DL-1-(1-Arylalkyl)imidazole-5-carboxylate Esters. A Novel Type of Hypnotic Agents

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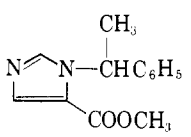
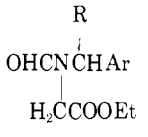
A number of 1-substituted imidazole-5-carboxylic acid esters of type IIIb have been synthesized. Many of these are extremely potent, rapid, and short-acting hypnotic agents in rats.

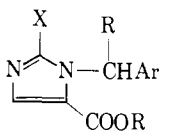
In these laboratories for a number of years we have been interested in imidazole derivatives as chemotherapeutic agents. During the course of this work we have had occasion to prepare a number of 1-aralkylimidazole-5-carboxylic acid esters. The observation that one of these (I), upon parenteral or oral administration to rats, induced a profound hypnotic state prompted us to prepare additional analogs of I, specifically type IIIb, in a effort to further delineate the structure–activity correlations governing this class of compounds.



I



II



IIIa, X = SH
b, X = H

Whereas certain imidazolones and hydantoins have been described as hypnotic agents,[1] "true" imidazoles, to the best of our knowledge, have hitherto not been known to elicit the hypnotic state.

The desired analogs (IIIb) were prepared most advantageously by a modification of the Jones procedure.[2] To this effect a number of 1-arylalkylamines were treated with ethyl chloroacetate in DMF containing triethylamine; the resulting N-substituted glycine esters were then N-formylated by means of formic acid in xylene to give II. Solubility considerations in the pyridyl series led us to carry out the alkylations in refluxing benzene. Amides II boiled between 150 and 200° (*ca.* 1 mm.) and were used as such. Successive treatments of types II with sodium methoxide–methyl formate in THF, followed by reaction of the resulting C-formyl derivative with HCl–HNCS afforded IIIa (note the concomitant ester exchange) in yields ranging from 30–74%. Oxidative desulfurizations then proceeded smoothly giving the desired analogs IIIb. A tabulation of these compounds (*i.e.*, **1–30**) is offered in Table I.

A desire to determine the pharmacological effect of side-chain alterations dictated the preparation of compounds **44–47** (type IV). Two of these had been described previously as ethyl esters.[2]

Hydrolysis of **2** in *ca.* 10 *N* NaOH solution gave the carboxylic acid. From it, *via* the acid chloride hydrochloride, esters **31–42** were obtained. In a similar fashion **20** was converted to **43**.

IV

44, R = C_6H_5[2]
45, R = $CH_2C_6H_5$[2]
46, R = $CH_2CH_2C_6H_5$
47, R = $CH(CH_3)CH_2C_6H_5$

Experimental

All melting points were recorded on a Fisher-Johns block. The reported yields were based frequently on one run and do not necessarily reflect the optimum ones attainable.

As illustration the preparation of **2** and its derivatives will be offered in detail.

N-(α-Methylbenzyl)-N-formylglycine Ethyl Ester (II, R = CH_3; Ar = C_6H_5).—To a solution of 132 g. (1.09 moles) of α-methylbenzylamine in 100 ml. of DMF were added successively 110 g. (1.09 moles) of triethylamine and 133 g. (1.09 moles) of ethyl chloroacetate. A gradual temperature increase to 50° was noted, and the mixture was stirred overnight. Ether was then added and most of the triethylamine hydrochloride was removed by filtration. The filtrate was washed thoroughly, dried, and stripped, leaving 219 g. of crude N-(α-methylbenzyl)glycine ethyl ester. This was dissolved in 600 ml. of xylene, 55.2 g. (1.2 moles) of absolute formic acid was added, and the solution was refluxed in an apparatus equipped with a water trap. Water evolution was complete within 2 hr. Scrubbing of the cooled solution with 20% formic acid, water, sodium bicarbonate solution, and water, respectively, followed by drying and evaporation of solvent gave a crude product; it was fractionated to furnish 144 g. (56% yield) of a pale yellow oil, b.p. 165–170° (0.8 mm.).

