The hydrochloride was recrystallized from ethanol-ether, m.p. 218–220° dec.

Anal. Calcd. for $C_{20}H_{18}ClN$: C, 78.05; H, 5.89; Cl, 11.52; N, 4.55. Found: C, 78.29; H, 6.00; Cl, 11.36; N, 4.59.

In a similar manner, hydriodic acid reduction of *21A* gave *21C*.

5-(2'-Piperidyl)dibenzo[a,d][1,4]cycloheptadiene (XIX). A mixture of XVIII hydrochloride (4.3 g.) and platinium oxide (0.15 g.) in dioxane (100 ml.) and water (50 ml.) was hydrogenated at 50 p.s.i. and at 70° for 46 hr.; about 76% of the theoretical quantity of hydrogen was consumed. The catalyst was removed and the solution evaporated; the residue was dissolved in isopropyl alcohol and on scratching the solution deposited crystals (0.8 g.), m.p. 329–330° dec. The isopropyl alcohol filtrate was evaporated and the residue was converted to the free base giving on trituration with a little ether an insoluble fraction (1.1 g.), m.p. 143–144°, undepressed on admixture wtih starting material. The ether-soluble portion was converted to the hydrochloride, combined with the original high-melting fraction, and recrystallized from ethanol-methanol-ether mixture. There was obtained the product (0.5 g.) in the form of short needles, m.p. 331° dec.

Anal. Calcd. for $C_{20}H_{24}ClN$: C, 76.54; H, 7.71; Cl, 11.30. Found: C, 76.78; H, 7.49; Cl, 11.52.

Hydrogenation of the analogous pyridylmethyl compound (*21C*) under similar conditions proceeded more readily to give *22C* in 24% yield.

Resolution studies. (+) *5-Hydroxy-5-(3'-dimethylamino-2'-methylpropyl)dibenzo[a,d][1,4]cycloheptadiene (13A).* (+) Camphorsulfonic acid was added to a large excess of 3-dimethylamino-2-methylpropyl chloride and the resulting salt was recrystallized; $[\alpha]_D$ +4.6° (c = 2; water). It was converted to the free base, the hydrochloride of which had m.p. 172–174° and $[\alpha]_D$ −19.0° (c = 2; water).

The Grignard reagent derived from this base halide (10.4 g., 0.077 mole) and magnesium (1.82 g., 0.075 mole) in tetrahydrofuran (75 ml.) was treated with ketone V (10.4 g., 0.05 mole). The reaction mixture was heated under reflux for 3 hr. and processed in the usual manner. Crystallization of the resulting product from ethyl acetate gave 11.9 g. (77% yield) of material m.p. 137–141°; $[\alpha]_D$ +231° (c = 1-chloroform). Purification was effected by treating an ethanolic solution with a small excess of (−) tartaric acid; recrystallization of the salt from ethanol and regeneration of the base. Treatment with (+) tartaric acid in a similar manner gave the diastereoisomeric salt. (See Table I.)

This basic alcohol could also be obtained in less satisfactory yield by resolution of the racemic form (*12A*) with (−) tartaric acid. There was obtained in addition to the desired (+) base·(−) tartrate salt, the diastereoisomeric (−) base· (−) tartrate which, however, could be separated by recrystallization. Treatment of these salts with aqueous sodium carbonate gave purified samples of the isomeric bases. (See Table I.)

(−)*5-Hydroxy-5-(3'-dimethylamino-2'-methylpropyl)dibenzo[a,d][1,4]-cycloheptadiene (14A).* A suspension of the racemic alcohol *12A* (77.3 g., 0.25 mole) in hot ethanol (600 ml.) was treated with a solution of (+) tartaric acid (39.2 g., 0.26 mole) in the same solvent (150 ml.) and the mixture was agitated for a short time to complete dissolution of the base. The bulk of the solvent was removed *in vacuo* and acetone (150 ml.) was added followed by a little ether to the turbidity point. The precipitate obtained after the mixture had been refrigerated for several days was recrystallized from ethanol giving the (−) base·(+) tartrate, m.p. 156–157° (17.0 g., 30% yield). Conversion of this salt to the base gave a pure sample of *14A*. (See Table I.)

