nmr[3] 2-NCH_3, δ 2.85 (s); 4-CH_2, 5.50 (s). *Anal.* ($C_9H_{16}N_2O$) C, H, N.

2-Dimethylamine-1-oxa-3-azaspiro[4.5]dec-2-ene (12).—Dimethylcarbamoyl chloride (21.5 g, 0.2 mol) was added to a solution of 1-aminomethylcyclohexanol (25.9 g, 0.2 mol) and Et_3N (30.3 g, 0.3 mol) in dry PhMe (400 ml) at 0°. A precipitate formed immediately. The mixture was stirred at 20° for 2 hr and filtered. The solid obtained was extracted with hot Et_2O (3 portions of 500 ml). The Et_2O solutions were dried ($MgSO_4$) and concentrated to yield pure 1-(2-hydroxy-2-spirocyclohexyl)-ethyl-3,3-dimethylurea (**11**), mp 96–97°, 61.3% yield. *Anal.* ($C_{10}H_{20}N_2O_2$) C, H, N.

The hydroxyurea **11** (20.0 g, 0.1 mol) was treated with $SOCl_2$ and then with boiling H_2O, as described above for the synthesis of **10**, but no H_2O-insoluble fraction was obtained. The aqueous solution was basified with a saturated solution of K_2CO_3 and extracted with CH_2Cl_2 (three portions of 250 ml). The CH_2Cl_2 solution was dried and concentrated under reduced pressure to an oil. The oil was distilled to yield **12** [bp 73–75° (0.85 mm), 30.6% yield; nmr[3] 2-$N(CH_3)_2$, δ 2.91 (s); 4-CH_2, 5.50 (s). *Anal.* ($C_9H_{18}N_2O$) C, H, N] and 1-(cyclohex-1-enyl)methyl-3,3-dimethylurea (**13**) [bp 130–132° (0.55 mm), 41.4% yield. *Anal.* ($C_{10}H_{18}N_2O$) C, H, N].

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3-Substituted 1,2,3,4-Tetrahydrocarbazoles

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In previous studies of heterocyclic compounds[1,2] it was found that *N*-alkylated 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole had antireserpine activity equal to imipramine with little antimorphine effect. Because this derivative was the sulfur isostere of the 3-carbon atom of 1,2,3,4-tetrahydrocarbazole, it was of interest to prepare various 3-substituted derivatives of 1,2,3,4-tetrahydrocarbazoles and examine their effect on the CNS.

The key intermediate, 3-carbethoxy-1,2,3,4-tetrahydrocarbazole **3**, Table I (III, R′ = H; R = C_2H_5, Scheme I), was prepared by the Fischer indole synthesis[3] employing 4-carbethoxycyclohexanone and phenylhydrazine which was converted into appropriate derivatives through the sequence shown in Scheme I. The compounds prepared are listed in Tables I, II, and III together with pertinent data. Although most of the reactions proceeded smoothly, it is to be noted that the best preparation of the dialkylaminoalkyl esters was by reaction of the potassium salt of **3** (R′ = H or CH_3; R = K) with the appropriate halide.

Representative compounds were submitted to a preliminary pharmacologic screen for general stimulation, depression, and autonomic activity.[4,5] None of the compounds exhibited significant activity. However, it is interesting in view of the studies of Bun-Hoï and coworkers[4] on the carcinogenic activity of large, multiple ring compounds that compound **16** exhibited a growth inhibition at a concentration of 1 μg ml in mammary carcinoma tissue.

Experimental Section[6]

All melting points (Thomas–Hoover capillary-type apparatus) are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ir spectra of all compounds corresponded with assigned structures. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Materials.—Ketones were prepared by the catalytic hydrogenation of commercially available 4-substituted phenols[6] followed by chromic acid oxidation of the resultant 4-substituted cyclohexanols.[7]

3-Carbethoxy-1,2,3,4-tetrahydrocarbazole (3). (III, R = C_2H_5; R′ = H). **Method A.**—The previous procedure[3] was employed using $PhNHNH_2$ (108 g, 1.0 mol), 4-carbethoxycyclohexanone (170 g, 1.0 mol), and 360 g of glacial AcOH. The product, mp 94.5–96.0° [C_6H_6–petroleum ether (bp 37–54°), 1:1], amounted to 210 g (86.4%). Compounds 1–11 in Table I were synthesized in this manner. *Anal.* ($C_{15}H_{17}NO_2$) C, H.