DL-1-(1-Phenethyl)-2-mercaptoimidazole-5-carboxylic Acid Methyl Ester (1).—Sodium methoxide (0.65 mole) was freshly prepared in THF by addition of 20.8 g. (0.65 mole) of methyl alcohol in 50 ml. of THF to 29.9 g. (0.65 mole) of 50% paraffinic sodium dispersion in 400 ml. of THF. To this suspension, at 10°, was added in one portion and with stirring, a solution of 108 g. (1.80 moles) of methyl formate and 144 g. (0.61 mole) of N-(α-methylbenzyl)-N-formylglycine ethyl ester. After stirring at 10° for 1 hr., the reaction was allowed to proceed overnight. The solvent was subsequently stripped and replaced with 600 ml. of water; the paraffin was washed out with ether. Concentrated HCl (114 ml., 1.35 moles) was added, followed by 600 ml. of methyl alcohol. After keeping the temperature at 40° for 0.5 hr., there was introduced a solution of 90 g. (0.93 mole) of potassium thiocyanate in 200 ml. of water. Within a few hours product started crystallizing out; stirring was continued overnight. The pale yellow imidazole was filtered off; the crude material (100 g., 63% yield) had m.p. *ca.* 130°. Analytical material, m.p. 133–134°, was prepared from 85% methanol.

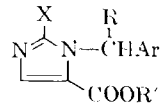
Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.53; H, 5.38; N, 10.68; S, 12.21. Found: C, 59.72; H, 5.20; N, 10.77; S, 11.95.

DL-1-(1-Phenethyl)imidazole-5-carboxylic Acid Methyl Ester Hydrochloride (2).—Compound 1 (66 g., 0.25 mole) was added

(1) K. W. Wheeler, "Medicinal Chemistry," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 1.

(2) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 644 (1949).

TABLE I DL-1-(1-ARALKYL)-5-IMIDAZOLECARBOXYLIC ACID ESTERS (III)

