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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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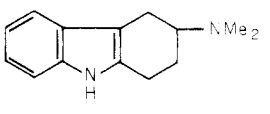
The synthesis is described of a series of cycloalkanoindoles, comprising tetrahydrocarbazoles, a cyclopentindole, and a cycloheptindole, all bearing an ethanamine side chain at position 1. The acute toxicities of these compounds were evaluated, as well as their potential antidepressant properties, using 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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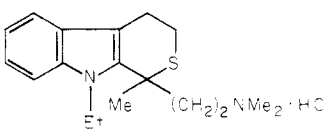

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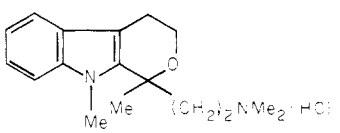

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Recent studies from our laboratories have shown that 9-ethyl-*N*,*N*,1-trimethyl-1,2,3,4-tetrahydrothiopyrano-[3,4-*b*]indole-1-ethanamine hydrochloride (**2**, tandamine hydrochloride, USAN) is a potent antidepressant as demonstrated in various models,[10-13] 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**.

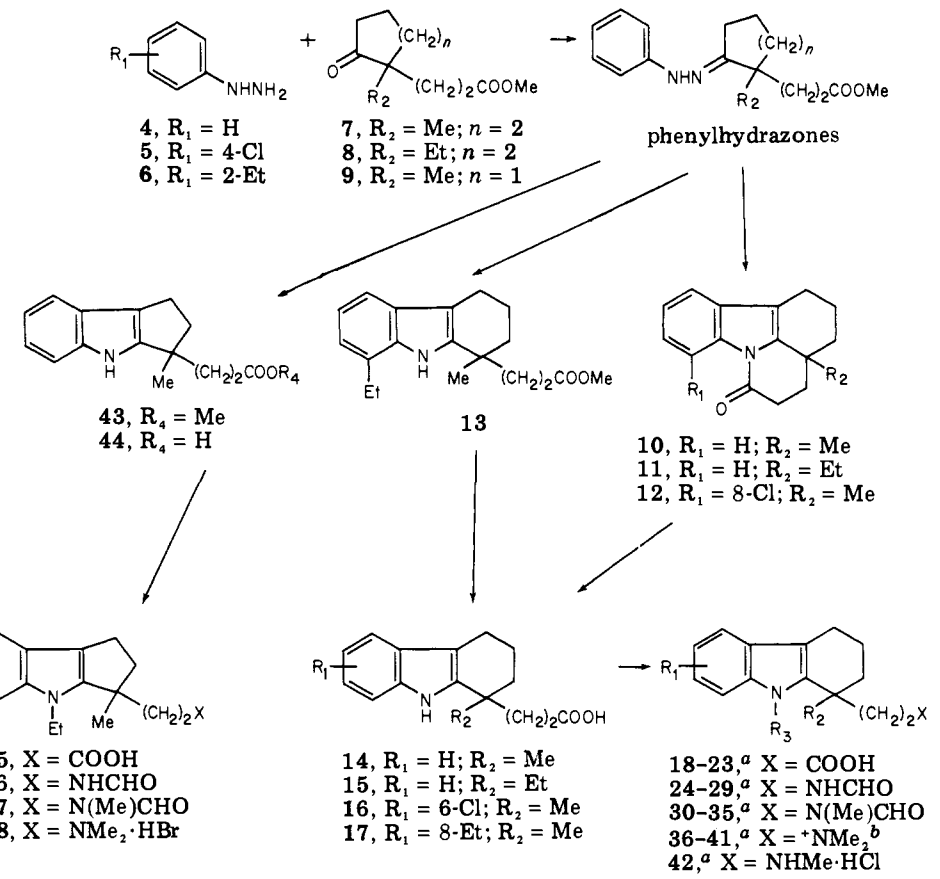
Chemistry. Ten novel cycloalkanoindole-1-ethylamines, **36–42**, **48**, **55**, and **59** (see Table I), were synthesized for biological evaluation. The route outlined in Scheme I was used for the preparation of the 1,9-dialkyltetrahydrocarbazoles **36–42** and for the 1,8-dialkylcyclopentindole **48**. 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

Scheme I



[a] The definitions of R_1-R_3 for 18-42 are for 18, 24, 30, 36, and 42, R_1 = H, R_2 = Me, R_3 = Et; for 19, 25, 31, and 37, R_1 = H, R_2 = R_3 = Et; for 20, 26, 32, and 38, R_1 = 6-Cl, R_2 = Me, R_3 = Et; for 21, 27, 33, and 39, R_1 = 8-Et, R_2 = Me, R_3 = Et; for 22, 28, 34, and 40, R_1 = H, R_2 = R_3 = Me; for 23, 29, 35, and 41, R_1 = H, R_2 = Me, R_3 = *n*-Pr. [b] See Table I for the nature of the anions.

31 afforded the secondary amine which was transformed to the hydrochloride salt 42.

A similar series of reactions, starting with 4 and 9, gave the cyclopentanoindole derivative 48 as shown in Scheme I. The Fischer indolization yielded the ester 43 as the major product, along with some of the acid 44 derived from hydrolysis. Alkylation of 44 with ethyl iodide and sodium hydride afforded the *N*-ethyl derivative 45, which was transformed via the intermediates 46 and 47 to the desired tertiary amine which was converted to the hydrobromide salt 48.

