Synthesis of Compounds with Potential Psychotomimetic Activity. III[1,2a]

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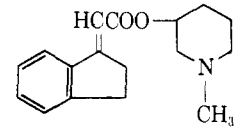
As a continuing study of structure–activity relationships of certain psychotomimetic agents, the N-methyl-3-piperidyl esters of the following acids were prepared: ethylphenylglycolic, vinylphenylglycolic, 1-hydroxytetralin-1-carboxylic, and indene-3-acetic. Biological data are presented on these esters. Cycloheptylphenylglycolic and ethynylphenylglycolic acids have been prepared, but they could not be converted to their N-methyl-3-piperidyl esters. The product of the Reformatsky addition of ethyl bromoacetate to 1-indanone has been prepared and its chemistry is discussed.

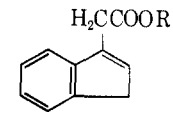
It has been shown that esters of N-methyl-3-hydroxypiperidine with certain disubstituted glycolic acids are capable of producing bizarre auditory, visual, tactile, and gustatory hallucinations in a high percentage of normal human subjects.[3a,b] When one substituent on the glycolic acid was phenyl and the other substituent was phenyl, cyclohexyl, cyclopentyl, cyclobutyl, or cyclopropyl, especially potent esters resulted.[1,3a] Cannon[3c] synthesized a series of ring-substituted benzilate esters of N-methyl-3-hydroxypiperidine, all of which were devoid of hallucinogenic activity. In contrast, the ester of 9-hydroxyfluorene-9-carboxylic acid demonstrated marked potency. On the basis of these findings, it has been suggested that a coplanar or a nearly coplanar arrangement of the two substituents on the glycolic acid portion of the ester is a requisite for psychotomimetic activity.[1]

The fact that cycloalkylphenylglycolate esters are active suggested that ethyl-, vinyl-, and ethynylphenylglycolate esters of N-methyl-3-hydroxypiperidine might also demonstrate hallucinogenic activity. The ester of 1-hydroxytetralin-1-carboxylic acid can be considered to be a rigid, nearly planar alkylphenylglycolic acid derivative, whose activity might parallel that of the ethylphenylglycolate ester. Cycloheptylphenylglycolic acid was prepared to complete a series of cycloalkylphenylglycolic acids; inspection of Dreiding and of Catalin models of this acid shows that the cycloheptane ring and the benzene ring cannot assume coplanarity or approximate coplanarity without serious nonbonded interactions. Thus, it was predicted that the ester of this acid should possess no hallucinogenic activity. Attempts to prepare the N-methyl-3-piperidyl ester of ethynylphenylglycolic acid by transesterification of its methyl ester and by a variety of alternate procedures were not successful. Cycloheptylphenylglycolic acid could not be converted to its methyl ester, and attempts to find alternate methods of preparation of N-methyl-3-piperidyl cycloheptylphenylglycolate did not succeed.

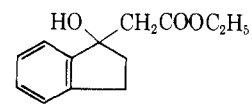
It was desired to prepare the 1-indanylideneacetic acid ester (I) to evaluate replacement of the α-hydroxyl group of a glycolic acid by a carbon–carbon double bond. von Braun and his co-workers[4a] had reported a synthesis of the ethyl ester of this acid by a Reformatsky reaction on 1-indanone. However, later workers[4b,c] have shown that the product isolated from the reaction is ethyl indene-3-acetate (II). None of these groups reported isolation of the initially formed Reformatsky product, ethyl 1-hydroxyindan-1-acetate (III); however, Oka[5] isolated a hydroxy ester product from a Reformatsky reaction of 1-indanone with ethyl 2-bromopropionate. In the present work, the sole product of the Reformatsky addition of ethyl bromoacetate to 1-indanone was the hydroxy ester III. Attempts to transesterify III with N-methyl-3-hydroxypiperidine in the presence of sodium methoxide led to the isolation of 2-indan-1′-yliden-1-indanone (IV)[6] as the sole identifiable product. III was converted to indene-3-acetic acid (V) by refluxing with KOH in aqueous ethanol, or (in better yield) by treatment of III with thionyl chloride followed by dehydrohalogenation.[7]



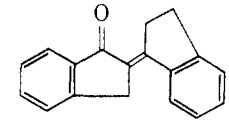
I



II, R=C_2H_5
V, R=H



III



IV

Experimental[8]

1-Ethynyl-1-tetralol was prepared in 71% yield by the method employed by Goldberg and Scott[9a] for 6-methoxy-1-ethynyl-1-tetralol; b.p. 84–86° (0.12 mm.), lit.[9b] b.p. 104° (0.2 mm.).