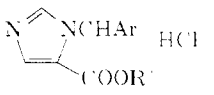


Compd.	X	R	R'	Ar	M.p., °C.	Yield, %	Ref. to starting material	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	SH	CH_3	CH_3	C_6H_5	133–134	63	*a*	$C_{13}H_{14}N_2O_2S$	59.53	5.38	10.68	59.72	5.40	10.77
2	H	CH_3	CH_3	C_6H_5	173–174			$C_{13}H_{14}N_2O_2 \cdot HCl$	58.53	5.67	10.50	58.63	5.94	10.73
3	SH	CH_3	CH_3	*p*-FC_6H_4	135–136	65	*a*	$C_{13}H_{13}FN_2O_2S$	55.70	4.68	9.99	55.79	4.77	9.91
4	H	CH_3	CH_3	*p*-FC_6H_4	137–138			$C_{13}H_{13}FN_2O_2 \cdot HCl$	55.84	4.96	9.84	55.10	5.17	9.74
5	SH	CH_3	CH_3	*p*-ClC_6H_4	164–165	63	*a*	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.80	4.49	9.37
6	H	CH_3	CH_3	*p*-ClC_6H_4	146–148			$C_{13}H_{13}ClN_2O_2 \cdot HCl$	51.84	4.69	9.30	51.92	4.95	9.24
7	SH	CH_3	CH_3	*m*-ClC_6H_4	179–180	74	*a*	$C_{12}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.79	4.64	9.54
8	H	CH_3	CH_3	*m*-ClC_6H_4	153–155			$C_{13}H_{13}ClN_2O_2 \cdot HCl$	51.84	4.69	9.30	51.69	4.91	9.33
9	SH	CH_3	CH_3	*o*-ClC_6H_4	187–189	46	*a*	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.43	4.71	9.63
10	H	CH_3	CH_3	*o*-ClC_6H_4	178–180			$C_{13}H_{13}ClN_2O_2 \cdot HCl$	51.84	4.69	9.30	51.82	4.79	9.51
11	SH	CH_3	CH_3	*p*-BrC_6H_4	157–161	52	*a*	$C_{13}H_{13}BrN_2O_2S$	45.76	3.84	8.21	45.91	3.91	8.28
12	H	CH_3	CH_3	*p*-BrC_6H_4	137–139			$C_{13}H_{13}BrN_2O_2 \cdot HCl$	45.17	4.08	8.11	44.85	4.32	7.91
13	SH	CH_3	CH_3	*p*-$CH_3OC_6H_4$	140–141	60	*a*	$C_{14}H_{16}N_2O_3S$	57.53	5.52	9.28	57.63	5.80	9.74
14	H	CH_3	CH_3	*p*-$CH_3OC_6H_4$	131–132			$C_{14}H_{16}N_2O_3 \cdot HCl$	56.66	5.78	9.44	56.35	5.88	9.19
15	SH	CH_3	CH_3	*p*-$CH_3C_6H_4$	163–165	50	*a*	$C_{14}H_{16}N_2O_2S$	60.36	5.84	10.10	60.59	6.05	10.40
16	H	CH_3	CH_3	*p*-$CH_3C_6H_4$	167–168			$C_{14}H_{16}N_2O_2 \cdot HCl$	59.89	6.10	9.98	59.57	6.16	10.00
17	SH	CH_3	CH_3	*m,p*-$(CH_3)_2C_6H_3$	137–139	50	*a*	$C_{15}H_{18}N_2O_2S$	62.05	6.25	9.65	62.16	6.45	9.60
18	H	CH_3	CH_3	*m,p*-$(CH_3)_2C_6H_3$	158–160			$C_{15}H_{18}N_2O_2 \cdot HCl$	61.11	6.50	9.50	61.20	6.63	9.27
19	SH	C_2H_5	CH_3	C_6H_5	210–211	70	*a*	$C_{14}H_{16}N_2O_2S$	60.86	5.84	10.10	60.75	5.57	10.40
20	H	C_2H_5	CH_3	C_6H_5	172–173			$C_{14}H_{16}N_2O_2 \cdot HCl$	59.89	6.10	9.98	59.58	6.25	9.87
21	SH	*n*-C_3H_7	CH_3	C_6H_5	175–177	50	*a*	$C_{15}H_{18}N_2O_2S$	62.05	6.25	9.65	61.92	6.16	9.43