The cycloheptindole and tetrahydrocarbazole derivatives 55 and 59 were prepared by the routes shown in Schemes II and III. Fischer cyclization, with sulfuric acid, of the intermediate phenylhydrazone obtained from 4 and 49 afforded a mixture of the cycloheptapyridazinone 50 and the tetracyclic lactam 51. The latter was hydrolyzed to the acetic acid 52, which was *N*-ethylated to give 53. Conversion to the dimethylamide 54 followed by lithium aluminum hydride reduction produced the tertiary amine which was converted to its hydrochloride salt 55. Compound 59 was prepared in an analogous manner, as shown in Scheme III, starting from the known acid 56[16] and proceeding via the intermediates 57 and 58. Chemical and physical data for the final products 36–42, 48, 55, and 59 are collected in Table I. Chemical data for all characterized intermediates and reaction conditions for the preparation of all new compounds are found in the Experimental Section.

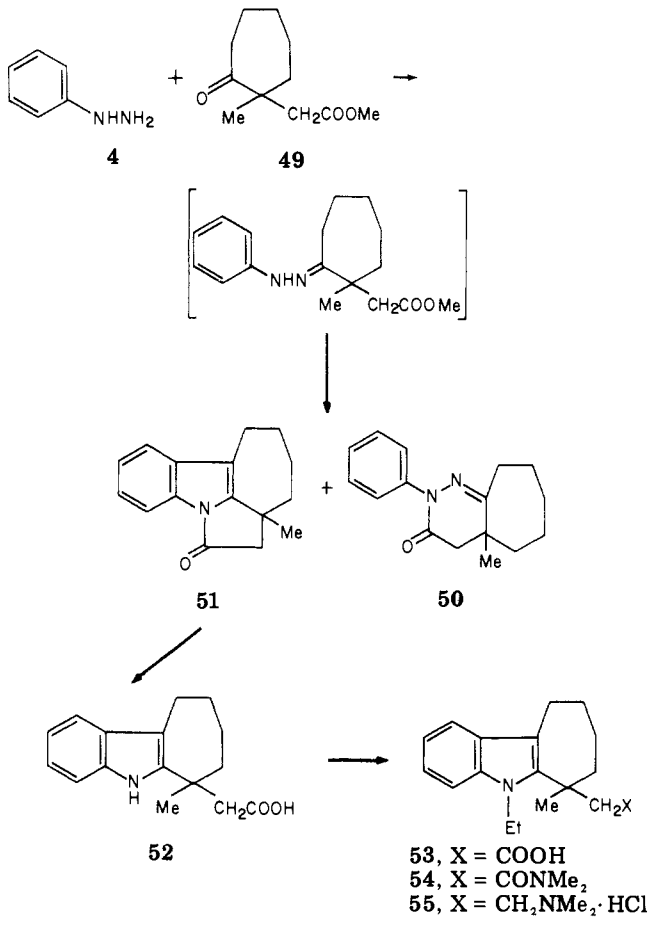
Pharmacology. Acute toxicities and effects on reserpine and tetrabenazine-induced ptosis of the cycloalkanoindoles listed in Table I were investigated. The results are shown in Table I along with those obtained with amitriptyline (61) and imipramine (62).

Acute toxicity was investigated ip in albino mice. Graded doses of the compounds were administered to groups of five animals each. The approximate LD_{50} was determined from the 5-day mortality data. Prevention of reserpine-induced ptosis was estimated ip in mice by an adaptation of the method of Petersen et al.[17] The percentage of mice in which ptosis was prevented was recorded. Prevention of tetrabenazine-induced ptosis was estimated in rats ip by a modification of the method of Giurgea et al.[18] The ED_{50}'s in both tests were determined according to the method of Finney.[19]

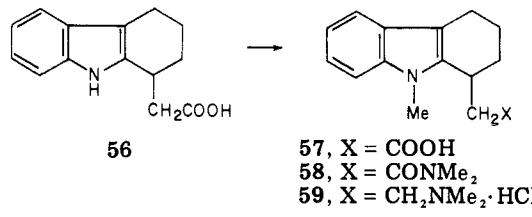
Inspection of the results shows that compound 36 is the most potent of the series in preventing reserpine-induced ptosis. This tetrahydrocarbazole bears 1-methyl, 9-ethyl, and 1-dimethylaminoethyl groups. The addition of a 6-chlorine atom to produce 38 does not have any marked effect on antireserpine activity. In contrast, the placement of an ethyl group at the 8 position (39) results in over a 100-fold loss of potency in comparison with 36. Changing the nature of the indolic nitrogen substituent, at position 9, from ethyl to methyl or *n*-propyl (compare 36 with 40 and 41), or changing the 1-alkyl substituent from methyl to ethyl (compare 36 and 37), results in a three- to sevenfold reduction in potency. Compound 42, the secondary amine corresponding to 36, is about 13 times less potent than 36. Replacing the alkyl substituent at position 1 by a hydrogen atom (compare 40 and 59) also leads to a reduction in potency in this series.

We have also tested the structurally related tetrahydrocarbazolemethanamine, 60, which is reported to have

Scheme II



Scheme III



antidepressant properties,[7] but in our hands it was found to be virtually devoid of activity. Compound **48**, the cyclopentano analogue of **36**, and compound **55**, the cycloheptano analogue, were both found to be very active compounds, having potencies in the reserpine ptosis test $^1/_6$ and $^1/_2$, respectively, of the most potent compound, **36**.