Method B.—1,2,3,4-Tetrahydrocarbazole-3-carboxylic acid (10 g, 0.05 mol) (**1**, III, R = R′ = H) was dissolved in 500 ml of absolute EtOH and cooled to 10° and dry HCl passed into the solution at a rapid rate for 4 hr. The solution was refluxed an additional 4 hr and cooled to room temperature and an equal volume of H_2O added. The precipitate was extracted with Et_2O, washed with H_2O and saturated $NaHCO_3$ until neutral, and dried (Na_2SO_4). Evaporation under reduced pressure yielded a brown residue which distilled [bp 183–188° (0.4 mm)], 8.7 g, 71.6%). The product solidified on standing and was recrystallized to give **3**, identical with that synthesized by method A.

Method C.—Oxalyl chloride (71 g, 0.56 mol) was added during 1 hr to a stirred suspension of **1** (135 g, 0.56 mol) in 1 l. of dry C_6H_6 while maintaining a constant temperature of 10°. The mixture was stirred at room temperature overnight, filtered through glass wool, and diluted to exactly 2 l. with dry C_6H_6. To a 1-l. aliquot of the acid chloride (ca. 61.2 g, 0.28 mol) was added 250 ml of absolute EtOH and the solution refluxed for 8 hr. Evaporation of the solvents, *in vacuo*, and distillation yielded **3**, 58 g, 85.3%). A mixture melting point with **3** from method A or B showed no depression.

3-Carbethoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (12). (III, R = C_2H_5; R′ = CH_3). **Method A.**—Compound **3** (12 g, 0.05 mol), dissolved in a minimum amount of DMF, was added dropwise to a stirred suspension of NaH (3 g of a 51% preparation, freed from mineral oil) in 10 ml of DMF. After the reaction subsided, MeI (7.1 g, 0.05 mol) was slowly added maintaining constant temperature. The mixture was stirred at room temperature overnight, after which it was warmed for 1 hr at 70°, cooled, poured into ice, and worked up in the usual manner. The product, a golden yellow oil [bp 157–163° (0.03 mm)], weighed 8.5 g (70.6%). Compound **14** in Table I was also prepared by this procedure. *Anal.* ($C_{17}H_{21}NO_2$) C, H, N.

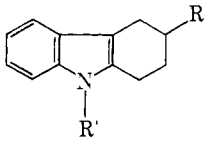
Method B.—4-Carbethoxycyclohexanone (34 g, 0.20 mol) in 175 g of glacial AcOH was heated to reflux and 1-Me-1-$PhNNH_2$ (24.4 g, 0.20 mol) was added over 1 hr. The mixture was refluxed an additional hour and 75 ml of glacial AcOH, previously saturated with dry HCl, was slowly added. After 1 hr the solution developed a precipitate which did not redissolve on refluxing for 12 hr. The ppt was removed by filtration of the cooled mixture, and the filtrate poured into 500 ml of H_2O and extracted with Et_2O. The product, after the usual work-up, was distilled as in method A; yield, 37.4 g, 72.7%). Compounds **13** and **14** in Table I were also prepared by this procedure.

3-Carbethoxy-9-(3-dimethylaminopropyl)-1,2,3,4-tetrahydrocarbazole (16). (IV, R′ = $(CH_2)_3N(CH_3)_2$).—To 3 g of NaH (51%) in 10 ml of DMF was added **3** (12 g, 0.05 mol) dissolved in

(1) L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, **7**, 313 (1964).
(2) M. E. Freed, E. Hertz, and L. M. Rice, *ibid.*, **7**, 628 (1964).
(3) C. C. Rogers and B. B. Corson, *J. Amer. Chem. Soc.*, **69**, 2910 (1947).
(4) Ng. Ph. Buu-Hoï, Ng. Hoán, and Ng. H. Khôi, *J. Org. Chem.*, **14**, 402 (1949).
(5) Roman numerals refer to Scheme I and arabic numerals refer to compounds in the tables.
(6) R. A. Finnegan and P. L. Bachanan, *J. Org. Chem.*, **30**, 4145 (1966).
(7) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