22	H	*n*-C_3H_7	CH_3	C_6H_5	151–152			$C_{15}H_{18}N_2O_2 \cdot HCl$	61.11	6.50	9.51	61.08	6.47	9.44
23	SH	CH_3	CH_3	2-Thienyl	162–164	61	*a*	$C_{11}H_{12}N_2O_2S_2$	49.25	4.51	10.44	49.42	4.43	10.74
24	H	CH_3	CH_3	2-Thienyl	137–138			$C_{11}H_{12}N_2O_2S \cdot HCl$	48.44	4.81	10.27	48.70	4.87	10.45
25	SH	CH_3	CH_3	2-Pyridyl	155–156	*ca.* 30	*b*	$C_{12}H_{13}N_3O_2S$	54.75	4.98	15.96	54.89	5.40	15.84
26	H	CH_3	CH_3	2-Pyridyl	181–183			$C_{12}H_{13}N_3O_2 \cdot 2HCl$	47.38	4.97	13.82	47.55	5.31	13.56
27	SH	CH_3	CH_3	3-Pyridyl	197–198	37	*b*	$C_{12}H_{13}N_3O_2S$	54.75	4.98	15.96	54.55	5.06	15.48
28	H	CH_3	CH_3	3-Pyridyl	184–187			$C_{12}H_{13}N_3O_2 \cdot 2HCl$	47.38	4.97	13.82	47.70	5.06	13.79
29	SH	CH_3	CH_3	4-Pyridyl	186–187	50	*b*	$C_{12}H_{13}N_3O_2S$	54.75	4.98	15.96	55.08	5.17	16.05
30	H	CH_3	CH_3	4-Pyridyl	81–82			$C_{12}H_{13}N_3O_2$	62.32	5.67	18.57	62.50	5.81	18.38
31	H	CH_3	C_2H_5	C_6H_5	142–143		*c*	$C_{14}H_{16}N_2O_2 \cdot HCl$	59.89	6.10	9.50	59.64	6.29	9.64
32	H	CH_3	*n*-C_3H_7	C_6H_5	156–157		*c*	$C_{15}H_{18}N_2O_2 \cdot HCl$	61.11	6.50	9.51	60.87	6.27	9.34
33	H	CH_3	*i*-C_3H_7	C_6H_5	175–181		*c*	$C_{15}H_{18}N_2O_2 \cdot HCl$	61.11	6.50	9.51	61.09	6.63	9.63
34	H	CH_3	*n*-C_4H_9	C_6H_5	139–140		*c*	$C_{16}H_{20}N_2O_2 \cdot HCl$	62.63	6.86	9.07	62.03	7.05	9.10
35	H	CH_3	*n*-C_5H_{11}	C_6H_5	136–137		*c*	$C_{17}H_{22}N_2O_2 \cdot HCl$	63.25	7.18	8.68	63.39	7.10	8.94
36	H	CH_3	$CH_2CH{=}CH_2$	C_6H_5	135–136		*c*	$C_{15}H_{16}N_2O_2 \cdot HCl$	61.54	5.85	9.57	61.53	5.69	9.56
37	H	CH_3	$CH_2C{\equiv}CH$	C_6H_5	92–93		*c*	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	71.14	5.70	11.02
38	H	CH_3	CH_2CH_2Cl	C_6H_5	85–87		*c*	$C_{14}H_{15}ClN_2O_2 \cdot HCl \cdot 0.5H_2O$	51.86	5.29	8.64	51.61	5.40	8.38
39	H	CH_3	$CH_2CH_2OCH_3$	C_6H_5	65–67		*c*	$C_{15}H_{18}N_2O_3 \cdot HCl$	57.97	6.16	9.01	57.86	6.42	8.85
40	H	CH_3	CH_2—◁	C_6H_5	150–151		*c*	$C_{16}H_{18}N_2O_2 \cdot HCl$	62.64	6.24	9.13	62.66	6.26	9.20
41	H	CH_3	$CH_2CH{=}CHCH_3$	C_6H_5	139–140		*c*	$C_{16}H_{18}N_2O_2 \cdot HCl$	62.64	6.24	9.13	62.36	6.29	8.93
42	H	CH_3	$CH_2C_6H_5$	C_6H_5	153–154		*c*	$C_{19}H_{18}N_2O_2 \cdot HCl$	66.56	5.59	8.17	66.73	5.59	8.10
43	H	C_2H_5	C_2H_5	C_6H_5	165–166		*c*	$C_{15}H_{18}N_2O_2 \cdot HCl$	61.11	6.50	9.51	60.96	6.23	9.80