The filtrate from the original precipitate was concentrated and the product was converted to the free base giving 52 g. of material, m.p. 134–140°. One recrystallization from ethyl acetate raised the m.p. to 148–150°; the material, $[\alpha]_D$ +7.7° (c = 1; chloroform) being slightly enriched with the (+) base. Treatment with (−) tartaric acid gave, as described in the case of the racemic alcohol, the (−) tartrates both the (+) and the (−) bases. (See Table I.)

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MONTREAL, CANADA

[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Esters of *N*-Methyl-3-hydroxypiperidine Having Psychotomimetic Activity. II[1,2]

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A series of esters of *N*-methyl-3-hydroxypiperidine has been prepared as a part of a study of the structure-activity relationship of certain compounds having hallucinogenic activity.

Esters of *N*-methyl-3-hydroxypiperidine (I) have been shown to be capable of eliciting striking psychic effects in humans as well as marked behavioral changes in animals.[5,6] The psychotomimetic or hallucinogenic episodes which these esters precipitated occurred most readily when R_1 was hydroxyl, R_2 was phenyl, and R_3 was phenyl or cyclohexyl or cyclopentyl.[6] In 1960, Cannon[2] synthesized a num-

(1) Presented before the Division of Medicinal Chemistry, 140th National Meeting, American Chemical Society, Chicago, Ill., September 1961.

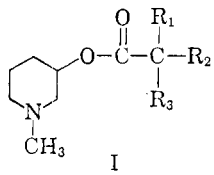
(2) J. G. Cannon, *J. Org. Chem.*, **25**, 959 (1960), should be considered as Part I of the series.

(3) National Institutes of Health Predoctoral Research Fellow (MF-10,122), 1959–1961. Present address: The Rockefeller Institute, New York 21, N. Y.

(4) To whom inquiries should be addressed.

(5) L. G. Abood, A. M. Ostfeld, and J. Biel, *Proc. Soc. Exptl. Biol. Med.*, **97**, 483 (1958).

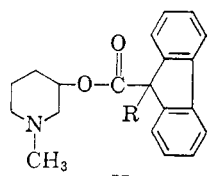
(6) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Arch. intern. pharmacodynamie*, **120**, 186 (1959).



I

ber of symmetrically disubstituted benzilate esters of *N*-methyl-3-hydroxypiperidine, all of which were found to be devoid of hallucinogenic activity.[7] The "planar benzilate" analog of this amino alcohol, *N*-methyl-3-piperidyl 9-hydroxyfluorene-9-carboxylate,[2] however, did exhibit a marked psychotomimetic effect.[7] In view of these findings, it might be considered that one of the requirements for psychotomimetic activity in disubstituted glycolate esters of *N*-methyl-3-piperidinol is the ability of the two cyclic substituents of the glycolic acid portion of the ester to lie in a coplanar or nearly coplanar configuration.

A series of 9-substituted-fluorene-9-carboxylic acid esters of *N*-methyl-3-hydroxypiperidine (II), in which R was (a) hydrogen, (b) methyl, (c) chlorine, (d) methoxy, and (e) acetoxy was synthesized for the purpose of comparing the psychotomimetic properties of these esters containing the planar fluorene group with an analogous series of similarly substituted diphenylacetate esters of the same amino alcohol.[8]



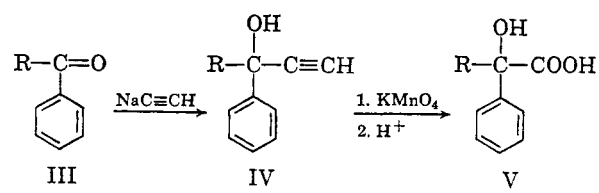
II

IIa. R = H
b. R = CH_3
c. R = Cl
d. R = OCH_3
e. R = $C_2H_3O_2$

In addition, *N*-methyl-3-piperidyl 9-hydroxyfluorene-9-carboxylate methiodide, *N*-methyl-3-piperidyl$^{\Delta 9,\alpha}$-fluoreneacetate, and *N*-methyl-3-piperidyl 3,3-diphenyl-3-hydroxypropionate were prepared.