TABLE I

ALKYLATED AND NONALKYLATED DERIVATIVES OF 1,2,3,4-TETRAHYDROCARBAZOLE-3-CARBOXYLIC ACID

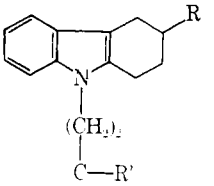


Compound	R	R'	Mp or bp, °C (mm)	Yield, %	Method	Formula	Analyses[a]
1	COOH	H	196–198[b]	88.0	A	$C_{13}H_{13}NO_2$	C, H, N
2	$COOCH_3$	H	68–69.5[c]	83.9	A	$C_{14}H_{15}NO_2$	C, H, N
3	$COOC_2H_5$	H	94.5–96[d]	86.4	A, B, C	$C_{15}H_{17}NO_2$	C, H
4	$COOC_3H_7$	H	102–104[c]	82.5	A	$C_{16}H_{19}NO_2$	C, H, N
5	$COOC_4H_9$	H	126.5–127.5[c]	84.4	A	$C_{17}H_{21}NO_2$	C, H, N
6	$COOC_5H_{11}$	H	74.5–75.5[c]	79.8	A	$C_{18}H_{23}NO_2$	C, H, N
7	$CH_2COOC_2H_5$	H	127.5–128[c]	87.8	A	$C_{16}H_{19}NO_2$	C, H, N
8	$(CH_2)_2COOC_2H_5$	H	200–202 (0.06)	84.4	A	$C_{17}H_{21}NO_2$	C, H, N
9[e]	$COOCH_3$	H	192–193.5[c]	82.6	A[f]	$C_{18}H_{17}NO_2$	C, H, N
10[e]	$COOC_2H_5$	H	179–180[c]	81.9	A[f]	$C_{19}H_{19}NO_2$	C, H, N
11	OCH_3	H	107.5–110[c]	78.6	A	$C_{13}H_{15}NO_2$	C, H, N
12	$COOC_2H_5$	CH_3	157–163 (0.03)	70.6	A, B	$C_{16}H_{19}NO_2$	C, H, N
13	$COOC_3H_7$	CH_3	167–173 (0.15)	71.9	B	$C_{17}H_{21}NO_2$	C, H, N
14	$CH_2COOC_2H_5$	CH_3	156–160 (0.025)	82.6	A	$C_{17}H_{21}NO_2$	C, H, N
15	$(CH_2)_2COOC_2H_5$	CH_3	165–173 (0.035)	72.6	B	$C_{18}H_{23}NO_2$	C, H, N
16	$COOC_2H_5$	$(CH_2)_3N(CH_3)_2$	162–169 (0.08)	62.3		$C_{20}H_{28}N_2O_2$[g,h]	C, H, N
17	$COOC_2H_5$	$(CH_2)_2N(C_2H_5)_2$	161–170 (0.05)	61.3		$C_{21}H_{30}N_2O_2$[i,j]	C, H, N
18	$COOC_2H_5$	$(CH_2)_2N(CH_3)_2$	165–170 (0.05)	38.2		$C_{19}H_{26}N_2O_2$[k]	C, H, N
19	$COOC_2H_5$	$(CH_2)_2N(CH_2)_4$[l]	159–166 (0.025)	10.6		$C_{21}H_{28}N_2O_2$[m]	C, H, N
20	$COOC_2H_5$	$(CH_2)_2N(CH_2)_4O$[n]	185–195 (0.03)	48.2		$C_{21}H_{28}N_2O_3$[o]	C, H, N
21	$COOC_2H_5$	$(CH_2)_2N(CH_2)_5$[p]	175–185 (0.04)	46.9		$C_{22}H_{30}N_2O_2$[q]	C, H, N
22	$COOC_2H_5$	$(CH_2)_3N(C_2H_5)_2$	172–180 (0.04)	57.6		$C_{22}H_{32}N_2O_2$[r]	C, H, N
23	$CH_2COOC_2H_5$	$(CH_2)_3N(CH_3)_2$	178–188 (0.06)	57.3		$C_{21}H_{30}N_2O_2$[s]	C, H, N
24	$(CH_2)_2COOC_2H_5$	$(CH_2)_3N(CH_3)_2$	175–185 (0.05)	55.9		$C_{22}H_{32}N_2O_2$	C, H, N
45	$CON(C_2H_5)_2$	H	130–131[t]	69.6		$C_{17}H_{22}N_2O$	C, H, N
46	$CH_2N(C_2H_5)_2$	H	150–155 (0.5)	87.9		$C_{17}H_{24}N_2$[u]	C, H, N
47	CH_2OH	H	95.5–98[v]	92.4		$C_{13}H_{15}NO$	C, H, N