1-Hydroxytetralin-1-carboxylic Acid.—Potassium permanganate (12.0 g., 0.08 mole) in 250 ml. of water was added dropwise

(1) Part II: S. B. Kadin and J. G. Cannon, *J. Org. Chem.*, **27**, 240 (1962).

(2) (a) This investigation was supported in part by Grant MH 07775 National Institute of Mental Health. Abstracted in part from a portion of a thesis submitted by R. J. A. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1964. (b) To whom all correspondence should be addressed.

(3) (a) J. H. Biel, L. G. Abood, W. K. Ilaya, H. A. Leiser, P. A. Nuhfer, and E. T. Khichesky, *J. Org. Chem.*, **26**, 4096 (1961); (b) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Proc. Soc. Expll. Biol. Med.*, **97**, 483 (1958); (c) J. G. Cannon, *J. Org. Chem.*, **25**, 959 (1960).

(4) (a) J. von Braun, E. Danziger, and Z. Kochler, *Ber.*, **50**, 56 (1917); (b) H. Ahmed and N. Campbell, *J. Chem. Soc.*, 4115 (1960); (c) D. A. H. Taylor, *ibid.*, 2805 (1960).

(5) K. Oka, *Yakugaku Zasshi*, **81**, 882 (1961).

(6) G. R. Clemo, L. H. Groves, L. Munday, and G. A. Swan, *J. Chem. Soc.*, 863 (1951).

(7) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(8) All melting points are corrected and boiling points are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer.

(9) (a) M. W. Goldberg and W. E. Scott, U. S. Patent 2,524,787 (Oct. 10, 1950); (b) M. W. Goldberg and P. Müller, *Helv. Chim. Acta*, **23**, 831 (1940).

TABLE I

METHYL ESTERS OF ACIDS

Acid	B.p. (mm.), °C.	$n^{25}D$	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1-Hydroxytetralin-1-carboxylic	88–90 (0.15)	1.5386	64	$C_{12}H_{14}O_3$	69.88	6.80	69.42	6.97
Ethynylphenylglycolic	82–84 (0.05)	1.5282	62	$C_{11}H_{10}O_3$	69.45	5.29	69.79	5.51
Vinylphenylglycolic	83–84 (0.3)	1.5225	75	$C_{11}H_{12}O_3$	66.65	6.71	66.85	6.47
Ethylphenylglycolic	64–66 (0.02)[a]	1.5062[a]						
Indene-3-acetic	114–116[b] (1.5)	1.5516						

[a] G. S. Skinner, J. B. Bicking, and J. R. Lovett [*J. Org. Chem.*, **24**, 1587 (1959)] reported b.p. 88–90° (0.9 mm.), $n^{25}D$ 1.5080. [b] J. Thiele and M. Rüdinger [*Ann.*, **347**, 275 (1906)] reported b.p. 148–150° (12 mm.).

over 3 hr. to a vigorously stirred mixture of 6.0 g. (0.03 mole) of 1-ethynyl-1-tetralol, 6 ml. of cyclohexane, and 200 ml. of water. The reaction mixture was maintained at 0–5° by immersing in an ice–salt bath. Stirring was continued an extra 3 hr., a large volume of Filter-Cel was added, and the mixture was centrifuged. The supernatant was decanted and was filtered; the filtrate was extracted with ether and was acidified with 10% HCl. The acidified mixture was repeatedly extracted with ether, and the combined ethereal extracts were dried ($MgSO_4$). Filtration and evaporation of the ether left an oil which crystallized on standing and which was recrystallized from Skellysolve B to give 1.5 g. (27%) of white crystals, m.p. 47–48°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.23. Found: C, 68.59; H, 6.10.