The potent psychotomimetic effects elicited by the cyclopentyl- and the cyclohexylphenylglycolate esters of *N*-methyl-3-hydroxypiperidine have been attributed to a slower detoxification rate of the cycloalkylphenylglycolate esters as compared to the parent benzilate ester and/or to a solubility effect wherein the greater lipoid solubility of these esters aids in achieving a higher concentration of drug at the site of action.[6] This suggested that the cyclopropyl- and the cyclobutylphenylglycolate esters of *N*-methyl-3-piperidinol might demonstrate similar psychotomimetic activity. Although neither the cyclopentyl nor the cyclohexyl group is flat,[9] an inspection of Fisher-Hirschfelder-Taylor molecular models indicates that both the cyclopentyl and the cyclohexyl moieties of the disubstituted glycolate esters can lie in approximately the same plane as the phenyl group without producing significant nonbonded atomic interactions. The three- and four-membered alicyclic ring systems are flat and would therefore be more capable of achieving a configuration which is approximately coplanar with the nearby phenyl group; in addition, because of their small size the cyclopropyl and cyclobutyl groups would not be expected to exhibit nonbonded atomic interactions with the benzene ring when they are coplanar with it.

Dupont,[10] in 1910, prepared atrolactic acid by treating 2,5-dihydroxy-2,5-diphenyl-3-hexyne with aqueous, neutral potassium permanganate. Recently, Zaugg and co-workers[11] synthesized dicyclopropylglycolic acid by oxidizing 1,1-dicyclopropyl-2-propyn-1-ol with aqueous, neutral potassium permanganate. Their attempt to prepare the acid through cyanohydrin synthesis and subsequent hydrolysis was unsuccessful because dicyclopropyl ketone did not react with hydrogen cyanide. The synthesis of cyclopropyl- and cyclobutylphenylglycolic acid was accomplished by the permanganate procedure. Cyclopropyl phenyl ketone (IIIa) reacted with sodium acetylide in liquid ammonia to afford 1-cyclopropyl-1-phenyl-2-propyn-1-ol (IVa) in excellent yield. Treatment of this acetylenic alcohol with aqueous, neutral potassium permanganate at 0–5° resulted in the formation of cyclopropylphenylglycolic acid (Va). In a similar manner, cyclobutyl phenyl ketone (IIIb), obtained by converting cyclobutanecarboxylic acid to its acid chloride followed by a Friedel-Crafts acylation, was converted first into its ethynylcarbinol derivative (IVb) and thence to cyclobutylphenylglycolic acid (Vb).



III IV V

a. R = cyclopropyl
b. R = cyclobutyl

When 9-ethynyl-9-fluorenol[12] was treated with aqueous, neutral potassium permanganate, no acidic material was isolated. Likewise, treatment of this ethynylcarbinol with ozone in an attempt to effect

(7) L. G. Abood, personal communication.

(8) For the syntheses of the diphenylacetate esters, see ref. 2 and J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, 74, 1485 (1952).

(9) W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry*, M. S. Newman, Ed., J. Wiley & Sons, Inc., New York, 1956, Chap. 1.

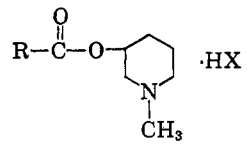
(10) G. Dupont, *Compt. rend.*, 150, 1524 (1910).

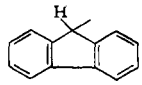
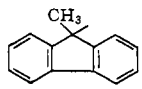
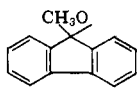
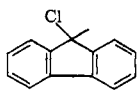
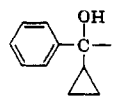
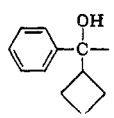
(11) H. E. Zaugg, N. R. Springer, and R. J. Michaels, *J. Org. Chem.*, 25, 645 (1960).

(12) G. F. Hennion and B. R. Fleck, *J. Am. Chem. Soc.*, 77, 3253 (1955).