[a] Analytical results obtained for the indicated elements were within ±0.4% of the theoretical values. [b] Glacial AcOH. [c] CH_3OH. [d] Petroleum ether–C_6H_6. [e] Benzo[*b*]1,2,3,4-tetrahydrocarbazole. [f] From naphthylhydrazine by addition of ketone to refluxing hydrazine. [g] Hydrochloride, mp 200–200.1°; *Anal.* ($C_{20}H_{29}ClN_2O_2$) C, H, Cl, N. [h] Methiodide, mp 144–146°; *Anal.* ($C_{21}H_{31}IN_2O_2$) I. [i] Maleate, mp 123–124°; *Anal.* ($C_{25}H_{34}N_2O_6$) C, H, N. [j] Methiodide, mp 148–148.5°; *Anal.* ($C_{22}H_{33}IN_2O_2$) I. [k] Methiodide, mp 185–187°; *Anal.* ($C_{20}H_{29}IN_2O_2$) I. [l] Pyrrolidinoethyl. [m] Maleate, mp 144–145°; *Anal.* ($C_{25}H_{32}N_2O_6$) C, H, N. [n] Morpholinoethyl. [o] Maleate, mp 160–161°; *Anal.* ($C_{23}H_{30}N_2O_7$) C, H, N. [p] Piperidinoethyl. [q] Maleate, mp 153–155°; *Anal.* ($C_{26}H_{34}N_2O_6$) C, H, N. [r] Fumarate, mp 119–121°; *Anal.* ($C_{26}H_{36}N_2O_6$) C, H, N. [s] Hydrochloride, mp 140°; *Anal.* ($C_{21}H_{31}ClNO_2$) Cl. [t] Et_2O. [u] Hydrochloride, mp 221–224°; *Anal.* ($C_{17}H_{25}ClN_2$)Cl. [v] Et_2O–ligroin.

TABLE II

N-SUBSTITUTED ACRYLONITRILE DERIVATIVES



Compound	R	R'	Mp, °C	Yield (%)	Formula[a]
25	$COOCH_3$	N	105–106.5[b]	82.2	$C_{17}H_{18}N_2O_2$
26	$COOC_2H_5$	N	90–92[c]	85.6	$C_{18}H_{20}N_2O_2$
27	$COOC_3H_7$	N	91.5–93[b]	84.4	$C_{19}H_{22}N_2O_2$
28	$COOC_4H_9$	N	77–77.5[d]	82.4	$C_{20}H_{24}N_2O_2$
29	$COOC_5H_{11}$	N	78–79[d]	79.7	$C_{21}H_{26}N_2O_2$
30	$CH_2COOC_2H_5$	N	60–61.5[b]	70.9	$C_{19}H_{22}N_2O_2$
31	$COOCH_3$	N	163–164.5[b]	74.6	$C_{21}H_{26}N_2O_2$
32	COOH	OOH	165–166.5[f]	71.6	$C_{16}H_{17}NO_4$

[a] Analytical results obtained for the indicated elements were within ±0.4% of the theoretical values. All compounds were analyzed for C, H, N. [b] MeOH. [c] Petr ether–MeOH. [d] Petr ether–C_6H_6. [e] Benzo[*b*]1,2,3,4-tetrahydrocarbazole. [f] EtOAc.

25 ml of DMF. After 1.5 hr, 6.1 g (0.05 mol) of $Me_2N(CH_2)_3Cl$ was added slowly, maintaining constant temperature. The mixture was stirred overnight and an additional 3.1 g (0.03 mol) of chloride added and heated for 1 hr at 70°. After cooling, it was worked up in the usual manner. Distillation of the residual oil gave **16**, 10.2 g, 62.3% [bp 162–169° (0.8 mm)]. Compounds **17–24** in Table I were also prepared by this procedure. *Anal.* ($C_{20}H_{28}N_2O_2$) C, H, N. The **hydrochloride** of **16** had mp 200–