Compound **36**[20] was compared with amitriptyline (**61**) and imipramine (**62**) for its capacity to prevent tetrabenazine-induced ptosis in rats. The results given in Table I show that **36** is considerably more potent than amitriptyline and imipramine in this test, as well as in preventing reserpine-induced ptosis in mice while having an acute toxicity in the same range as those of amitriptyline and imipramine.

The results described herein, in the reserpine-ptosis test, with the tetrahydrocarbazole **36** (ED_{50} 0.12 mg/kg), the cyclopentanoindole **48** (ED_{50} 0.75 mg/kg), and the cycloheptanoindole **55** (ED_{50} 0.27 mg/kg), considered in conjunction with the recently published value for the pyranoindole **3** (ED_{50} 0.51 mg/kg),[14] and the potent antidepressant properties of the thiopyrano indole **2**[10-13] (ED_{50} 0.13 mg/kg in the reserpine-ptosis test[12]) show that these five nuclei, when similarly substituted, are almost equally endowed with antidepressant-like pharmacological properties. The partially saturated rings of each of these five nuclei would be expected to assume a different conformation, and the nature of these conformations in **2** and **3** has been suggested previously.[21,22] It therefore follows that the receptor involved in mediating these antidepressant effects is not particularly discriminating in at least some of its steric requirements.

In marked contrast is the observation that when the pyranoindole and tetrahydrocarbazole nuclei of **3** and **36** bear acetic acid chains at position 1, along with appropriately located lower alkyl substituents, potent antiinflammatory properties are found,[1,21,23] while the analogously substituted cyclopentanoindole **48** has only moderate antiinflammatory properties,[1] and the cycloheptanoindole and thiopyranoindole nuclei of **55** and **2** afforded compounds with only marginal antiinflammatory activity.[1,22] These observations suggest that the receptor involved with the antiinflammatory actions of these compounds is very sensitive to conformational changes in the partially saturated ring.

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. All ir spectra were taken in $CHCl_3$. Melting points were taken on a Thomas-Hoover apparatus and need no correction.

Methyl 1-Ethyl-2-oxocyclohexanepropionate (8). 2-Ethylcyclohexanone (132.0 g, 1.05 mol) was added during 30 min to a stirred solution of potassium *tert*-butoxide (5.76 g, 0.051 mol) in *tert*-butyl alcohol (320 ml) under N_2. Methyl acrylate (98.4 g, 1.05 mol) was then added during 30 min while maintaining the temperature below 30°. After stirring for 4 h at 22°, aqueous H_2SO_4 (175 ml of 2 N) was added slowly and the mixture was extracted with Et_2O. The Et_2O extracts were washed with brine, dried with $MgSO_4$, and fractionally distilled to afford 95.6 g (43%) of the product: bp 117–120° (0.4 mm); NMR δ 0.75 (3, t, J = 7.5 Hz, CH_2CH_3), 3.7 (3, s, OCH_3); ir 1740 (COOMe), 1705 cm^{-1} (CO).

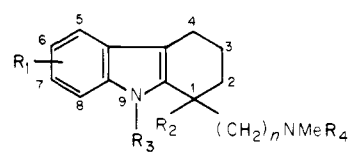
1,2,3,3a,4,5-Hexahydro-3a-methyl-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (10). A mixture of phenylhydrazine (82.9 g, 0.77 mol), methyl 1-methyl-2-oxocyclohexanepropionate (**7**,[24] 152 g, 0.77 mol), and MeOH (500 ml) was heated as reflux for 2 h. The MeOH was removed in vacuo at 45° and the residue was heated at reflux with 20% aqueous H_2SO_4 (1250 ml) for 2.5 h. After cooling, the mixture was extracted with $CHCl_3$. The extract was washed with 10% aqueous NaOH and brine. After drying, the $CHCl_3$ was removed in vacuo and the residue was chromatographed on a silica gel column. Elution with C_6H_6 gave 106 g (58%) of the product, mp 98–100° (Et_2O–pentane). Anal. ($C_{16}H_{17}NO$) C, H, N. Further elution with C_6H_6–EtOAc (20:1) afforded **methyl 1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionate (14 methyl ester)** in 5% yield as an oil: NMR δ 1.27 [3, s, $(C)_3CCH_3$], 3.6 (3, s, OCH_3), 7.9 (1, broad, NH).

1,2,3,3a,4,5-Hexahydro-3a-ethyl-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (11). The reaction between phenylhydrazine and methyl 1-ethyl-2-oxocyclohexanepropionate (**8**), using the conditions described for the preparation of **10**, afforded the product **11** in 51% yield: mp 97–99° (C_6H_6–hexane). Anal. ($C_{17}H_{19}NO$) C, H, N.

1,2,3,3a,4,5-Hexahydro-9-chloro-3a-methyl-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (12). The reaction between 4-chlorophenylhydrazine (**5**) and methyl 1-methyl-2-oxocyclohexanepropionate (**7**), using the conditions described for the preparation of **10**, produced the product **12** in 90% yield: mp 135–136.6° (C_6H_6–hexane). Anal. ($C_{16}H_{16}ClNO$) C, H, N.