TABLE I

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



No.	R	X	Yield, %	M.P.	Formula		Calcd.	Found
I		Chloride	55.5[a]	237–239 dec.[b]	$C_{20}H_{22}ClNO_2$	C	69.87	69.18
						H	6.40	6.32
						Cl	10.33	9.95
						N	4.08	3.99
II		Chloride	26.6[c]	233–235[b]	$C_{21}H_{24}ClNO_2$	C	70.49	70.31
						H	6.71	6.90
						Cl	9.93	9.86
						N	3.92	3.91
III		Chloride	38.4[a]	244–246 dec.[b]	$C_{21}H_{24}ClNO_3$	C	67.47	67.05
						H	6.43	6.28
						Cl	9.50	9.23
						N	3.75	4.00
IV		Chloride	20[c]	211–214 dec.[d]	$C_{20}H_{21}Cl_2NO_2$	C	63.49	63.15
						H	5.55	5.94
						Cl	18.78	18.35
						N	3.70	3.99
V		Bifumarate	41[a]	132–134	$C_{21}H_{27}NO_7$	C	62.22	62.39
						H	6.67	6.93
						N	3.46	3.30
VI		Bifumarate	46[a]	140–142	$C_{22}H_{29}NO_7$	C	63.01	62.99
						H	6.92	7.02
						N	3.34	3.12

[a] Using sodium hydride. [b] From ethanol-ether. [c] Using sodium methoxide. [d] From 1-butanol–ether.

the synthesis of 9-hydroxyfluorene-9-carboxylic acid was unsuccessful. Recently, Copeland and coworkers[13] found that the 1,2-bond of the fluorene molecule undergoes facile attack by ozone and this may account for the lack of success when 9-ethynyl-9-fluorenol was treated with ozone. The reaction of 9-acetyl-9-fluorenol[12] with sodium hypochlorite resulted in a quantitative yield of fluorenone. This unexpected consequence probably occurred as a result of the further oxidation of the product of the haloform reaction, 9-hydroxyfluorene-9-carboxylic acid. The synthesis of 9-hydroxyfluorene-9-carboxylic acid was achieved by the benzilic acid rearrangement of 9,10-phenanthrenequinone[14] and by the reaction of fluorenone with potassium in liquid ammonia followed by carbonation.

The *N*-methyl-3-piperidyl esters were prepared by transesterification of their corresponding methyl esters (except for *N*-methyl-3-piperidyl fluorene-9-carboxylate for which the ethyl ester was used). Isolation of the esters was accomplished through the formation of either their hydrochloride or their bifumarate salts. The latter were more easily prepared in analytically pure form.

In an attempt to prepare *N*-methyl-3-piperidyl fluorene-9-glycolate, methyl fluorene-9-glycolate was treated with *N*-methyl-3-hydroxypiperidine in the presence of a small amount of sodium hydride. Transesterification was accompanied by elimination of the elements of water, and the resulting product was *N*-methyl-3-piperidyl $^{\Delta 9,\ \alpha}$-fluoreneacetate. That elimination occurred in addition to transesterification was shown by carbon-hydrogen analysis, by infrared analysis which exhibited double bond (6.10 μ), as well as ester carbonyl absorption (5.81 μ), but no hydroxyl absorption, and by the fact that the reaction mixture as well as the final product, isolated as the hydrochloride salt, was colored yellow, a property which might be expected of such a highly conjugated system.

The results of the biological tests of the compounds reported herein will be published in detail elsewhere. The esters containing the cyclopropyl and the cyclobutyl groups exhibited, as expected, marked psychotomimetic activity. In general, the 9-substituted fluorene-containing esters were more active than their corresponding α-substituted di-

(13) P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, 3230 (1960).

(14) H. Klinger, *Ann.*, **389**, 237 (1912).

phenylmethane analogs. Also, those compounds exhibiting maximal psychotomimetic activity contained a hydroxyl group alpha to the carboxyl moiety.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Analyses are by Huffman Microanalytical Laboratories, Wheatridge, Colo. and by Drs. Weiler and Strauss, Oxford, England.

Ethyl fluorene-9-carboxylate. This compound was prepared from fluorene-9-carboxylic acid[15] in 48.5% yield by the method of Adickes[16]; b.p. 160°/0.2 mm., m.p. 37–39° (lit.[17] b.p. 209–210°/17 mm., m.p. 43–45°).

9-Methylfluorene-9-carboxylic acid. This acid was synthesized in 67% yield from 9-methylfluorene[18] by the method utilized by Burtner and Cusic[19] for the preparation of fluorene-9-carboxylic acid, m.p. 171–172° (lit.[20] m.p. 166°).