SCHEME I

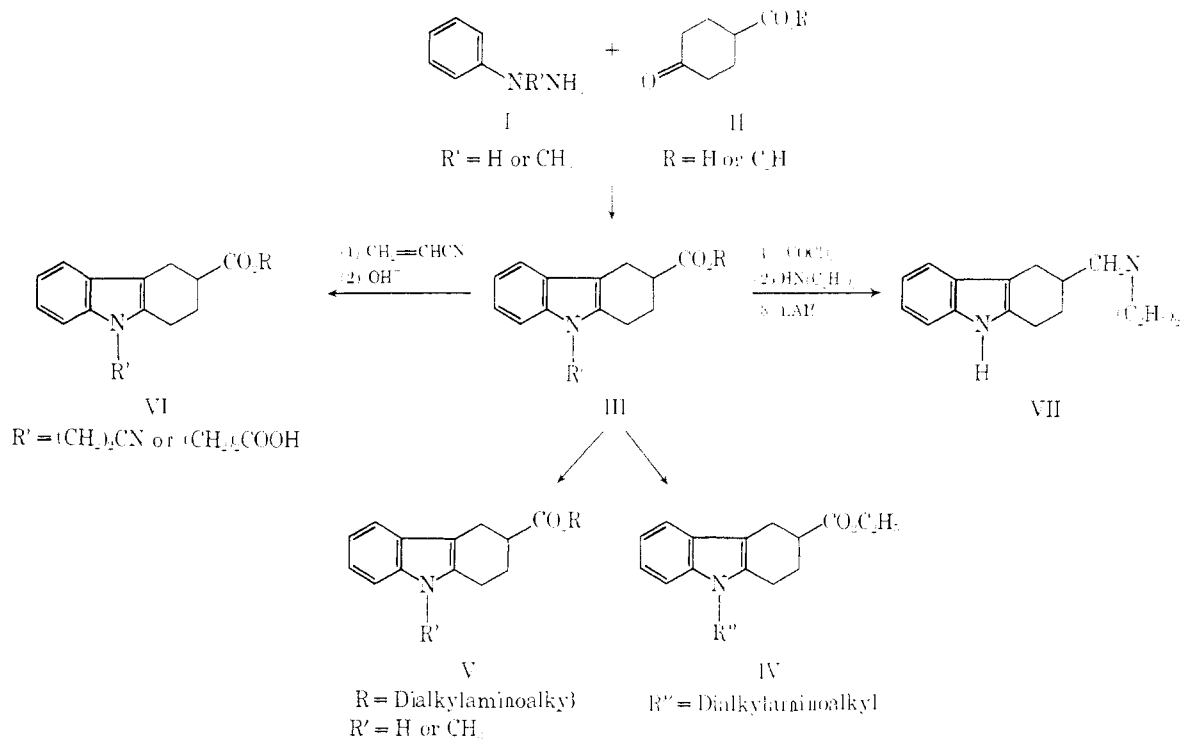
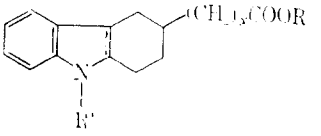


TABLE III

3-ACID AND ESTER EXCHANGE DERIVATIVES



Compound	R	R'	x	Mp or bp, °C (mm)	Yield, %	Method[a]	Formula	Anal.[b]
33	H	CH_3	0	174–177[c]	93.8		$C_{14}H_{15}NO_2$	C, H, N
34	H	CH_3	1	136–137.5[c]	92.5		$C_{15}H_{17}NO_2$	C, H, N
35	H	CH_3	2	155–156.5[c]	88.3		$C_{16}H_{19}NO_2$	C, H, N
36	H	H	1	203–204[d]	90.3		$C_{14}H_{13}NO_2$	C, H, N
37	H	H	2	136–137.5[c]	93.8		$C_{15}H_{17}NO_2$	C, H, N
38	$(CH_2)_2N(C_2H_5)_2$	H	0	190–191[e]	17.4	A	$C_{19}H_{27}ClN_2O_2$	C, H, Cl, N
39	$(CH_2)_2N(CH_2)_4O$[f]	H	0	182–184[e]	10.2	A	$C_{19}H_{25}ClN_2O_3$	C, H, Cl, N
40	$(CH_2)_3N(CH_3)_2$	H	0	195–199 (0.15)	58.7	B	$C_{17}H_{24}N_2O_2$	C, H, N
41	$(CH_2)_2N(CH_2)_4O$[f]	CH_3	0	205–210 (0.10)	62.2	B	$C_{20}H_{29}N_2O_3$[g]	C, H, N
42	$(CH_2)_3N(CH_3)_2$	CH_3	0	180–187 (0.07)	60.9	B	$C_{19}H_{28}N_2O_2$[h]	C, H, N
43	$(CH_2)_3N(CH_3)_2$	CH_3	1	190–191 (0.10)	64.8	B	$C_{20}H_{28}N_2O_2$	C, H, N
44	$(CH_2)_3N(CH_3)_2$	CH_3	2	202–207 (0.07)	62.9	B	$C_{21}H_{30}N_2O_2$[i]	C, H, N