[a] Leuckart reaction based on A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, and G. Jennings, *J. Am. Chem. Soc.*, **58**, 1808 (1936). [b] Reduction of corresponding oxime: H. G. Kolthoff and J. H. Hunter, *ibid.*, **63**, 490 (1941). [c] Prepared from appropriate acid chloride (see Experimental).

TABLE II

PHARMACOLOGICAL DATA



Compd.	R	R'	Ar	ED50, mg./kg. i.v. (confidence limits)[a] AD50	HD50	LD50	Safety ratio, LD50/HD50 (confidence limits)	Duration of action, min.
31	CH_3	C_2H_5	C_6H_5	1.1 (0.88–1.3)	2.9 (2.4–3.6)	35 (28–43)	12 (9.0–16)	30
33	CH_3	i-C_3H_7	C_6H_5	0.77 (0.53–1.1)	2.9 (2.3–3.3)	22 (18–26)	8.0 (6.2–10)	30
34	CH_3	n-C_3H_7	C_6H_5	0.79 (0.53–1.2)	3.0 (2.4–3.7)	24 (20–28)	8.0 (6.1–11)	24
2	CH_3	CH_3	C_6H_5	1.3 (0.85–2.1)	4.4 (3.5–5.6)	50 (33–73)	11 (7.1–18)	33
4	CH_3	CH_3	p-FC_6H_4	1.3 (0.73–2.3)	4.7 (3.9–5.7)	38 (31–46)	8.1 (6.2–11)	28
20	C_2H_5	CH_3	C_6H_5	2.0 (1.4–2.9)	6.3 (4.3–9.3)	57 (45–71)	9.1 (4.4–19)	46
36	CH_3	Allyl	C_6H_5	2.0 (1.4–3.0)	6.5 (4.7–8.8)	35 (24–52)	5.5 (3.3–9.0)	38
43	C_2H_5	C_2H_5	C_6H_5	2.5 (2.0–3.2)	6.6 (4.9–8.9)	36 (30–44)	5.5 (3.8–7.8)	34
6	CH_3	CH_3	p-ClC_6H_4	1.5 (1.1–2.2)	9.2 (7.3–12)	57 (46–70)	5.0 (3.7–6.8)	36
16	CH_3	CH_3	p-$CH_3C_6H_4$	5.4 (4.6–6.3)	11 (9.5–13)	57 (46–70)	5.2 (4.1–6.7)	24
45	H	CH_3	C_6H_5	Toxic	Inactive	60 (55–66)	Inactive	Inactive
Pentobarbital sodium				3.6 (2.8–4.7)	17 (14–20)	83 (66–105)	5.0 (3.7–6.7)	180
Phenobarbital sodium				40 (30–54)	103 (81–131)	210 (153–288)	2.0 (1.4–3.0)	>220

[a] Values given for ataxia (AD_{50}), hypnosis (HD_{50}), and mortality (LD_{50}).

portionwise and with stirring to a mixture of 80 ml. of nitric acid and 200 ml. of water containing 0.50 g. of sodium nitrite; the temperature was kept at 33–38°. Upon completion of the addition, stirring was continued for another hour, after which time the solution was rendered alkaline by addition of sodium carbonate. The basic product was removed by ether extraction. Addition of HCl in isopropyl alcohol to the dried ethereal solution furnished 61.0 g. (92%) of desired product, m.p. 170–173°. Recrystallization from methyl alcohol–ether raised the melting point to 173–174°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2 \cdot HCl$: C, 58.53; H, 5.67; N, 10.50. Found: C, 58.63; H, 5.94; N, 10.77.

DL-1-(1-Phenethyl)imidazole-5-carboxylic Acid.—To a solution of 100 g. of sodium hydroxide in 250 ml. of water was added 100 g. (0.383 mole) of **2**. Upon refluxing for 1 hr. the solution was diluted with 250 ml. of water; addition of 150 g. of acetic acid gave 73 g. of solid product, m.p. 186–188°, representing a 95% yield. An analytical sample, prepared from water, melted at 188–189°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 65.65; H, 5.59. Found: C, 66.78; H, 5.42.

DL-1-(1-Phenethyl)imidazole-5-carboxylic Acid Chloride Hydrochloride.—The carboxylic acid (73 g., 0.34 mole) was added to 220 ml. of thionyl chloride. Refluxing this mixture for 1 hr., followed by addition of isopropyl ether gave, upon cooling, 79 g. of product, melting at 148–149°. Esterification of the acid chloride by the usual methods gave compounds **21–42**; the preparation of **36** exemplifies such a conversion.

DL-1-(1-Phenethyl)imidazole-5-carboxylic Acid Allyl Ester Hydrochloride (36).—A mixture of 4 g. (0.0148 mole) of acid chloride hydrochloride in 30 ml. of allyl alcohol was refluxed for 3 hr. The solvent was then removed and replaced with water. Basification and ether extraction gave a solution of the base, which was isolated as the **hydrochloride** salt, m.p. 135–136° (isopropyl alcohol–isopropyl ether), yield 2.9 g.