Ethynylphenylglycolic acid was prepared in 93% yield from phenylglyoxylic acid by the method of Iwai and Yura[10a]; m.p. 136–137° dec., lit.[10b] m.p. 133.5–134°.

Vinylphenylglycolic Acid.—Vinyl bromide (133.0 g., 1.24 moles) in 250 ml. of purified[11] tetrahydrofuran (THF) was added dropwise over 3 hr. to 29.29 g. (1.2 g.-atoms) of magnesium turnings, and the mixture was permitted to stir 1 additional hr. The vinylmagnesium bromide suspension was added dropwise over 2 hr. to a solution of 64.5 g. (0.43 mole) of phenylglyoxylic acid in 1 l. of purified THF. The reaction mixture was stirred at room temperature overnight, then an excess of cold 50% H_2SO_4 was added. The resulting organic layer was separated; the aqueous layer was washed with 200 ml. of ether, and the combined organic phases were washed repeatedly with 20% K_2CO_3 solution. These combined aqueous extracts were acidified with 50% H_2SO_4, and the resulting suspension was extracted with three 250-ml. portions of ether. The combined ethereal extracts were dried (Na_2SO_4) and filtered, and the ether was removed. The resulting oily residue solidified on standing and was recrystallized from Skellysolve C to give 30 g. (39%) of white crystals, m.p. 104–105°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.44; H, 5.64. Found: C, 67.23; H, 5.67.

Cycloheptylphenylglycolic acid was synthesized in 16% yield from phenylglyoxylic acid and cycloheptylmagnesium bromide[12] by the method described for vinylphenylglycolic acid; m.p. 134–135°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.56; H, 8.20.

Ethylphenylglycolic acid was prepared by the method of McKenzie and Ritchie[10c]; m.p. 132–133°, lit. m.p. 129–131°[10c] and 127–127.5°.[10b]

Ethyl 1-Hydroxyindan-1-acetate (III).—To 24.5 g. (0.378 g.-atom) of purified[13] zinc dust was added 25 ml. of a solution of 25 g. (0.19 mole) of 1-indanone (Eastman White Label) and 31.57 g. (0.189 mole) of ethyl bromoacetate in 200 ml. of anhydrous benzene, and the resulting mixture was stirred and heated on a steam bath until a reaction commenced. The remainder of the benzene solution was added at such a rate as to maintain gentle reflux; the reaction was then stirred for 1 hr., cooled to room temperature, and 500 ml. of ice-cold 20% H_2SO_4 was added. The benzene layer was separated, and the aqueous layer was washed twice with 200-ml. portions of benzene. The combined benzene extracts were washed successively with 100 ml. of 5% H_2SO_4 and 100 ml. of 10% Na_2CO_3, dried (Na_2SO_4), and filtered. Evaporation of the benzene left a yellow oil which was diluted with 100 ml. of Skellysolve B; 0.8 g. (2%) of 2-indan-1'-yliden-1-indanone (IV) separated as a light yellow solid and was recrystallized from Skellysolve B; m.p. 145–147°, lit. m.p. 140–141.5°[6] and 142–143°.[14] The mother liquor was distilled, yielding 13.7 g. (33%) of a colorless oil, b.p. 112–114° (0.26 mm.), $n^{25}D$ 1.5505. The infrared spectrum (10% in chloroform) showed bands at 2.9 (OH) and 5.85 μ (C=O).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.26. Found: C, 70.94; H, 7.28.

Indene-3-acetic Acid (V). **A.**—A solution of 2 g. (0.009 mole) of III and 2 g. of KOH in 10 ml. of water and 20 ml. of ethanol was refluxed 3 hr. on a steam bath, after which time it was cooled and acidified with 10% HCl. This mixture was extracted twice with 50-ml. portions of ether. The combined ethereal extracts were dried (Na_2SO_4) and filtered, and the filtrate was evaporated on a steam bath under a stream of nitrogen. The dark oily residue was heated with 25 ml. of chloroform from which the crude product crystallized on cooling. This material was recrystallized from Skellysolve B, yielding 0.5 g. (33%) of crystals, m.p. 90–92° dec., lit.[4b] m.p. 93–95°.