[a] See Experimental Section. [b] Analytical results obtained for the indicated elements were within ±0.4% of the theoretical values. [c] MeOH. [d] *i*-PrOH–H_2O. [e] EtOH (as hydrochloride). [f] Morpholinoethyl. [g] Hydrochloride, mp 180–181.5°; *Anal.* ($C_{20}H_{27}ClN_2O_3$) Cl. [h] Hydrochloride, mp 188–190.5°; *Anal.* ($C_{19}H_{27}ClN_2O_2$) C, H, Cl, N. [i] Hydrochloride, mp 124–127; *Anal.* ($C_{21}H_{31}ClN_2O_2$) Cl.

209.1° (EtOH–Et_2O). *Anal.* ($C_{29}H_{23}ClN_2O_2$) C, H, Cl, N. The **methiodide** of **16** had mp 144–146° (EtOAc). *Anal.* ($C_{21}H_{31}IN_2O_2$) I.

3-Carbethoxy-9-(3-cyanoethyl)-1,2,3,4-tetrahydrocarbazole (26) (**VI, R = C_2H_5; R' = CH_2CH_2CN**).—To 15 g (0.052 mol) of **3** in 75 ml of dry C_6H_6 was added 1.5 ml of trimethylbenzylammonium methoxide (40% in MeOH), followed by the slow dropwise addition of acrylonitrile (5.5 g, 0.104 mol). After the addition, the solution was stirred and refluxed for 18 hr, cooled, acidified with HCl (1:1), washed with saturated NaCl, and dried (Na_2SO_4). Removal of the solvent produced a thick, brown oil which solidified. Recrystallization (MeOH–petroleum ether) yielded white crystals, mp 90–92°, 13.2 g, 85.6%. Compounds **25–31** in Table II were prepared by this procedure. *Anal.* ($C_{18}H_{20}N_2O_2$) C, H, N.

9-(2-Carboxyethyl)-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid (32) (**VI, R = H; R' = $(CH_2)CO_2H$**).—Compound **26** (10 g, 0.03 mol) was dissolved in 400 ml of 90% EtOH containing 83.2 g (1.48 mol) of KOH. The solution was refluxed for 48–72 hr and cooled, the solvents were removed under reduced pressure, and the dry cake was dissolved in H_2O, filtered, and acidified with concentrated HCl. Three recrystallizations (EtOAc) produced **32**, mp 165–166.5°, 7.0 g, 71.6%. Compounds **25–29** in Table II produced the same diacid. *Anal.* ($C_{16}H_{17}NO_4$) C, H, N. **Diethyl ester** was obtained as a yellow oil [bp 189–194° (0.1 mm)]. *Anal.* ($C_{20}H_{25}NC_4$) C, H, N.

9-Methyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic Acid (33) (**III, R' = CH_3; R = H**).—Compound **12** (25.4 g, 0.1 mol) and 8.4 g (0.15 mol) of KOH were dissolved in 500 ml of 95% EtOH and the solution was refluxed for 1.5 hr. Evaporation produced a solid which was dissolved in H_2O, filtered, acidified with 10% HCl, filtered, washed with H_2O, and dried. Recrystallization (MeOH) gave 21.5 g, 93.8%, of **33**, mp 174–177°. *Anal.* ($C_{13}H_{15}NO_2$) C, H, N.

Compounds **2–6** in Table I produced the same acid, **1**, while **12** and **13** produced the same acid, **34**.

