3, s, $(C)_3CCH_3$], 1.8 [6, m, $(CH_2)_3$], 2.41 (1, d, J = 16 Hz, CHC=O), 2.72 (1, d, J = 16 Hz, CHC=O), 3.65 (3, s, OCH_3); ir 1705 (CO), 1735 cm^{-1} (COOMe).

The following 1-alkyl-2-oxocycloalkaneacetic acids and esters were prepared from the appropriate 2-alkyl-2-allylcycloalkanones as described above.

Methyl 1-Ethyl-2-oxocyclohexaneacetate (11). Oxidation of 2-allyl-2-ethylcyclohexanone[26] (**18**) afforded **1-ethyl-2-oxocyclohexaneacetic acid (11a)**, mp 63–65° (Et_2O–hexane), in 79% yield. Anal. ($C_{10}H_{16}O_3$) C, H. The methyl ester **11** had bp 116° (6 mm): NMR δ 0.8 (3, t, J = 7.0 Hz, CH_2CH_3), 3.62 (3, s, OCH_3); ir 1705 (CO), 1735 cm^{-1} (COOMe). Anal. ($C_{11}H_{18}O_3$) H; C: calcd, 66.64; found, 67.05.

Ethyl 1-Propyl-2-oxocyclohexaneacetate (12). Oxidation of 2-allyl-2-propylcyclohexanone[27] (**19**) afforded **1-propyl-2-oxocyclohexaneacetic acid (12a)**, mp 61–62° (Et_2O–hexane), in 77% yield. Anal. ($C_{11}H_{18}O_3$) C, H. The ethyl ester **12** had bp 98° (0.5 mm): NMR δ 0.9 [3, m, $(CH_2)_2CH_3$], 1.25 (3, t, J = 7.0 Hz, OCH_2CH_3), 2.35 (1, d, J = 17.5 Hz, CHC=O), 2.68 (1, d, J = 17.5 Hz, CHC=O), 4.15 (2, q, J = 7.0 Hz, OCH_2CH_3); ir 1705 (CO), 1725 cm^{-1} (COOEt). Anal. ($C_{13}H_{22}O_3$) C, H.

Ethyl 1-Methyl-2-oxocyclopentaneacetate (13). Oxidation of 2-allyl-2-methylcyclopentanone (**21**) afforded **1-methyl-2-oxocyclopentaneacetic acid (13a)**, mp 70–72° (Et_2O–hexane) (lit.[25] mp 73.5–74.5°), in 77% yield. Anal. ($C_8H_{12}O_3$) C, H. The ethyl ester **13**[28] had bp 63–65° (0.5 mm): NMR δ 1.05 [3, s, $(C)_3CCH_3$], 1.25 (3, t, J = 7.0 Hz, CH_2CH_3), 4.15 (2, q, J = 7.0 Hz, OCH_2); ir 1730 cm^{-1} (CO). Anal. ($C_{10}H_{16}O_3$) H; C: calcd, 65.19; found, 65.61.

Methyl 1-Ethyl-2-oxocyclopentaneacetate (14). Oxidation of 2-allyl-2-ethylcyclopentanone (**20**) afforded **1-ethyl-2-oxocyclopentaneacetic acid (14a)**, bp 160° (0.3 mm), in 82% yield. Anal. ($C_9H_{14}O_3$) C, H. The methyl ester **14** had bp 121–123° (9 mm): NMR δ 0.86 (3, t, J = 7.0 Hz, CH_2CH_3), 1.50 (2, q, J = 7.0 Hz, CH_2CH_3), 2.00 [4, m, ring $(CH_2)_2$], 2.38 (2, t, J = 6.0 Hz, CH_2CO), 2.40 (1, d, J = 16.5 Hz, CHCOO), 2.75 (1, d, J = 16.5 Hz, CHCOO), 3.65 (3, s, OCH_3); ir 1730 cm^{-1} (CO).