Anal. Calcd. for $C_{15}H_{16}N_2O_2 \cdot HCl$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.53; H, 5.69; N, 9.56.

Physical properties of **46** and **47**, together with those of their 2-mercapto precursors, are given below; their preparations paralleled the ones offered for **1** and **2**.

DL-(2-Phenethyl)-2-mercaptoimidazole-5-carboxylic acid methyl ester, obtained in 70% yield, melted at 164–165°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.77; H, 5.59; N, 10.40.

DL-(2-Phenethyl)imidazole-5-carboxylic Acid Methyl Ester (46).—The base, upon recrystallization from benzene–petroleum ether, melted at 63–64°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.21; N, 11.92.

DL-1-(1-Phenyl-2-propyl)-2-mercaptoimidazole-5-carboxylic Acid Methyl Ester.—The compound, obtained in 38% yield from α-methylphenethylamine, melted at 140–141° (aqueous methyl alcohol).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.84; N, 10.1. Found: C, 60.75; H, 6.64; N, 10.1.

DL-1-(1-Phenyl-2-propyl)imidazole-5-carboxylic Acid Methyl Ester Hydrochloride (47).—An analytical sample, prepared from methyl alcohol–ether, melted at 165–166°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2 \cdot HCl$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.64; H, 6.10; N, 10.2.

Pharmacology.—The results were obtained as follows. Aqueous solutions of the hydrochloride salts were administered by rapid intravenous injection to young female Wistar rats (190 ± 10 g.). The animals were then observed for a period of 220 min. to determine the following parameters: (1) onset and duration of ataxia, (2) onset and duration of "hypnosis," (3) lethal effects, and (4) miscellaneous behavioral effects, such as excitation, muscular twitches, or convulsions.

In order to avoid subjective bias and to secure adequate randomization, all observations were made by unbiased technicians working with coded solutions, each rat of a given experimental session receiving a different type of treatment. Groups of 10 rats were used per dose level (160, 80, 40, . . . 2.5, 1.25 mg./kg.) and each compound was investigated at 6 or more dose levels, ranging from complete inactivity to 100% lethality. Ataxia was scored using an ordinal scale for ranking the degree of confidence of the observer in his own judgment.[3]

Hypnotic activity was determined by placing the animals on their backs on an undulated metal surface (30°), disappearance of the righting reflex being taken as measure of activity. The dose level at which this state manifested itself in 50% of the animals is considered the HD_{50} value. Similarly the AD_{50} value corresponds to the dose level producing ataxia in half of the animals. LD_{50} values refer to 72-hr. mortality data; however, the large majority of fatalities occurred within a few hours after injection. The duration of action is defined as the graphically estimated median value for the duration of ataxia at the HD_{50} dose level. The symbols AD_{50}, HD_{50}, and LD_{50} are median effective dose levels (ED_{50} values), expressed in mg./kg. of body weight. All symbols defined above were arrived at by means of probit analysis using the classical graphical method of Litchfield and Wilcoxon (P 0.05).

Results

As seen from Table II, a number of 1-(1-aralkyl)-imidazole-5-carboxylic acid esters exhibit extremely potent and short-acting hypnotic activity in rats; furthermore, they are relatively atoxic when their thera-

(3) P. A. J. Janssen, *Psychopharmacologia*, **2**, 141 (1961).

peutic ratios are compared to those of pentobarbital or phenobarbital.

Preliminary structure–activity correlations led us to make the following general statements. (1) The nature of the N-substituent is critical. One-carbon interruption between the aryl moiety and the nitrogen atom as well as alkyl branching of the α-carbon are prerequisites for sustaining hypnotic activity. Lengthening of the side chain to include two carbon atoms, with or without branching (*i.e.*, **46** and **47**), or omission of branching, *à la* **45**, or direct attachment of the aryl group upon the nitrogen (**44**), leads to total loss of hypnotic properties. (2) Differences in hypnotic potency among the various esters are relatively minor. The presence of the ester moiety *per se* is essential; the corresponding carboxylic acids are totally inactive. A detailed pharmacological study, including test results obtained in other animals, will be published elsewhere.

