

was heated at 95°. The oily free aldehyde that formed was extracted into Et₂O. The Et₂O was evaporated and the residue was dissolved in a mixture of MeOH (30 ml), H₂O (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. (C₁₁H₁₀Cl₂O₄) 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. (C₁₄H₁₅Cl₂NO₅) 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 H₂SO₄ (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. (C₁₂H₁₁Cl₂NO₅) C, H, N.

(*E*)-[2,3-Dichloro-4-(2-nitropropenyl)phenoxy]acetamide (**39**). A solution of **5** (4.0 g, 0.013 mol) and SOCl₂ (4.0 g, 0.033 mol) in benzene (50 ml) was boiled under reflux for 2 h. Solvent and excess SOCl₂ were then distilled at reduced pressure. The residue was treated with concentrated NH₄OH (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. (C₁₁H₁₀Cl₂N₂O₄) C, H, Cl.

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

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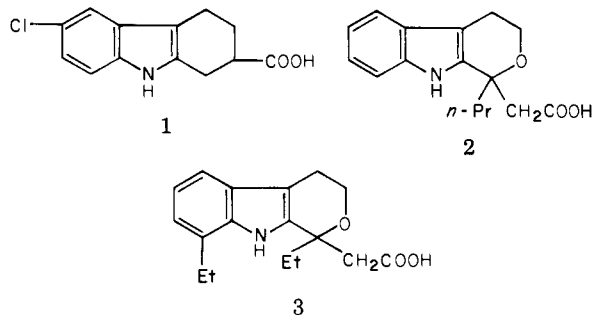
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A novel series of acidic cycloalkanoindoles comprising tetrahydrocarbazole-, cyclopentindole-, and cycloheptindole-1-acetic acids has been synthesized via the Fischer indolization between a phenylhydrazine and a 1-alkyl-2-oxocycloalkaneacetic acid 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 ED₅₀ 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



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.

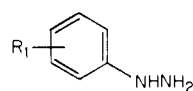
Chemistry. The novel cycloalkanoindole-1-acetic acid derivatives prepared are collected in Table I. They were synthesized via the Fischer indolization between the phenylhydrazines **4–9** and the 1-alkyl-2-oxocycloalkaneacetic acid esters **10–16**. The recently reported synthesis of **24**¹⁰ could not 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 oxidation¹¹ 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

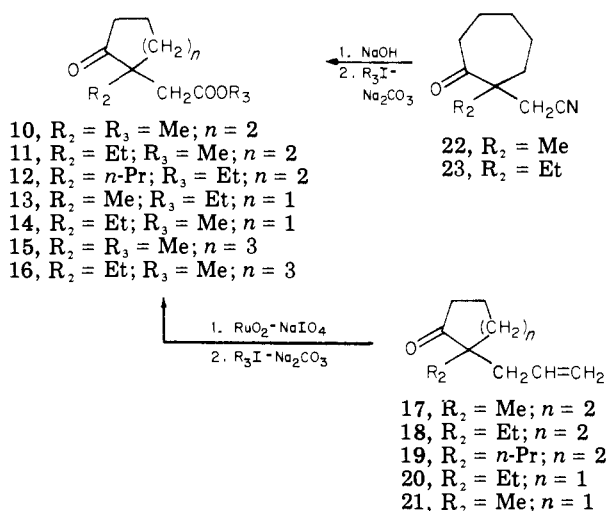
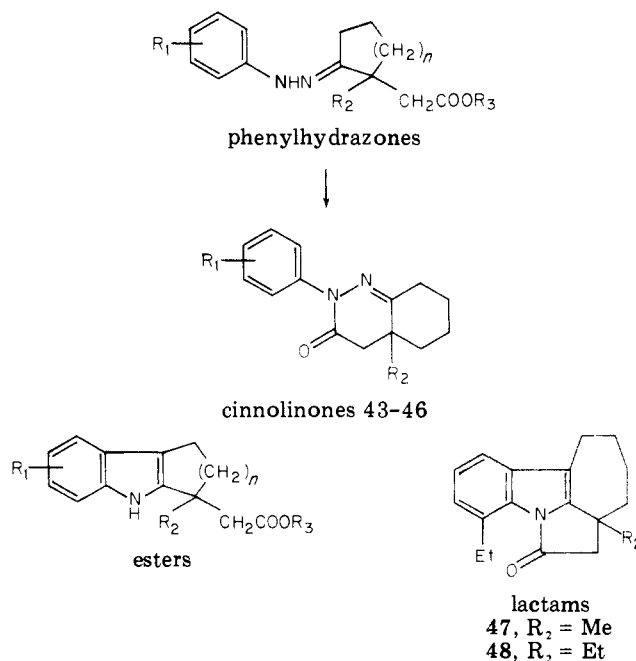
No.	Nucleus	R ₁	R ₂	Mp, °C	Recrystn solvent ^a	% yield ^b	Formula ^c	"Therapeutic test" in arthritic rats, ED ₅₀ , mg/kg ± SE
24	A	H	H	134-136 ^d	I	24.0	C ₁₄ H ₁₅ NO ₂	Inactive ^e
25	A	H	Me	188-189	I, II	20.0	C ₁₅ H ₁₇ NO ₂	Inactive ^e
26	A	H	Et	148-150	I, II	22.0	C ₁₆ H ₁₉ NO ₂	3.3 ± 1.4
27	A	H	<i>n</i> -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- <i>n</i> -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- <i>n</i> -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 ED₅₀ 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°. ^k Lit.⁴ mp 249-250°.