(b) **Via Alkylation of 2-Oxocycloheptaneacetonitrile. Methyl 1-Methyl-2-oxocycloheptaneacetate (15).** To a stirred solution of 2-oxocycloheptaneacetonitrile[12] (44.6 g, 0.297 mol) and MeI (42.6 g, 0.3 mol) in C_6H_6 (200 ml) was added, under a N_2 atmosphere, a solution of sodium *tert*-amylate in toluene (240 ml, 0.297 mol). The mixture was stirred at 65° for 4 h, kept at 22° for 18 h, washed with 1% aqueous HCl, H_2O, and saturated aqueous NaCl solution, and dried. Fractionation afforded **1-methyl-2-oxocycloheptaneacetonitrile (22)**: bp 152–158° (14 mm) (43.7 g, 90%); NMR δ 1.27 (3, s, CH_3), 2.38 (1, d, J = 17.5 Hz, CHCN), 2.78 (1, d, J = 17.5 Hz, CHCN). The nitrile **22** (34.3 g) was refluxed with 500 ml of 10% aqueous NaOH solution to

give **1-methyl-2-oxocycloheptaneacetic acid (15a**, 36.3 g, 95%), mp 43–45° (Et_2O–hexane). Anal. ($C_{10}H_{16}O_3$) C, H. The methyl ester **15** was prepared with MeI and K_2CO_3 as described above to afford the product as an oil: NMR δ 1.2 [3, s, $(C)_3CCH_3$], 2.55 (2, s, CH_2CO), 3.67, (3, s, OCH_3); ir 1700 (CO), 1730 cm^{-1} (COOMe).

Methyl 1-ethyl-2-oxocycloheptaneacetate (16) was prepared as described above, using EtI as the alkylating agent to afford **1-ethyl-2-oxocycloheptaneacetonitrile (23)**, mp 93–95° (hexane–pentane), in 68% yield: NMR δ 0.8 (3, t, J = 7.0 Hz, CH_2CH_3), 1.75 (2, q, J = 7.0 Hz, CH_2CH_3). Alkaline hydrolysis of the nitrile **23** gave **1-ethyl-2-oxocycloheptaneacetic acid (16a)**, mp 59–61° (hexane–Et_2O), in 95% yield. Anal. ($C_{11}H_{18}O_3$) C, H. The methyl ester **16** had bp 100–101° (0.7 mm): NMR δ 0.83 (3, t, J = 7.0 Hz, CH_2CH_3), 2.38 (1, d, J = 15 Hz, CHC=O), 2.74 (1, d, J = 15 Hz, CHC=O), 3.6 (3, s, OCH_3); ir 1695 (CO), 1730 cm^{-1} (COOMe).

2-Allyl-2-ethylcyclopentanone (20). To a stirred solution of 2-ethylcyclopentanone[29] (10.8 g, 0.089 mol) and allyl bromide (11.5 g, 0.095 mol) in Et_2O (150 ml) was added, during 30 min under N_2, a solution of sodium *tert*-amylate (7.1 g, 0.075 mol) in Et_2O (75 ml). The mixture was refluxed for 2 h and washed with aqueous 1% HCl, H_2O, and concentrated NaCl solution. After drying, fractionation afforded the product as an oil (8.2 g, 60%): bp 90–100° (18 mm); NMR δ 0.83 (3, t, J = 7.0 Hz, CH_2CH_3). Anal. ($C_{10}H_{16}O$) C, H.

2-Allyl-2-methylcyclopentanone (21) was obtained from 2-methylcyclopentanone, as described above for **20**, in 67% yield: bp 69–72° (12 mm); NMR δ 1.05 (3, s, CH_3), 4.85–6.15 (3, m, $CH=CH_2$).