Ester exchange. Method A. 3-(2-Diethylaminoethyl)-1,2,3,4-tetrahydrocarbazole-3-carboxylate (38) [**V, R' = H; R**

= $(CH_2)_2N(C_2H_5)_2$.—Compound **3** (70 g, 0.30 mol) was dissolved in 850 ml of xylene and added over 15 min to a cool mixture of $Et_2N(CH_2)_2OH$ (0.60 mol and 2 g (0.10 g-atom) of Na. After refluxing for 5 hr, the condenser was disconnected and 100 ml of distillate collected. Fresh xylene (100 ml) was added and the reaction proceeded overnight. The solvents were removed until about 50 ml remained. After cooling, the residue was triturated with concentrated HCl (200 ml) until a solid residue formed. This solid was dissolved in EtOAc–Et_2O (5:1) and treated with 20% NaOH until basic. The aqueous extracts were reextracted with EtOAc–Et_2O (2:1), and the organic layers were combined, washed with saturated NaCl, and dried ($CaCl_2$). Evaporation of the solvents and treatment of the residue with alcoholic HCl, and Et_2O and refrigeration, yielded crude **38**·HCl, which on treatment with C and recrystallization from absolute EtOH gave 17.4 g, 16.5%, of **38**, mp 190–191°. *Anal.* ($C_{13}H_{27}ClN_2O_2$) C, H, Cl, N.

Method B. 3-(3-Dimethylaminopropyl)-9-methyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate (42) [V, R′ = CH_3; R = $(CH_2)_3N(CH_3)_2$].—Compound **12**, 48 g (0.20 mol), was dissolved in 150 ml of absolute EtOH and added to a solution of KOH (11.2 g, 0.20 mol) in 250 ml of absolute EtOH. After refluxing for 1.5 hr, the solvent removed *in vacuo*, the K salt (III, R′ = CH_3; R = K, 16 g, 0.07 mol) was suspended in 300 ml of dry toluene, stirred, and heated to reflux, and 10 g (0.07 mol) of $(Me)_2N(CH_2)_3Cl$ in 50 ml of dry toluene added over 1 hr. After 8 hr an additional 5 g of chloride was added and the mixture refluxed for a total of 72 hr. The mixture was cooled and worked up in the usual manner. Distillation produced an oil, 13.4 g, 60.9% [bp 180–187° (0.07 mm)]. *Anal.* ($C_{19}H_{28}N_2O_2$) C, H, N. The **hydrochloride** of **42** had mp 188–190° (EtOH). *Anal.* ($C_{19}H_{27}ClN_2O_2$) C, H, Cl, N. Compounds **40–45** in Table III were synthesized by this method.

3-Diethylcarboxamido-1,2,3,4-tetrahydrocarbazole (45).—To a 500-ml aliquot of the acid chloride of III (R = R′ = H, *ca.* 30.6 g, 0.14 mol) in a 1-l. flask was added a 3 *M* excess (30.7 g) of Et_2NH and the solution refluxed for 1 hr. After cooling, the solution was washed (10% HCl, H_2O, 10% NaOH, and saturated NaCl). The organic layer was dried (Na_2SO_4) and evaporated to an oil which, after distillation [bp 215–220° (0.2 mm)], solidified into a glass; yield, 22 g, 69.9%. Recrystallization produced crystals, mp 130–131° (Et_2O). *Anal.* ($C_{17}H_{22}N_2O$) C, H, N.

3-Diethylaminomethyl-1,2,3,4-tetrahydrocarbazole (46) (VII).—The amide **45** (6 g, 0.02 mol), dissolved in a mixture of dry C_6H_6 (100 ml) and anhyd Et_2O (100 ml), was added to a solution containing 3.5 g of LAH in anhyd Et_2O. After refluxing overnight, the mixture was decomposed with H_2O and worked up in the usual manner. The residue was distilled [bp 150–155° (0.5 mm)] to produce a yellow oil, 4.5 g (87.9%). *Anal.* ($C_{17}H_{24}N_2$) C, H, N. **46**·HCl had mp 221–224° (EtOH). *Anal.* ($C_{17}H_{25}ClN_2$) Cl.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole (47).—Reduction of 12.5 g (0.05 mol) of **3** with 7 g of LAH occurred on refluxing overnight. The carbinol, **47**, mp 95.5–98.5° (Et_2O–ligroin), 9.7 g, 92.4%, was obtained on distillation of the residue [bp 167–177° (0.1 mm)]. *Anal.* ($C_{13}H_{15}NO$) C, H, N.