- 4, R₁ = H
5, R₁ = 2-Et
6, R₁ = 2-(2-Pr)
7, R₁ = 2-(*n*-Pr)
8, R₁ = 2-(*n*-Bu)
9, R₁ = 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-oxocycloheptanecetonitrile¹² to give the nitriles 22 and 23 which

Scheme I**Scheme II**

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 ₅₀ , 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 ED₅₀'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 cyclohexanophenylhydrazones (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 cyclopentanophenylhydrazones (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 cycloheptanophenylhydrazones (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 ED₅₀ 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 ana-

logue 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 UD₅₀ (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 ED₅₀ 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 recently⁹ 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 ED₅₀'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 ED₅₀ of 6.2 mg/kg. In an accompanying report¹⁷ 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 ED₅₀'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 (ED₅₀ 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 CDCl₃ using a Varian A-60A spectrometer and the chemical shifts are reported as parts per million downfield from Me₄Si. Melting points were taken on a Thomas-Hoover apparatus and need no correction.

Preparation of Substituted Phenylhydrazines. The general procedure of Carlin and Carlson²⁰ was used to prepare the following new phenylhydrazines.

2-(2-Propyl)phenylhydrazine (6). A solution of NaNO₂ (14 g, 0.2 mol) in H₂O (140 ml) was added at 0° during 20 min to a stirred mixture of 2-(2-propyl)aniline²¹ (27 g, 0.2 mol), concentrated HCl (150 ml), and H₂O (160 ml). After stirring for 60 min at 0° a solution of SnCl₂·2H₂O (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–Et₂O). The free base was an oil: NMR δ 1.2 [6, d, *J* = 6.5 Hz, CH(CH₃)₂], 2.82 (1, m, CH), 3.95 (3, m, NH and NH₂), 7.1 (4, m, aromatic H's).

2-*n*-Propylphenylhydrazine (7) was prepared from 2-*n*-propylaniline²² using the method described above. The HCl salt was obtained in 43% yield and had mp 188–190° dec (MeOH–Et₂O). The free base was an oil: NMR δ 0.92 (3, t, *J* = 7 Hz, CH₃), 1.6 (2, m, CH₂CH₃), 2.4 (2, m, C₆H₄CH₂), 3.9 (3, m, NH and NH₂), 7.0 (4, m, aromatic H's).