Fischer Indolizations. (a) Preparation of 1,2,3,4-Tetrahydrocarbazole-1-acetic Acids. 1-Ethyl-8-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-acetic Acid (29). A mixture of 2-*n*-propylphenylhydrazine (8.1 g, 0.054 mol) and methyl 1-ethyl-2-oxocyclohexaneacetate (10.0 g, 0.050 mol) and EtOH (125 ml) was heated at reflux under N_2 for 21 h. The solvent was removed by evaporation and the residue was heated with 120 ml of a 20% aqueous H_2SO_4 solution under N_2 for 30 min at a bath temperature of 160°. The reaction mixture was poured onto crushed ice and extracted with 2 × 100 ml of Et_2O. The Et_2O extracts were washed with 50 ml of a 5% aqueous NaOH solution and then with a saturated aqueous NaCl solution. The dried Et_2O extracts were concentrated to give a residue (8.0 g) which was chromatographed on a silica gel column. Elution with C_6H_6 afforded **29** methyl ester (3.2 g, 20%), mp 99–100° (hexane). Anal. ($C_{20}H_{27}NO_2$) C, H, N. Elution with C_6H_6–Me_2CO (25:1) afforded **2-(2-*n*-propylphenyl)-4a-ethyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (43)** (4.0 g, 26%) as an oil. Anal. ($C_{19}H_{26}N_2O$) C, H, N. The methyl ester (2.85 g, 0.0095 mol), K_2CO_3 (1.5 g, 0.011 mol), MeOH (60 ml), and H_2O (10 ml) were heated at reflux for 18 h to afford the product, **29**, in 97% yield, mp 127–128° (see Table I).

The other 1,2,3,4-tetrahydrocarbazole-1-acetic acids reported in Table I were prepared as described above, using the appropriate phenylhydrazine and 2-oxocyclohexaneacetic acid ester. In most cases the intermediate esters were directly hydrolyzed to the acids listed in Table I. The following esters were characterized: **24** ethyl ester [mp 72–73° (Et_2O–hexane). Anal. ($C_{16}H_{19}NO_2$) C, H, N], **26** methyl ester [mp 67–71° (C_6H_6). Anal. ($C_{17}H_{21}NO_2$) C, H, N], and **27** ethyl ester [mp 64–66° (hexane). Anal. ($C_{19}H_{25}NO_2$) C, H, N]. The following cinnolinone by-products were characterized: **4a-ethyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (44)** [mp 51–55° (Me_2CO–hexane). Anal. ($C_{16}H_{20}N_2O$) C, H, N], **4a-*n*-propyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (45)** [mp 59–61° (pentane). Anal. ($C_{17}H_{22}N_2O$) C, H, N], and **4a-methyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (46)** [mp 82–83° (Et_2O–hexane). Anal. ($C_{15}H_{18}N_2O$) C, H, N].

(b) Preparation of Cyclopentindole-1-acetic Acids. Cyclopentindole-1-acetic acids were prepared according to the general procedure outlined above except that the phenylhydrazines were used as their HCl salts. The crude esters obtained after chromatography were hydrolyzed directly to the acids **33–36** (see Table I).