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16-Oxygenated 17α-Methyl-5β-androstanes

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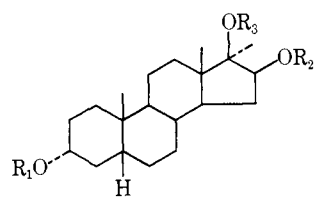
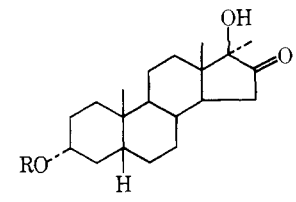
Very recently, we have demonstrated that in rabbits 17α-methyltestosterone, a more potent androgen than testosterone in oral therapy, is converted into 16-oxygenated 17α-methyl-5β-androstanes, **1** and **4**, in high yields, and **6** in very minor yield.[1] The preferential formation of the 16β-hydroxy-5β-steroid to its 16α-hydroxy isomer was the first instance with respect to the metabolism of C_{19} and other steroids in the animal body and seemed to be attributable to a steric effect of the 17α-Me since 16-hydroxylation of C_{19} steroids is known to occur at α *in vivo*[2,3] and *in vitro*.[4–6] Our attention, therefore, has been focused on the role of the 17α-Me in the conversion of 17α-methyltestosterone into **1** and interconversion of **1** into **6** through **4**. Further systematic investigations on this problem were required on these 16-oxygenated steroids, of which **1** has already been synthesized in good yield from 3α,17-dihydroxy-5β-androst-16-ene diacetate.[1] We now wish to report the synthesis of **4**, **6**, and their derivatives.



1, $R_1 = R_2 = R_3 = H$

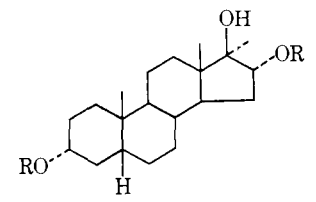
2, $R_1 = COPh$; $R_2, R_3 = =C(CH_3)_2$

3, $R_1 = COPh$; $R_2 = R_3 = H$



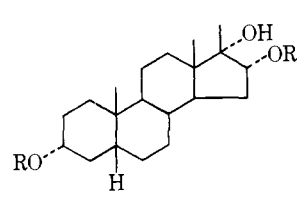
4, R = H

5, R = COPh



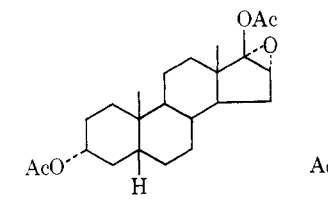
6, R = H

7, R = Ac

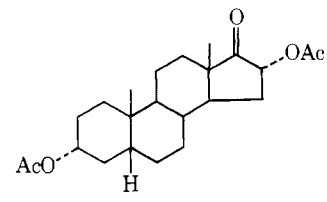


8, R = H

9, R = Ac



10



11

The 16α-hydroxy steroid **6** was synthesized by the acid treatment of **10**,[1] followed by the Grignard reaction of the resulting 16α-acetoxy-17-ketosteroid **11**. The reaction of **11** with MeMgI did not proceed stereoselectively and gave a mixture of two triols, **6** and **8**, in a ratio of 3:1, while the same Grignard reaction of 16-epimer of **11** resulted in specific production of **1**. This indicates an interfering effect of the 16α-OH on the α-side attack of the reagent at the 17-C=O. Assignment of the structures of both triols was carried out by the acetonide formation test and comparison of chemical shift value of 18-Me protons of their diacetates, **7**

(1) T. Watabe, S. Yagishita, and S. Hara, *Biochem. Pharmacol.*, in press.
(2) R. Neher and G. Stark, *Experientia*, **17**, 510 (1961).
(3) W. E. Easterling, Jr., H. H. Simmer, W. J. Dignam, M. V. Flankland, and F. Naftolin, *Steroids*, **8**, 157 (1966).
(4) A. H. Conney and A. Klutch, *J. Biol. Chem.*, **238**, 1611 (1963).
(5) G. Pangels and H. Breuer, *Naturwissenschaften*, **49**, 106 (1962).
(6) W. L. Heinrichs, H. H. Feder, and A. Cólas, *Steroids*, **7**, 91 (1966).