Methyl 8-Ethyl-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionate (13). A mixture of 2-ethylphenylhydrazine (**6**,[25] 13.4 g, 0.1 mol), compound **7** (19.8 g, 0.1 mol), and anhydrous EtOH (250 ml) was heated at reflux for 1 h under N_2. The solvent was evaporated and the residue was heated with 20% aqueous H_2SO_4 (250 ml) for 30 min at 150°. The cooled mixture was saturated with NaCl and extracted with Et_2O. The extracts were washed

Table I. Chemical and Pharmacological Data on Cycloalkanoindoleethanamines



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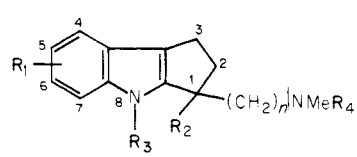

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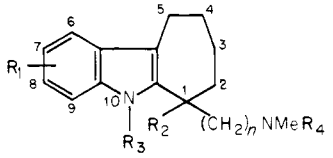

C

No.	Nucleus	n	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent[a]	Yield,[b] %	Formula[c]	Acute toxicity in mice, LD_{50}, mg/kg	Prevention of reserpine ptosis in mice, ED_{50}, mg/kg ± SE	Prevention of tetrabenazine ptosis in rats, ED_{50}, mg/kg ± SE
36	A	2	H	Me	Et	Me	206-209	I, II, III	50	$C_{19}H_{28}N_2 \cdot HCl$	125	0.12 ± 0.02	**3.3** ± 0.8
37	A	2	H	Et	Et	Me	207-210	I, II, III, IV	64	$C_{20}H_{30}N_2 \cdot HBr$	175	0.7 ± 0.2	
38	A	2	6-Cl	Me	Et	Me	214-216	I, III	75	$C_{19}H_{24}N_2 \cdot HCl$	*d*	0.19 ± 0.07	
39	A	2	8-Et	Me	Et	Me	82-84	I, II, III	67	$C_{21}H_{32}N_2 \cdot C_4H_4O_4$	*d*	19 ± 2.7	
40	A	2	H	Me	Me	Me	226-227	I, III	40	$C_{18}H_{26}N_2 \cdot HCl$	125	0.8 ± 0.2	
41	A	2	H	Me	*n*-Pr	Me	230-233	I, III, IV	40	$C_{20}H_{30}N_2 \cdot HCl$	125	0.4 ± 0.08	
42	A	2	H	Me	Et	H	213-216	I, II, III	74	$C_{18}H_{26}N_2 \cdot HCl$	125	1.6 ± 0.3	
59	A	2	H	H	Me	Me	257-259	II, III, IV	58	$C_{17}H_{24}N_2 \cdot HCl$	125	5 ± 1.4	
60	A	1	6-Cl	H	H	Me[e]					*d*	>30	
48	B	2	H	Me	Et	Me	217-220	I, III	50	$C_{18}H_{26}N_2 \cdot HBr$	*d*	0.75 ± 0.2	
55	C	2	H	Me	Et	Me	194-197	*f*	73	$C_{20}H_{30}N_2 \cdot HCl$	85	0.27 ± 0.05	
61	Amitriptyline										94	4.7 ± 0.7	37 ± 7
62	Imipramine										115	6.0 ± 0.6	22.6 ± 9

[a] I = methylene dichloride; II = benzene; III = ether; IV = methanol. The solvent mixtures indicated were used. [b] The yields reported for **36–42**, **59**, **48**, and **55** are based on the transformation of the intermediates **30–35**, **58**, **47**, and **54**. [c] All new compunds were analyzed for C, H, and N except for **38** and **55** which were analyzed only for N. The results were within ±0.4% of the calculated values, with the exception of **38** (C: calcd, 70.06; found, 70.51). [d] Not determined. [e] Prepared as described in ref 7. [f] Triturated with ether.

with brine, dried ($MgSO_4$), and evaporated to give a residue which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1) gave 5.1 g of the product as an oil: NMR δ 1.33 [3, s, $(C)_3CCH_3$], 1.35 (3, t, J = 8 Hz, CH_2CH_3), 2.88 (2, q, J = 8 Hz, CH_2CH_3), 3.60 (3, s, OCH_3), 3.79 (1, broad, NH). Continued elution gave 8.0 g of the corresponding acid **17**.

Methyl 1-Methyl-1,2,3,8-tetrahydrocyclopent[*b*]indole-1-propionate (43). By using the procedure described above for the preparation of **13**, phenylhydrazine (**4**) and methyl 1-methyl-2-oxocyclopentanepropionate (**9**)[26] were allowed to react together to afford a crude product which was chromatographed on silica gel. Elution with C_6H_6–Me_2CO (19:1) gave 66% of the product **43** as an oil: NMR δ 1.30 [3, s, $(C)_3CCH_3$], 3.55 (3, s, OCH_3), 8.10 (1, broad, NH). Elution with C_6H_6–Me_2CO (4:1) gave 15% of the corresponding acid **44**.

1-Methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (14). A solution of the pyridocarbazolone **10** (0.5 g, 0.002 mol) in EtOH (10 ml) and 10% aqueous NaOH (2 ml) was heated at reflux for 3 h. The EtOH was removed in vacuo and H_2O was added. The aqueous solution was washed with Et_2O, acidified to pH 3.0, and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated to give the product (0.48 g). A sample, crystallized from $CHCl_3$, had mp 204–206°. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

1-Ethyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (15). Using the procedure described for the preparation of **14**, the pyridocarbazolone **11** afforded the product **15** in 82% yield: mp 141–142° (CH_2Cl_2–C_6H_6–hexane). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

6-Chloro-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (16). Using the procedure described above for the preparation of **14**, the pyridocarbazolone **12** afforded the product **16** in 87% yield: mp 142.5–143.5° ($CHCl_3$–hexane). Anal. ($C_{16}H_{18}ClNO_2$) C, H, N.