(c) Preparation of Cycloheptindole-1-acetic Acids. Condensation of Keto Ester 15 with 2-Ethylphenylhydrazine Hydrochloride. A mixture consisting of methyl 1-methyl-2-oxocycloheptaneacetate (5.0 g, 0.025 mol), 2-ethylphenylhydrazine (4.4 g, 0.025 mol), and 2-ethylphenylhydrazine hydrochloride (3.0 g, 0.017 mol) was heated at reflux in anhydrous EtOH for 18 h under an N_2 atmosphere. After removal of the EtOH in vacuo the residue was heated at 160° with 50 ml of 20% aqueous H_2SO_4 for 45 min. The mixture was worked up as described above to give an oil (6.3 g) which was chromatographed on silica gel. Elution with increasing concentrations of Me_2CO in C_6H_6 (2–5%) gave **methyl 9-ethyl-1,2,3,4,5,10-hexahydro-1-methylcyclohept[*b*]indole-1-acetate (37** methyl ester) (0.65 g, 8.5%) as an oil: NMR δ 1.25 (3, m, CH_2CH_3), 1.50 (3, s, angular CH_3), 1.90 (6, m, aliphatic CH_2), 2.85 (6, m, CH_2C=O, aryl-CH_2), 3.65 (3, s, OCH_3), 7.0–7.5 (3, m, aromatic H). Continued elution afforded **10-ethyl-2,2a,3,4,5,6-hexahydro-2a-methyl-1*H*-10b-azabenzo[*a*]cyclopent[*c*,*d*]azulen-1-one (47)** (0.45 g, 6.8%) as an oil which solidified on standing (mp 82–83°): NMR δ 1.25 (3, t, J = 7 Hz, CH_2CH_3), 1.57 (3, s, angular CH_3), 1.9 (6, m, aliphatic CH_2), 2.85 (2, s, CH_2C=O), 3.0 (4, m, aryl-CH_2), 7.0–7.4 (2, m, aromatic H), 7.95 (1, doublet of doublets, J = 7.5 and 2 Hz, aromatic H). **37** methyl ester and lactam **47** were combined in MeOH (30 ml) with K_2CO_3 (1.0 g) in H_2O (5 ml) and heated at reflux under N_2 for 20 h to afford the acid **37**, mp 148–151° (see Table I).

Condensation of Keto Ester 16 with 2-Ethylphenylhydrazine Hydrochloride. A mixture consisting of methyl 1-ethyl-2-oxocycloheptaneacetate (8.0 g, 0.038 mol), 2-ethylphenylhydrazine (2.0 g, 0.014 mol), and 2-ethylphenylhydrazine hydrochloride (6.5 g, 0.038 mol) was heated at reflux in EtOH (50 ml) for 18 h under an N_2 atmosphere. The EtOH was removed and the residue was pyrolyzed at 160° for 50 h. After cooling, the residue was distributed between H_2O and Et_2O. The Et_2O extracts were washed with 1 N HCl and then with 1 N NaOH. After drying and removal of solvent, the residue was chromatographed on silica gel. Elution with C_6H_6 afforded **2a,10-diethyl-2,2a,3,4,5,6-hexahydro-1*H*-10b-azabenzo[*a*]cyclopent[*c*,*d*]azulen-1-one (48)** (3.0 g, 28%) as an oil: NMR δ 0.83 (3, t, J = 7 Hz, CH_3), 1.27 (3, t, J = 7 Hz, CH_3), 3.35 (2, quartet of doublets, J = 7 and 2 Hz, CH_2C=O), 6.9–7.5 (3, m, aromatic H).

The lactam **48** was hydrolyzed, as described above for **47**, to afford the acid **38** in 81% yield: mp 103–107°; NMR δ 1.33 (3, t, J = 7 Hz, CH_3), 1.87 (3, t, J = 7 Hz, CH_3), 7.0–7.5 (3, m, aromatic H), 8.7 (1, s, NH), 10.75 (1, broad, COOH).

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Cycloalkanoindoles. 2.[1] 1-Alkyl-1,2,3,4-tetrahydrocarbazole-1-ethanamines and Related Compounds. Potential Antidepressants

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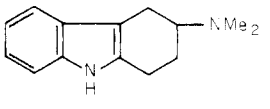
The synthesis is described of a series of cycloalkanoindoles, comprising tetrahydrocarbazoles, a cyclopentindole, and a cycloheptindole, all bearing an ethanamine side chain at position 1. The acute toxicities of these compounds were evaluated, as well as their potential antidepressant properties, using tests based on the prevention of ptosis induced by reserpine and tetrabenazine. 9-Ethyl-*N*,*N*,1-trimethyl-1,2,3,4-tetrahydrocarbazole-1-ethanamine (AY-24 614) was found to be the most potent analogue, having an ED_{50} of 0.12 mg/kg ip in preventing reserpine-induced ptosis in mice and an ED_{50} at 3.3 mg/kg ip in preventing tetrabenazine-induced ptosis in rats.