Methyl 9-methylfluorene-9-carboxylate. An excess of an ethereal solution of diazomethane was added to an ethereal solution of 11.2 g. (0.5 mole) of 9-methylfluorene-9-carboxylic acid. Upon evaporation of the excess diazomethane, the ethereal residue was extracted once with 10% sodium carbonate solution and was dried over magnesium sulfate. After filtration and removal of the ether on a steam bath, the remaining oil was crystallized and recrystallized from methanol to give 7.0 g. (0.029 mole, 58%) of white material, m.p. 109° (lit.[21] m.p. 108–109°).

9-Hydroxyfluorene-9-carboxylic acid. This acid was prepared in 55.5% yield by the method of Klinger[14] and in 27% yield by the method of Hamrick and Hauser[22] for the preparation of benzilic acid from benzophenone, m.p. 165–166° (lit.[14] m.p. 166–167°).

Methyl 9-chlorofluorene-9-carboxylate. The procedure of Klinger[14] was followed to prepare this compound in 45% yield from 9-hydroxyfluorene-9-carboxylic acid and methanolic hydrogen chloride, m.p. 110–111° (lit.[14] m.p. 113–114°).

Methyl 9-methoxyfluorene-9-carboxylate. This ester was prepared in 71.5% yield from 9-hydroxyfluorene-9-carboxylic acid by the method of Noyce and Fessenden[23] for the preparation of methyl *cis*-3-methoxy-cyclopentanecarboxylate, m.p. 125–126° (lit.[24] m.p. 124°).

Fluorene-9-glycolic acid. This compound was prepared in 77% yield by the reduction of ethyl fluorene-9-glyoxylate,[25] synthesized by the method of Kuhn and Levy[26] for the methyl ester, with zinc amalgam and hydrochloric acid according to the directions of Wislicenus and Weitemeyer[27]; m.p. 197–198° (lit.[27] m.p. 194–195°).

Methyl fluorene-9-glycolate. This ester was synthesized in 51% yield from fluorene-9-glycolic acid and diazomethane by the procedure described for methyl 9-methylfluorene-9-carboxylate, m.p. 92° (lit.[27] m.p. 96°).

1-Cyclopropyl-1-phenyl-2-propyn-1-ol (IVa). To 250 ml. of liquid ammonia contained in a 500 ml. flask equipped with a stirrer, a dropping funnel, and a Dry Ice–acetone-filled cold finger topped with a drying tube filled with soda lime was added 5.75 g. (0.25 g.-atom) of sodium and acetylene was then added until the blue color disappeared and for 5 minutes thereafter (total time, approximately 10 min.). A solution of 29.2 g. (0.20 mole) of cyclopropyl phenyl ketone (Aldrich Chemical Co.) in 50 ml. of dry ether was added dropwise over 1 hr. Stirring was continued for 1 hr. more, and the ammonia was permitted to evaporate from a steam bath by replacing the cold finger with an air condenser. The volume of the mixture was maintained by the slow addition of ether from the dropping funnel. After removal of the ammonia was complete the reaction mixture was poured with stirring over 500 ml. of an ice water slurry. The layers were separated, and the water was extracted once with ether. The combined ether fractions were dried over magnesium sulfate, filtered, and the ether was evaporated leaving an oil. This material was distilled to give 31.0 g. (0.18 mole, 90%) of a colorless oil, b.p. 120–122°/7 mm., n_D^{25} 1.5472. An infrared spectrum of a liquid film sample exhibited peaks attributable to alcoholic hydroxyl (2.93 μ) and acetylenic hydrogen (3.04 μ) but showed no carbonyl absorption.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.72; H, 6.98. Found: C, 83.72, 83.46; H, 7.00, 6.94.

Cyclobutanecarbonyl chloride. To 25.0 g. (0.25 mole) of cyclobutanecarboxylic acid (Aldrich Chemical Co.) contained in a 100 ml. flask was added 50 ml. of redistilled phosphorus trichloride, and the mixture was refluxed for 2 hr. Distillation at atmospheric pressure removed most of the unchanged phosphorus trichloride, and the remaining material was distilled at reduced pressure. That fraction boiling at 56–58°/48 mm. was collected. The yield was 19.0 g. (0.16 mole, 62.5%) of a colorless liquid. (Roberts and Simmons[28] reported 60°/50 mm.).