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Hypocholesteremic Agents. III.[1] Basic Carbinols and Related Compounds

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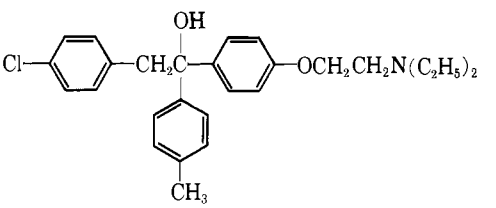
A series of 58 basic carbinols and related compounds has been synthesized, mostly by means of the Grignard reaction, and examined for hypocholesteremic activity. One compound, α-[4-(2-diethylaminoethoxy)phenyl]-α-phenyl-5-acenaphthenemethanol, proved to be considerably more potent than triparanol in both rats and mice.

Much effort in recent years has been expended in the search for chemical agents which will significantly lower the blood cholesterol level of hypercholesteremic individuals. The rationale behind use of such drugs is the belief, not conclusively proven, that formation of atherosclerotic plaques is directly connected to the amount of cholesterol in the blood.[2,3] Although a number of drugs are known to possess hypocholesteremic activity, none are entirely satisfactory.[3,4] In 1959, triparanol was introduced for this purpose, and both animal and clinical studies indicate it to be both effective and consistent in its activity.[5,6] It was soon discovered, however, that, as the level of cholesterol is reduced, the level of its biogenetic precursor, desmosterol, is increased and total sterol concentration of the plasma is not reduced as much as determinations of cholesterol would seem to indicate.[2,3,6] A further possible disadvantage of triparanol is its lack of potency. A typical dose for human patients is 250 mg. daily.[6] For drugs which are given over long periods of time, it might be advantageous to be able to give one effective at a lower dose. This work, then, was undertaken for two reasons; first, to find a drug similar to triparanol effective at a dose of no more than 50 mg./day, and, second, one which would give a better reduction in total sterols.

Chemically, triparanol (I) is a derivative of 1,1,2-triphenylethanol. As such, there are many possible modifications which might lead to interesting structure–activity relationships. In a previous publication,[7] we established that the 4-(2-(diethylaminoethoxy)phenyl group may be replaced by a pyridine ring and activity maintained. The most potent compound of that series is 1,1-diphenyl-2-(4-pyridyl)-ethanol. Its potency is about the same as that of I. Investigation of pyridine derivatives is continued in this paper, and modifications of the diethylaminoethoxy side chain have been studied extensively. Triarylmethanol homologs have also been investigated, as has replacement of benzene rings with polynuclear ring systems. In addition, a group of tetrahydrofuran derivatives and some ethylene derivatives has been synthesized.



I

Chemistry.—Four general methods were used to obtain the carbinols (IV, VI, IX, and XI), ethers, and ethylene derivatives described in Table I.

(1) Paper II: M. Freifelder and H. B. Wright, *J. Med. Chem.*, **7**, 664 (1964).

(2) "New and Nonofficial Drugs, 1962," J. B. Lippincott Co., Philadelphia, Pa., 1962, p. 616.

(3) R. H. Furman and C. W. Robinson, Jr., *Med. Clin. N. Am.*, **45**, 935 (1961).

(4) C. Moses, *Angiology*, **13**, 59 (1962).

(5) W. Hollander and A. Chobanian, *BMQ, Boston Med. Quart.*, **10**, 37 (1959).

(6) (a) M. Friedman, S. O. Byers, and R. H. Rosenman, *Progr. Cardiovascular Diseases*, **4**, 419 (1962); (b) W. Hollander, A. V. Chobanian, and R. W. Wilkins, *J. Am. Med. Assoc.*, **174**, 5 (1960).

(7) H. B. Wright, D. A. Dunnigan, and U. Biermacher, *J. Med. Chem.*, **7**, 113 (1964).