B.—A mixture of 2 g. (0.009 mole) of III, 15 ml. of sodium-dried benzene, 9 ml. of dry pyridine, and 2.9 g. (0.024 mole) of $SOCl_2$ was stirred 1 hr. at room temperature. The reaction mixture was cooled in an ice bath and was extracted with three 100-ml. portions of water. The organic layer was diluted with 33 ml. of methanol containing 2.4 g. (0.043 mole) of KOH, and was heated 2 hr. on a steam bath. The methanol and benzene were then removed on the steam bath in a jet of air, the volume being maintained by addition of water. The resulting solution was repeatedly extracted with ether, then was shaken with charcoal and filtered. The pale yellow filtrate was cooled in an ice bath and was acidified with 5% HCl. The white solid which separated was collected on a filter and was recrystallized from Skellysolve B, yielding 1.2 g. (80%) of crystals, m.p. 90–92° dec.

Methyl Esters.—All of the methyl esters were prepared by treating an ethereal solution or suspension of the acid with an excess of an ethereal solution of diazomethane. After effervescence had ceased, the ether and excess diazomethane were removed on a steam bath, and the crude ester was distilled (see Table I).

Esters of N-methyl-3-hydroxypiperidine were prepared by transesterification of the corresponding methyl ester in the presence of 0.10–0.15 g. of Na or sodium methoxide and were isolated as their bifumarate salts[1] (see Table II).

Attempted Transesterification of Ethyl 1-Hydroxyindan-1-acetate (III).—III (4.0 g., 0.018 mole) was subjected to the transesterification procedure[1] in the presence of 0.1 g. of Na. After 24 hr., the brown solution was cooled and washed with water until the washings were neutral to litmus. The organic layer was then extracted with five 100-ml. portions of 5% HCl; no N-methyl-3-piperidyl ester could be isolated from this extract. The organic layer was concentrated and cooled; a brownish yellow solid separated, which was recrystallized from Skellysolve B; 0.3-g. (14%) yield of golden yellow crystals of 2-indan-1'-yliden-1-indanone (IV), m.p. 144–145°, lit. m.p.

(10) (a) I. Iwai and Y. Yura [*Yakugaku Zasshi*, **80**, 1199 (1960)] employed menthyl or bornyl phenylglyoxylate as their starting material, rather than the free acid. (b) I. Iwai and Y. Yura, *ibid.*, **80**, 1193 (1960). (c) A. McKenzie and A. Ritchie, *Ber.*, **70B**, 23 (1937).

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 292.

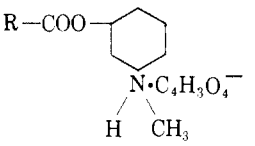
(12) L. Ruzicka, P. Barman, and V. Prelog, *Helv. Chim. Acta*, **34**, 401 (1951).

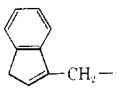
(13) Washed successively with 5% HCl, water, ethanol, and acetone and dried at 105° for 5 hr.

(14) F. Bergmann and Y. Hirshberg, *J. Am. Chem. Soc.*, **65**, 1429 (1943).

TABLE II

BIFUMARATE SALTS OF ESTERS OF N-METHYL-3-HYDROXYPIPERIDINE



No.	R	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	$C_6H_5C(OH)C_2H_5$	16[a]	173–175[b]	$C_{20}H_{27}NO_7$	61.10	6.92	3.55	61.50	6.99	3.29
2	$C_6H_5C(OH)CH{=}CH_2$	14[a]	163–165[c]	$C_{20}H_{25}NO_7$	61.37	6.43	3.57	61.41	6.29	3.69
3		13[c]	154–156[b]	$C_{21}H_{25}NO_6$	65.10	6.50	3.51	65.12	6.22	3.63
4		41[d]	172–174[e]	$C_{19}H_{25}NO_5$[f]	65.68	7.25	4.02	65.66	7.33	4.00

[a] Na used in transesterification. [b] From anhydrous 1-butanol. [c] Triturated in anhydrous ether. [d] Sodium methoxide used in transesterification. [e] From anhydrous 2-propanol. [f] This compound was isolated as the fumarate salt, rather than as the bifumarate.