Cyclobutyl phenyl ketone (IIIb). A solution of 19.0 g. (0.16 mole) of cyclobutanecarbonyl chloride in 50 ml. of dry benzene was added dropwise over 1 hr. to a stirred and gently refluxing solution of 26.6 g. (0.20 mole) of anhydrous aluminum chloride in 200 ml. of dry benzene. Refluxing was continued for 1 hr. more, and the cooled reaction mixture was poured over 1 l. of chipped ice. The layers were separated, and the water was extracted with benzene. The combined benzene fractions were dried over magnesium sulfate, filtered, evaporated, and the residual oil was distilled to give 21.0 g. (0.13 mole, 81%) of a colorless compound, b.p. 116–118°/7 mm., n_D^{25} 1.5453 (lit.[29] b.p. 114.4–114.5°/7 mm., n_D^{25} 1.5452).

1-Cyclobutyl-1-phenyl-2-propyn-1-ol (IVb). This compound was prepared in 88.5% yield by the procedure described for 1-cyclopropyl-1-phenyl-2-propyn-1-ol, b.p. 130–132°/7 mm., n_D^{25} 1.5460.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.87; H, 7.53. Found: C, 83.81, 83.61; H, 7.49. 7.58.

Cyclopropylphenylglycolic acid (Va). A solution of 30.0 g. (0.19 mole) of potassium permanganate in 500 ml. of water was added dropwise over 3 hr. and with vigorous stirring to a mixture of 12.0 g. (0.07 mole) of 1-cyclopropyl-1-phenyl-2-propyn-1-ol and 50 ml. of water. The reaction mixture was maintained at 0–5° by immersing the reaction flask in an ice-salt bath. Stirring was continued for an additional 2 hr.; a large volume of Filter-cel was then added, and the reaction mixture was centrifuged. The supernatant was decanted from the residue of manganese dioxide and Filter-cel and was filtered. The filtrate was extracted with ether and was then acidified with 10% hydrochloric acid. The mixture became

(15) R. T. Arnold, W. E. Parham, and R. M. Dodson, *J. Am. Chem. Soc.*, **71**, 2439 (1949).
(16) F. Adickes, *J. prakt. Chem.*, **145**, 235 (1936).
(17) H. Staudinger, *Ber.*, **39**, 3064 (1906).
(18) K. L. Schoen and E. I. Becker, *Org. Syntheses*, **39**, 43 (1959).
(19) R. R. Burtner and J. Cusic, *J. Am. Chem. Soc.*, **65**, 262 (1943).
(20) H. Meerwein and H. Probst, *Ann.*, **396**, 200 (1913).
(21) H. Stubbs and S. Tucker, *J. Chem. Soc.*, 3288 (1950).
(22) P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 493 (1959).
(23) D. S. Noyce and J. Fessenden, *J. Org. Chem.*, **24**, 715 (1959).
(24) H. Klinger, *Ann.*, **390**, 371 (1912).
(25) W. Wislicenus, *Ber.*, **33**, 771 (1900).
(26) R. Kuhn and E. Levy, *Ber.*, **61**, 2240 (1928).
(27) W. Wislicenus and H. Weitemeyer, *Ann.*, **436**, 1 (1924).
(28) J. D. Roberts and H. E. Simmons, Jr., *J. Am. Chem. Soc.*, **73**, 5487 (1951).
(29) R. P. Mariella and R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952).

cloudy, and it was repeatedly extracted with ether; the combined ethereal extracts were dried over magnesium sulfate. Filtration and evaporation of the ether left an oil which crystallized on standing and which was recrystallized from benzene–Skelly B to give 4.0 g. (0.021 mole, 30%) of white crystals, m.p. 91–92°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 69.05, 69.00; H, 6.29, 6.21.

Cyclobutylphenylglycolic acid (Vb). This acid was prepared in 24% yield by the procedure described for cyclopropylphenylglycolic acid. It was recrystallized from benzene–Skelly B, m.p. 143–143.5°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.76, 69.77; H, 7.00, 6.85.

Methyl cyclopropylphenylglycolate. This compound was prepared in 78% yield from cyclopropylphenylglycolic acid and diazomethane by the method described for methyl 9-methylfluorene-9-carboxylate, b.p. 84–88°/0.3 mm., n_D^{25} 1.5214.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.76, 69.50; H, 6.72, 6.79.