8-Ethyl-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (17). The corresponding methyl ester **13** (5.0 g, 0.0167 mol) was hydrolyzed with K_2CO_3 (1.38 g, 0.01 mol) in H_2O (4 ml) and MeOH (75 ml) by refluxing under N_2 for 20 h. A conventional workup afforded the product, **17**, in 93% yield as an oil, which slowly solidified: mp 134–136°; NMR δ 1.33 (3, t, J = 7 Hz, CH_2CH_3), 1.33 [3, s, $(C)_3CCH_3$], 2.8 (2, q, J = 7 Hz, CH_2CH_3), 7.68 (1, broad, NH), 10.6 (1, broad, COOH).

1-Methyl-1,2,3,8-tetrahydrocyclopent[*b*]indole-1-propionic Acid (44). By using the procedure described for the preparation of **17** the cyclopent[*b*]indole-1-propionate **43** was hydrolyzed to the product in 54% yield. It had mp 182–184° ($CHCl_3$–pentane). Anal. ($C_{15}H_{17}NO_2$) H, N; C: calcd, 74.05; found, 73.24.

9-Ethyl-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (18). To a solution of compound **14** (33.4 g, 0.13 mol) and EtBr (36 ml, 0.48 mol) in anhydrous DMF (75 ml) was added sodium hydride (13.5 g of a 57% dispersion in mineral oil, 0.32 mol) portionwise, with stirring under N_2. The slightly exothermic reaction mixture was stirred for 30 min, then cooled, and diluted with H_2O until a clear solution was obtained. Neutral material was removed by extraction with Et_2O, and the aqueous solution was acidified with 6 N aqueous HCl and extracted with Et_2O. The Et_2O extract afforded the product **18** (14.1 g, 38%) as an oil which crystallized from $CHCl_3$–hexane and had mp 154–157°. Anal. ($C_{18}H_{23}NO_2$) C, H, N. The neutral ester fraction (ir 1725 cm^{-1}) was hydrolyzed to afford an additional 22.3 g of **18** for a total yield of 95%.

1,9-Diethyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (19). Ethylation of compound **15**, using the procedure described above, gave the product **19**, mp 122.5–124.5° ($CHCl_3$–hexane). Anal. ($C_{19}H_{25}NO_2$) C, H, N. The corresponding ethyl ester (ir 1735 cm^{-1}) was isolated from the neutral fraction. Hydrolysis of the ester led to a total yield of 85% of **19**.

8,9-Diethyl-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (21). Ethylation of compound **17**, as described above for **14** and **15**, gave the product **21** as an oil: NMR δ 1.15 (3, t, J = 8 Hz, CH_2CH_3), 1.30 (3, t, J = 7 Hz, CH_2CH_3), 1.45 [3, s, $(C)_3CCH_3$], 3.0 (2, q, J = 8 Hz, aryl-CH_2), 4.35 (2, q, J = 7 Hz, NCH_2). The ethyl ester contained in the neutral fraction was hydrolyzed to give **21** in a total yield of 39%.

1-Methyl-9-*n*-propyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (23). Alkylation of compound **14** with *n*-propyl bromide using the procedure described for the preparation of **21** gave the product **23**, mp 82.5–86° (Et_2O–pentane). Anal. ($C_{19}H_{25}NO_2$) C, H, N. The *n*-propyl ester (ir 1735 cm^{-1}) contained

in the neutral fraction was hydrolyzed to give the acid **23** in a total yield of 71%.

1,9-Dimethyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (22). A solution of compound **14** (13.0 g, 0.048 mol) in anhydrous THF (150 ml) was added under N_2 to a stirred suspension of sodium hydride (6.0 g of a 50% dispersion in mineral oil, 0.12 mol) in THF (150 ml). After stirring for 15 min, MeI (9.0 ml) was added dropwise and the reaction mixture was maintained at 40° for 60 min. H_2O (300 ml) was added and the solution was washed with Et_2O. After acidification, the solution was extracted with Et_2O. The extract was dried and evaporated to give a residue which was chromatographed on a silica gel column. Elution with C_6H_6–Me_2CO (3:1) afforded the pure product as an oil in 87% yield: NMR 1.4 [3, s, $(C)_3CCH_3$], 3.76 (3, s, NCH_3), 10.8 (1, broad, COOH).

6-Chloro-9-ethyl-1-methyl-1,2,3,4-tetrahydrocarbazole-1-propionic Acid (20). Alkylation of compound **17** with ethyl iodide, using the procedure described above for the preparation of **22**, and elution from a silica gel column with C_6H_6–Et_2O (9:1) afforded the product **20**, mp 99–104° ($CHCl_3$–hexane), in 50% yield: NMR δ 1.35 (3, t, J = 7 Hz, CH_2CH_3), 4.2 (2, q, J = 7 Hz, NCH_2), 8.0 (1, broad, COOH). Anal. ($C_{18}H_{22}ClNO_2$) N.