2-*n*-Butylphenylhydrazine (8) was prepared from 2-*n*-butylaniline²³ as described above. The HCl salt was obtained in 55% yield and had mp 193–196° (MeOH–Et₂O). Anal. (C₁₀H₁₇ClN₂) C, H, N. The free base was an oil: NMR δ 0.92 (3, t, *J* = 6.5 Hz, CH₃), 1.5 [4, m, (CH₂)₂CH₃], 2.5 (2, t, *J* = 7.5 Hz, C₆H₄CH₂), 3.85 (3, m, NH and NH₂), 7.1 (4, m, aromatic H's).

Preparation of 1-Alkyl-2-oxocyclohexaneacetic Acids and Esters. (a) **Via Oxidative Cleavage of 2-Alkyl-2-allyl-**

cycloalkanones. **Methyl 1-Methyl-2-oxocyclohexaneacetate (10).** To a stirred solution of ruthenium dioxide (1.6 g, 0.012 mol) in CCl₄ (200 ml) at 0° under a N₂ atmosphere was added a solution of NaIO₄ (12.5 g, 0.058 mol) in H₂O (100 ml). After stirring for 30 min, the yellow CCl₄ layer containing ruthenium tetraoxide was separated and to it was added under N₂, during 1.5 h, a solution of 2-allyl-2-methylcyclohexanone²⁴ (17, 17.3 g, 0.114 mol) in Me₂CO (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 NaIO₄ (125 g in 1.5 l. of H₂O and 300 ml of Me₂CO). 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 Et₂O. The Et₂O phase was extracted three times with saturated aqueous NaHCO₃ and the basic solution was acidified with concentrated HCl, saturated with NaCl, and extracted with Et₂O. The Et₂O 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° (Et₂O–hexane) (lit.²⁵ mp 77–78°). The acetic acid 10a (15.3 g, 0.09 mol) in Me₂CO (225 ml) was refluxed with K₂CO₃ (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)₃CCH₃], 1.8 [6, m, (CH₂)₃], 2.41 (1, d, *J* = 16 Hz, CHC=O), 2.72 (1, d, *J* = 16 Hz, CHC=O), 3.65 (3, s, OCH₃); 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-ethylcyclohexanone²⁶ (18) afforded 1-ethyl-2-oxocyclohexaneacetic acid (11a), mp 63–65° (Et₂O–hexane), in 79% yield. Anal. (C₁₀H₁₆O₃) C, H. The methyl ester 11 had bp 116° (6 mm): NMR δ 0.8 (3, t, *J* = 7.0 Hz, CH₂CH₃), 3.62 (3, s, OCH₃); ir 1705 (CO), 1735 cm⁻¹ (COOMe). Anal. (C₁₁H₁₈O₃) H; C: calcd, 66.64; found, 67.05.

Ethyl 1-Propyl-2-oxocyclohexaneacetate (12). Oxidation of 2-allyl-2-propylcyclohexanone²⁷ (19) afforded 1-propyl-2-oxocyclohexaneacetic acid (12a), mp 61–62° (Et₂O–hexane), in 77% yield. Anal. (C₁₁H₁₈O₃) C, H. The ethyl ester 12 had bp 98° (0.5 mm): NMR δ 0.9 [3, m, (CH₂)₂CH₃], 1.25 (3, t, *J* = 7.0 Hz, OCH₂CH₃), 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, OCH₂CH₃); ir 1705 (CO), 1725 cm⁻¹ (COOEt). Anal. (C₁₃H₂₂O₃) 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° (Et₂O–hexane) (lit.²⁵ mp 73.5–74.5°), in 77% yield. Anal. (C₉H₁₂O₃) C, H. The ethyl ester 13²⁸ had bp 63–65° (0.5 mm): NMR δ 1.05 [3, s, (C)₃CCH₃], 1.25 (3, t, *J* = 7.0 Hz, CH₂CH₃), 4.15 (2, q, *J* = 7.0 Hz, OCH₂); ir 1730 cm⁻¹ (CO). Anal. (C₁₀H₁₆O₃) 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. (C₉H₁₄O₃) C, H. The methyl ester 14 had bp 121–123° (9 mm): NMR δ 0.86 (3, t, *J* = 7.0 Hz, CH₂CH₃), 1.50 (2, q, *J* = 7.0 Hz, CH₂CH₃), 2.00 [4, m, ring (CH₂)₂], 2.38 (2, t, *J* = 6.0 Hz, CH₂CO), 2.40 (1, d, *J* = 16.5 Hz, CHCOO), 2.75 (1, d, *J* = 16.5 Hz, CHCOO), 3.65 (3, s, OCH₃); ir 1730 cm⁻¹ (CO).