Tetrahydrocarbazoles bearing basic substituents at positions 1, 2, 3, or 4 have been the subject of a number of recent investigations. Members of this class are claimed to be hypoglycemic agents,[2] coccidiostats,[3] analgesics,[4] antiinflammatory agents,[5] cardiotonic agents,[6] and antidepressants.[7,8] This latter activity has been confirmed in man for 3-dimethylamino-1,2,3,4-tetrahydrocarbazole (**1**).[9]



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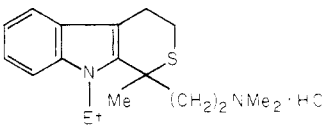

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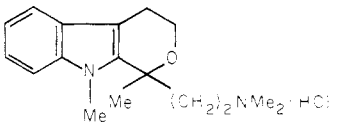

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Recent studies from our laboratories have shown that 9-ethyl-*N*,*N*,1-trimethyl-1,2,3,4-tetrahydrothiopyrano-[3,4-*b*]indole-1-ethanamine hydrochloride (**2**, tandamine hydrochloride, USAN) is a potent antidepressant as demonstrated in various models,[10-13] including prevention of reserpine-induced ptosis.[10,12] An oxygen analogue, *N*,*N*,1,9-tetramethyl-1,2,3,4-tetrahydropyrano[3,4-*b*]-indole-1-ethanamine hydrochloride (**3**, AY-23 671), has also been found to have potential antidepressant properties as reflected by its activity in the reserpine ptosis test.[14]

In contrast to the tetrahydrocarbazoles cited above,[2-9] compounds **2** and **3** possess, apart from their novel nuclei, dimethylaminoethyl groups at position 1 as well as alkyl groups at the 1 and 9 positions. Studies of numerous analogues of **2** and **3** have indicated that their antidepressant-like properties are associated with these structural features.[12-14] We have now investigated the effects of replacing the dihydrothiopyrano and dihydropyrano rings of **2** and **3** with partially saturated carbocyclic systems, and the present report describes the synthesis and biological evaluation of a series of cycloalkanoindoles having substitution patterns found to be relevant for the antidepressant-like properties of **2** and **3**.

Chemistry. Ten novel cycloalkanoindole-1-ethylamines, **36–42**, **48**, **55**, and **59** (see Table I), were synthesized for biological evaluation. The route outlined in Scheme I was used for the preparation of the 1,9-dialkyltetrahydrocarbazoles **36–42** and for the 1,8-dialkylcyclopentindole **48**. It comprised the condensation of a phenylhydrazine with a 1-alkyl-2-oxocycloalkanepropionate, followed directly by a Fischer cyclization of the intermediate phenylhydrazone with sulfuric acid.

Thus, the condensations of **4** with **8**, and of **5** with **7**, led to the tetracyclic lactams **11** and **12**, respectively, while the condensation of **4** with **7** afforded the lactam **10**, along with a trace of the anticipated **14** methyl ester. In contrast, the reaction of **6** with **7** afforded the ester **13**, along with the acid **17**, but without any of the corresponding lactam.

Hydrolysis of the lactams **10–12**, and of the ester **13**, gave the tetrahydrocarbazole-1-propionic acids **14–17**. When these were allowed to react with sodium hydride and an alkyl halide, in tetrahydrofuran, only the *N*-alkylpropionic acids **18–23** were obtained. When dimethylformamide was used as solvent, the *N*-alkylpropionic acids were accompanied by the corresponding alkyl esters derived from concomitant esterification of the carboxyl group.

The *N*-alkylpropionic acids **18–23** were transformed by a Curtius rearrangement to the corresponding isocyanates which were reduced directly to the formamides **24–29** with formic acid according to a method developed in our laboratories.[15] Methylation of **24–29** gave the *N*-methylformamides **30–35**, which were reduced with lithium aluminum hydride to tertiary amines which were converted to the salts **36–41**. Hydrolysis of the *N*-methylformamide