8-Ethyl-1-methyl-1,2,3,8-tetrahydrocyclopent[*b*]indole-1-propionic Acid (45). Alkylation of the cyclopent[*b*]indole-1-propionic acid **44** (12.1 g) with ethyl iodide, using the procedure described for the preparation of **22**, gave an oil which partially solidified on standing. It was triturated with Et_2O and the Et_2O phase was extracted with 5% aqueous $NaHCO_3$. The alkaline extract was acidified and extracted with Et_2O to afford an oil which was chromatographed on silica gel. Elution with C_6H_6–Me_2CO (19:1) gave the product **45** (3.3 g, 25%) as an oil: NMR δ 1.38 (3, t, J = 7 Hz, CH_2CH_3), 1.45 [3, s, $(C)_3CCH_3$], 4.17 (2, q, J = 7 Hz, NCH_2), 10.8 (1, s, COOH).

***N*-[2-(1,9-Dimethyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (28).** To a solution of the propionic acid **18** (11.0 g, 0.04 mol), THF (200 ml), and Et_3N (7.25 g, 0.07 mol) was added, at 0° under N_2, ClCOOEt (6.5 g, 0.06 mol). The mixture was kept at 0° for 1 h and then cooled to −10°. A solution of NaN_3 (3.5 g, 0.055 mol) in H_2O (18 ml) was added slowly. After 1 h at −10°, Et_2O (100 ml) was added. The organic phase was dried ($MgSO_4$) and evaporated at 22° (caution!) to give the crude azide (ir 2160 cm^{-1}) as an oil. It was dissolved in C_6H_6 (150 ml) and the solution was heated at reflux for 30 min to afford, after evaporation of the solvent, the oily isocyanate (ir 2250 cm^{-1}). To a solution of the isocyanate in toluene at −50° was added 88% HCOOH (5 ml). The temperature was allowed to rise to 20° and after 1 h at 20°, the mixture was kept at 50° for 1 h. The solution was washed with 2 N HCl and then with brine, dried, and evaporated to give a residue which was chromatographed on a silica gel column. Elution with C_6H_6–Me_2CO (9:1) gave 5.0 g (50% based on the acid **18**) of the product, **28**, as an oil: NMR δ 1.4 [3, s, $(C)_3CCH_3$], 5.66 (1, broad, NH), 7.97 (1, d, J = 2 Hz, NCHO).

In an analagous manner the formamides **24–27, 29,** and **46** were prepared.

***N*-[2-(9-Ethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (24)** was obtained as an oil in 30% yield from the propionic acid **18**: NMR δ 1.38 (3, t, J = 7 Hz, CH_2CH_3), 1.43 [3, s, $(C)_3CCH_3$], 4.3 (2, q, J = 7 Hz, NCH_2CH_3), 5.5 (1, broad, NH), 8.0 (1, s, NCHO).

***N*-[2-(1,9-Diethyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (25)** was obtained as an oil from the propionic acid **19** in 59% yield: NMR δ 0.8 (3, t, J = 7 Hz, CH_2CH_3), 1.35 (3, t, J = 7 Hz, CH_2CH_3), 4.25 (2, q, J = 7 Hz, NCH_2CH_3), 5.45 (1, broad, NH), 7.90 (1, s, NCHO).

***N*-[2-(6-Chloro-9-ethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (26)** was obtained from the propionic acid **20** by chromatography of the reaction product. Elution with C_6H_6–MeOH (19:1) gave 43% of **26** as an oil: ir 3450, 1670 cm^{-1}. Prior elution with C_6H_6–Et_2O (9:1) gave 20% of the ethyl ester of the starting material **20**: NMR δ 1.2 (3, t, J = 7 Hz, CH_2CH_3), 1.43 (3, t, J = 7 Hz, CH_2CH_3), 1.45 [3, s, $(C)_3CCH_3$], 4.15 (2, q, J = 7 Hz, OCH_2CH_3), 4.33 (2, q, J = 7 Hz, NCH_2CH_3).

***N*-[2-(8,9-Diethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (27)** was obtained as an oil from the propionic acid **21** in 26% yield: NMR δ 1.16 (3, t, J = 7 Hz, CH_2CH_3), 1.25 (3, t, J = 7 Hz, CH_2CH_3), 1.48 (3, s, $(C)_3CCH_3$), 4.36 (2, q, J = 7 Hz, NCH_2CH_3), 5.55 (1, broad, NH), 8.0 (1, s, NCHO).

***N*-[2-(1-Methyl-9-*n*-propyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]formamide (29)** was obtained as an oil from the propionic acid **23** in 76% yield: NMR 1.0 [3, t, J = 7 Hz, $(CH_2)_2CH_3$], 1.41 [3, s, $(C)_3CCH_3$], 4.1 (2, m, $NCH_2CH_2CH_3$), 5.6 (1, broad, NH), 7.95 (1, s, NCHO).

***N*-[2-(8-Ethyl-1-methyl-1,2,3,8-tetrahydrocyclopent[*b*]indol-1-yl)ethyl]formamide (46)** was obtained as an oil from the acid **46** in 38% yield: NMR δ 1.38 (3, t, J = 7 Hz, CH_2CH_3), 1.42 [3, s, $(C)_3CCH_3$], 4.16 (2, q, J = 7 Hz, NCH_2CH_3), 5.41 (1, broad, NH), 7.95 (1, s, NCHO).