(b) **Via Alkylation of 2-Oxocycloheptaneacetonitrile.**

Methyl 1-Methyl-2-oxocycloheptaneacetate (15). To a stirred solution of 2-oxocycloheptaneacetonitrile¹² (44.6 g, 0.297 mol) and MeI (42.6 g, 0.3 mol) in C₆H₆ (200 ml) was added, under a N₂ 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, H₂O, 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, CH₃), 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° (Et₂O–hexane). Anal. (C₁₀H₁₆O₃) C, H. The methyl ester **15** was prepared with MeI and K₂CO₃ as described above to afford the product as an oil: NMR δ 1.2 [3, s, (C)₃CCH₃], 2.55 (2, s, CH₂CO), 3.67, (3, s, OCH₃); 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, CH₂CH₃), 1.75 (2, q, $J = 7.0$ Hz, CH₂CH₃). Alkaline hydrolysis of the nitrile **23** gave **1-ethyl-2-oxocycloheptaneacetic acid (16a)**, mp 59–61° (hexane–Et₂O), in 95% yield. Anal. (C₁₁H₁₈O₃) C, H. The methyl ester **16** had bp 100–101° (0.7 mm): NMR δ 0.83 (3, t, $J = 7.0$ Hz, CH₂CH₃), 2.38 (1, d, $J = 15$ Hz, CHC=O), 2.74 (1, d, $J = 15$ Hz, CHC=O), 3.6 (3, s, OCH₃); ir 1695 (CO), 1730 cm⁻¹ (COOMe).

2-Allyl-2-ethylcyclopentanone (20). To a stirred solution of 2-ethylcyclopentanone²⁹ (10.8 g, 0.089 mol) and allyl bromide (11.5 g, 0.095 mol) in Et₂O (150 ml) was added, during 30 min under N₂, a solution of sodium *tert*-amylate (7.1 g, 0.075 mol) in Et₂O (75 ml). The mixture was refluxed for 2 h and washed with aqueous 1% HCl, H₂O, 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, CH₂CH₃). Anal. (C₁₀H₁₆O) 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, CH₃), 4.85–6.15 (3, m, CH=CH₂).