140–141.5°[28] and 142–143°.[14] An infrared spectrum of this compound (10% in $CHCl_3$) showed a peak at 5.96 μ (conjugated C=O).

Pharmacology.—Preliminary biological evaluation[15] of the four N-methyl-3-piperidyl esters (Table II) is summarized as follows. The compounds were administered intravenously. The ester of ethylphenylglycolic acid (**1**, Table II) produced in mice initial CNS stimulating effects followed by CNS depressant effects, at dose levels between 10 and 100 mg./kg. The stimulant activity was of short duration. The ester of vinylphenylglycolic acid (**2**, Table II) could not be clearly classified either as a CNS stimulant or as a depressant. It prolonged the hexobarbital sleeping time in mice at dose levels of 5 mg./kg., and at 3 mg./kg. it produced increased gross activity in mice. Dose levels between 10 and 100 mg./kg. produced transient initial hyperactivity and mydriasis, followed by prolonged (4–24 hr.) miosis and decreased gross activity. The ester of indene-3-acetic acid (**3**, Table II) showed CNS depressant and hypotensive properties in mice at doses of 10–30 mg./kg. However, it was not an anticonvulsant at a dose of 17 mg./kg., and at a similar dose level it did not prolong hexobarbital sleeping time. The ester of 1-hydroxytetralin-1-carboxylic acid (**4**, Table II), at dose levels of 31 mg./kg. in mice, showed slight CNS depressant activity, preceded by initial short-term signs of central stimulation. A dose of 5.6 mg./kg. had a slight hypotensive effect in rats, which seemed to be of longer duration than that seen following administration of the ester of indene-3-acetic acid (**3**). No anticonvulsant activity was observed.

Preliminary screening of the four esters in mice, using the intravenous route for hyperactivity cage and swimming maze evaluation tests,[16] revealed that **3** and **4** were inactive and that **1** and **2** (at a dose of 1 mg./kg.) were approximately as potent as atropine and $^1/_{10}$ as active as N-ethyl-3-piperidyl cyclopentylphenylglycolate[17] in producing hyperactivity and confused behavior in the swimming maze.

(15) The following biological data were provided by the Hazleton Laboratories, Inc., under the supervision of the scientific staff of the Psychopharmacology Service Center and the testing was supported under Contract No. PH43-63-555 from the National Institute of Mental Health, Bethesda, Md.

(16) We are indebted to Dr. Leo G. Abood, Illinois Neuropsychiatric Institute, Chicago, Ill., for these preliminary data.

(17) Ditran®.

Adrenergic Neurone Blocking Agents Derived from 1,4-Benzodioxan

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The structure–activity relationships existing between closely related groups of adrenergic neurone blocking agents are reviewed. 2-Guanidinomethyl-1,4-benzodioxan is an antihypertensive agent which acts primarily by preventing the release of the sympathetic transmitter from postganglionic adrenergic nerve endings. A summary of the pharmacology is given. A number of related compounds have been synthesized, and their structure–activity relationships are discussed.

In recent years great progress has been made in the drug treatment of hypertension with the advent of compounds which interfere with stimulus–release coupling at postganglionic adrenergic nerve endings, in contrast to earlier compounds which prevented transmission at the ganglionic synapse, and which caused many side effects through their indiscriminate blockade of both sympathetic and parasympathetic ganglia.

Xylocholine (I)[1] and bretylium (II)[2] have been shown to prevent the release of the adrenergic transmitter at sympathetic nerve endings. Later, guanethidine (III) emerged as an effective antihypertensive agent and was shown to exert its effects by preventing the release

(1) "TM-10": P. Her and G. L. Wiley, *Brit. J. Pharmacol.*, **9**, 471 (1954).

(2) (a) A. L. A. Boura, F. C. Copp, W. G. Duncombe, A. F. Green, and A. McCombrey, *ibid.*, **15**, 265 (1960); (b) A. L. A. Boura and A. F. Green, *ibid.*, **14**, 536 (1959).