***N*-[2-(1,9-Dimethyl-1,2,3,4-tetrahydrocarbazol-1-yl)-ethyl]-*N*-methylformamide (34).** To a suspension of sodium hydride (2.5 g of a 50% dispersion in mineral oil, 0.05 mol) in xylene (25 ml) was added a solution of the formamide **28** (5.0 g, 0.018 mol) in xylene (75 ml). After heating at reflux for 18 h under N_2, MeI (10 ml) was added and heating was continued for 5 h. H_2O was added and the organic phase was dried and evaporated to afford a residue which was chromatographed on a silica gel column. Elution with C_6H_6–Me_2CO (7:3) afforded the product **34**, as an oil, in 98% yield: NMR δ 1.4 [3, s, $(C)_3CCH_3$], 2.8 [3, s, $N(CH_3)CHO$], 3.80 (3, d, J = 5 Hz, NCH_3), 7.90 (1, d, J = 4 Hz, NCHO).

In an analagous manner, the *N*-methylformamides **31–33, 35,** and **47** were obtained as oils.

***N*-[2-(9-Ethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)-ethyl]-*N*-methylformamide (30)**: from **24** in 95% yield; NMR δ 1.4 (3, t, J = 7 Hz, CH_2CH_3), 1.45 [3, s, $(C)_3CCH_3$], 2.82 [3, s, $N(CH_3)CHO$], 4.25 (2, dq, J = 3.5 and 7.0 Hz, CH_2CH_3), 7.9 (1, d, J = 3 Hz, NCHO).

***N*-[2-(1,9-Diethyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]-*N*-methylformamide (31)**: from **25** in 95% yield; NMR δ 0.85 (3, t, J = 7.5 Hz, CH_2CH_3), 1.3 (3, dt, J = 7 and 1 Hz, CH_2CH_3), 2.8 [3, s, $N(CH_3)CHO$], 4.28 (2, dq, J = 7 and 4 Hz, NCH_2CH_3), 7.90 (1, d, J = 4 Hz, NCHO).

***N*-[2-(6-Chloro-9-ethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]-*N*-methylformamide (32)**: from **26** in 63% yield; NMR δ 1.4 (3, t, J = 7 Hz, CH_2CH_3), 1.45 [3, s, $(C)_3CCH_3$], 2.85 [3, d, J = 2 Hz, $N(CH_3)CHO$], 4.30 (2, dq, J = 7 and 3.5 Hz, NCH_2CH_3), 8.00 (1, d, J = 5 Hz, NCHO).

***N*-[2-(8,9-Diethyl-1-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]-*N*-methylformamide (33)**: from **27** in 79% yield; NMR δ 1.15 (3, dt, J = 8 and 1.5 Hz, CH_2CH_3), 1.30 (3, t, J = 7 Hz, CH_2CH_3), 1.50 [3, s, $(C)_3CCH_3$], 2.80 [3, s, $N(CH_3)CHO$], 4.35 (2, dq, J = 7 and 4 Hz, NCH_2CH_3), 7.90 (1, d, J = 3.5 Hz, NCHO).

***N*-[2-(1-Methyl-9-*n*-propyl-1,2,3,4-tetrahydrocarbazol-1-yl)ethyl]-*N*-methylformamide (35)**: from **29** in 84% yield; NMR δ 1.00 [3, t, J = 7 Hz, $(CH_2)_2CH_3$], 2.8 [3, s, $N(CH_3)CHO$], 4.15 (2, m, $NCH_2CH_2CH_3$), 7.9 (1, d, J = 4 Hz, NCHO).

***N*-[2-(8-Ethyl-1-methyl-1,2,3,8-tetrahydrocyclopent[*b*]indol-1-yl)ethyl]-*N*-methylformamide (47)**: from **46** in 98% yield; NMR δ 1.42 (3, dt, J = 7 and 1 Hz, CH_2CH_3), 1.48 [3, s, $(C)_3CCH_3$], 2.84 [3, s, $N(CH_3)CHO$], 4.2 (2, dq, J = 7 and 2.5 Hz, NCH_2CH_3), 8.00 (1, d, J = 3 Hz, NCHO).

***N*,*N*,1,9-Tetramethyl-1,2,3,4-tetrahydrocarbazole-1-ethanamine Hydrochloride (40).** A mixture of the *N*-methylformamide **34** (5.0 g, 0.017 mol), $LiAlH_4$ (0.5 g, 0.015 mol), and THF (150 ml) was stirred at 25° for 2 h. H_2O was added and a conventional workup procedure gave the free base of the product (3.0 g). The HCl salt was prepared with ethereal HCl and had mp 226–227° (CH_2Cl_2–Et_2O). Further data for **40** are shown in Table I.

Using the method described above, the *N*-methylformamides **30–33, 35,** and **47** were reduced to the tertiary amines **36–39, 41,** and **48**, respectively. They were converted to the acid addition salts indicated in Table I, and chemical data on these salts are contained therein.

***N*,1-Dimethyl-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-ethanamine Hydrochloride (42).** The *N*-methylformamide **36** (2.1 g) and 10% aqueous KOH (50 ml) were stirred and heated at reflux for 48 h. The mixture was acidified, extracted with Et_2O, basified with aqueous KOH, and extracted with Et_2O. The latter Et_2O extracts were dried and evaporated to afford the free base of the product (1.4 g), which was converted to the HCl salt with

ethereal HCl. It had mp 213–216° ($CHCl_2$–Et_2O). Further data on **42** are shown in Table I.