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 N₂ for 21 h. The solvent was removed by evaporation and the residue was heated with 120 ml of a 20% aqueous H₂SO₄ solution under N₂ for 30 min at a bath temperature of 160°. The reaction mixture was poured onto crushed ice and extracted with 2 × 100 ml of Et₂O. The Et₂O extracts were washed with 50 ml of a 5% aqueous NaOH solution and then with a saturated aqueous NaCl solution. The dried Et₂O extracts were concentrated to give a residue (8.0 g) which was chromatographed on a silica gel column. Elution with C₆H₆ afforded **29** methyl ester (3.2 g, 20%), mp 99–100° (hexane). Anal. (C₂₀H₂₇NO₂) C, H, N. Elution with C₆H₆–Me₂CO (25:1) afforded **2-(2-*n*-propylphenyl)-4a-ethyl-4,4a,5,6,7,8-hexahydro-3(2H)-cinnolinone (43)** (4.0 g, 26%) as an oil. Anal. (C₁₉H₂₆N₂O) C, H, N. The methyl ester (2.85 g, 0.0095 mol), K₂CO₃ (1.5 g, 0.011 mol), MeOH (60 ml), and H₂O (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° (Et₂O–hexane)]. Anal. (C₁₈H₁₉NO₂) C, H, N], **26** methyl ester [mp 67–71° (C₆H₆)]. Anal. (C₁₇H₂₁NO₂) C, H, N], and **27** ethyl ester [mp 64–66° (hexane)]. Anal. (C₁₉H₂₃NO₂) C, H, N]. The following cinnolinone by-products were characterized: **4a-ethyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2H)-cinnolinone (44)** [mp 51–55° (Me₂CO–hexane)]. Anal. (C₁₆H₂₀N₂O) C, H, N], **4a-*n*-propyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2H)-cinnolinone (45)** [mp 59–61° (pentane)]. Anal. (C₁₇H₂₂N₂O) C, H, N], and **4a-methyl-2-phenyl-4,4a,5,6,7,8-hexahydro-3(2H)-cinnolinone (46)** [mp 82–83° (Et₂O–hexane)]. Anal. (C₁₅H₁₈N₂O) 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 N₂ atmosphere. After removal of the EtOH in vacuo the residue was heated at 160° with 50 ml of 20% aqueous H₂SO₄ 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 Me₂CO in C₆H₆ (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, CH₂CH₃), 1.50 (3, s, angular CH₃), 1.90 (6, m, aliphatic CH₂), 2.85 (6, m, CH₂C=O, aryl-CH₂), 3.65 (3, s, OCH₃), 7.0–7.5 (3, m, aromatic H). Continued elution afforded **10-ethyl-2,2a,3,4,5,6-hexahydro-2a-methyl-1H-10b-azabenzocyclopent[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, CH₂CH₃), 1.57 (3, s, angular CH₃), 1.9 (6, m, aliphatic CH₂), 2.85 (2, s, CH₂C=O), 3.0 (4, m, aryl-CH₂), 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 K₂CO₃ (1.0 g) in H₂O (5 ml) and heated at reflux under N₂ 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 N₂ atmosphere. The EtOH was removed and the residue was pyrolyzed at 160° for 50 h. After cooling, the residue was distributed between H₂O and Et₂O. The Et₂O 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 C₆H₆ afforded **2a,10-diethyl-2,2a,3,4,5,6-hexahydro-1H-10b-azabenzocyclopent[c,d]azulen-1-one (48)** (3.0 g, 28%) as an oil: NMR δ 0.83 (3, t, $J = 7$ Hz, CH₃), 1.27 (3, t, $J = 7$ Hz, CH₃), 3.35 (2, quartet of doublets, $J = 7$ and 2 Hz, CH₂C=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, CH₃), 1.87 (3, t, $J = 7$ Hz, CH₃), 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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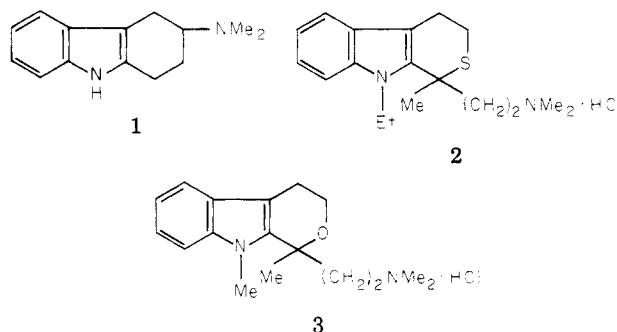
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The synthesis is described of a series of cycloalkanoindoles, comprising tetrahydrocarbazoles, a cyclopentindole, and a cycloheptindole, all bearing an ethanamine side chain at position 1. The acute toxicities of these compounds were evaluated, as 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 ED₅₀ of 0.12 mg/kg ip in preventing reserpine-induced ptosis in mice and an ED₅₀ 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 cardiogenic agents,⁶ and antidepressants.^{7,8} This latter activity has been confirmed in man for 3-dimethylamino-1,2,3,4-tetrahydrocarbazole (1).⁹



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