2,2a,3,4,5,6-Hexahydro-2a-methyl-1*H*-10b-azabenzo[*a*]cyclopent[*d*]azulen-1-one (51). A mixture of $C_6H_5NHNH_2$ (8 g, 0.07 mol), $C_6H_5NHNH_2$·HCl (12.0 g, 0.08 mol), methyl 1-methyl-2-oxocycloheptaneacetate,[1] **49** (16.0 g, 0.08 mol), and EtOH (100 ml) was heated at reflux for 20 h. H_2O was added and the mixture extracted with C_6H_6. The solvent was evaporated and the residue was heated with 20% aqueous H_2SO_4 (230 ml) at 150° for 1 h. The reaction mixture was poured onto ice and extracted with C_6H_6 and then with Et_2O. The organic phases afforded a residue which was chromatographed on silica gel. Elution with C_6H_6 afforded the product **51** as an oil (3.6 g, 19%): NMR 1.42 (3, s, CH_3), 2.90 (2, s, CH_2CO), 7.0–7.7 (3, m, aromatic H's), 7.9–8.2 (1, m, aromatic H). Further elution with C_6H_6 gave 3.5 g (17%) of **2,4,4a,5,6,7,8,9-octahydro-4a-methyl-2-phenyl-3*H*-cyclohepta[*c*]pyridazin-3-one (50)** as an oil which solidified on standing: NMR δ 1.18 (3, s, CH_3), 2.18 (2, d, J = 16.5 Hz, CH_2CO). Anal. ($C_{16}H_{20}N_2O$) C, H, N.

1-Methyl-1,2,3,4,5,10-hexahydrocyclohept[*b*]indole-1-acetic Acid (52). Using the procedure described above for the preparation of **17**, the lactam **51** was hydrolyzed to the product **52** in 67% yield. It had mp 119–122° (C_6H_6–hexane). Anal. ($C_{16}H_{19}NO_2$) N.

10-Ethyl-1-methyl-1,2,3,4,5,10-hexahydrocyclohept[*b*]indole-1-acetic Acid (53). Using the alkylation procedure described for the preparation of **22** the acetic acid **52** was converted to the product **53** in 40% yield. It had mp 141–143° ($CHCl_3$–pentane). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

9-Methyl-1,2,3,4-tetrahydrocarbazole-1-acetic Acid (57). Using the alkylation procedure described for the preparation of **22**, 1,2,3,4-tetrahydrocarbazole-1-acetic acid[16] (**56**) was converted to the product **57** in 55% yield. It had mp 143–145°. Anal. ($C_{15}H_{17}NO_2$) H, N; C: calcd, 74.05; found, 73.55.

10-Ethyl-*N*,*N*,1-trimethyl-1,2,3,4,5,10-hexahydrocyclohept[*b*]indole-1-acetamide (54). To a stirred solution of the acetic acid **53** (1.55 g, 0.006 mol) in THF (60 ml) at −15° was added Et_3N (3 ml) and ClCOOEt (1.5 g, 0.13 mol). After 30 min, the solution was added slowly to a 40% aqueous solution of Me_2NH (100 ml). The mixture was stirred for 30 min at 22° and then extracted with Et_2O to afford a residue which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1) gave the product as an oil in 76% yield: NMR δ 1.4 (3, t, J = 7 Hz, CH_2CH_3), 1.73 [3, s, $(C)_3CCH_3$], 2.75 [3, s, $CON(CH_3)_2$], 2.85 [3, s, $CON(CH_3)_2$], 4.4 (2, q, J = 7 Hz, NCH_2CH_3).

***N*,*N*,9-Trimethyl-1,2,3,4-tetrahydrocarbazole-1-acetamide (58).** Using the procedure described for the preparation of **54**, the acetic acid **57** was converted to the product **58** in 80% yield. It had mp 93–95° (Et_2O): NMR δ 2.93 [3, s, $CON(CH_3)_2$], 3.00 [3, s, $CON(CH_3)_2$], 3.63 (3, s, NCH_3), 7.25 (4, m, aromatic H's). Anal. ($C_{17}H_{20}N_2O$) N.

10-Ethyl-*N*,*N*,1-trimethyl-1,2,3,4,5,10-hexahydrocyclohept[*b*]indole-1-ethanamine Hydrochloride (55). Using the procedure described for the preparation of **40**, the acetamide **54** was reduced with $LiAlH_4$ to the corresponding oily tertiary amine in 73% yield. The HCl salt **55** had mp 194–197° when precipitated out of Et_2O with ethereal HCl: NMR δ 1.38 (3, t, J = 7 Hz, CH_2CH_3), 1.58 [3, s, $(C)_3CCH_3$], 2.68 [3, d, J = 5 Hz, $N(CH_3)_2$], 2.75 [3, d, J = 5 Hz, $N(CH_3)_2$], 4.42 (2, q, J = 7 Hz, CH_2CH_3), 7.3 (4, m, aromatic H's), 12.3 (1, broad, NH^+). Anal. ($C_{20}H_{31}ClN_2$) N.

***N*,*N*,9-Trimethyl-1,2,3,4-tetrahydrocarbazole-1-ethanamine Hydrochloride (59).** Using the procedure described for the preparation of **40** the acetamide **58** was reduced with $LiAlH_4$ to the corresponding oily tertiary amine in 58% yield. The HCl salt **59** had mp 257–259° (MeOH–C_6H_6–Et_2O). Anal. ($C_{17}H_{25}ClN_2$) C, H, N.

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