Methyl cyclobutylphenylglycolate. This compound was prepared in 93% yield from cyclobutylphenylglycolic acid and diazomethane by the method described for methyl 9-methylfluorene-9-carboxylate, b.p. 102–104°/0.5 mm., m.p. 56–57°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.83, 70.73; H, 7.37, 7.29.

Esters of N-methyl-3-hydroxypiperidine. These esters were prepared by transesterification of the corresponding methyl esters (except in the case of *N*-methyl-3-piperidyl fluorene-9-carboxylate for which the ethyl ester was used). Equimolar amounts of *N*-methyl-3-hydroxypiperidine[30] and of the appropriate methyl ester in 1.5 l. of *n*-heptane were stirred and refluxed for 20 hr. in the presence of 0.10–0.15 g. of sodium hydride or of sodium methoxide. Methanol was periodically removed by means of a Dean-Stark trap equipped with a condenser containing a Drierite-filled drying tube. The volume of the reaction mixture was reduced under vacuum to 200–300 ml.; upon cooling 600–700 ml. of ether was added to the flask. The resulting mixture was transferred to a 2 l. separatory funnel and was repeatedly extracted with water, then with 5% hydrochloric acid. Upon treating the combined hydrochloric acid extracts with 10% sodium hydroxide solution the mixture became cloudy. Extraction with ether ensued and the combined ether extracts were dried over magnesium sulfate. The heterocyclic esters were isolated as their hydrochloride or bifumarate salts. The former were prepared by the addition of ethereal hydrogen chloride to an ethereal solution of the heterocyclic ester. The hydrochloride salt, which precipitated immediately, was collected on a filter and was recrystallized. The bifumarate salts were prepared by adding a saturated solution of fumaric acid, obtained by stirring an excess of fumaric acid with 700–800 ml. of dry ether for 12–15 hr. and removing the undissolved acid by filtration, to an ethereal solution of the amino ester. The resulting clear solution was placed in a refrigerator where fine white needles slowly formed. These were collected by suction filtration (see Table I).

N-Methyl-3-piperidyl 9-acetoxyfluorene-9-carboxylate hydrochloride. This compound was prepared by refluxing 2.5 g. (0.007 mole) of *N*-methyl-3-piperidyl 9-hydroxyfluorene-9-carboxylate hydrochloride[2] with 50 ml. of redistilled acetic anhydride for 2.5 hr. On cooling, small white crystals separated from the reaction mixture and were collected by suction filtration. Recrystallization from 1-butanol–ether yielded 2.7 g. (0.0067 mole, 95.5%) of white crystals, m.p. 220–222° dec.

Anal. Calcd. for $C_{22}H_{27}ClNO_4$: C, 65.75; H, 5.98; Cl, 8.84; N, 3.49. Found: C, 65.12; H, 6.23; Cl, 8.83; N, 3.52.

N-Methyl-3-piperidyl 9-hydroxyfluorene-9-carboxylate methiodide. Four and one-half grams (0.0125 mole) of *N*-methyl-3-piperidyl 9-hydroxyfluorene-9-carboxylate hydrochloride[2] was dissolved in a small amount of water, and the aqueous solution was made basic by the addition of 5% sodium hydroxide solution. The cloudy mixture was repeatedly extracted with ether, and the combined ether extracts were dried over magnesium sulfate. After filtration, 1.78 g. (0.0125 mole) of methyl iodide was added, and the ethereal solution was placed in a refrigerator. White crystals soon separated and were collected by suction filtration. Recrystallization from ethanol-ether gave 5.2 g. (0.011 mole, 88%) of the methiodide, m.p. 235–236° dec.

Anal. Calcd. for $C_{21}H_{24}INO_3$: C, 54.19; H, 5.16; I, 27.3; N, 3.01. Found: C, 53.91; H, 5.59; I, 26.9; N, 2.85.

N-Methyl-3-piperidyl$^{\Delta 9,\alpha}$-fluoreneacetate hydrochloride. Two and eight-tenths grams (0.011 mole) of methyl fluorene-9-glycolate was transesterified by the procedure described previously with 1.27 g. (0.011 mole) of *N*-methyl-3-hydroxypiperidine using a catalytic amount of sodium hydride. Isolation of the hydrochloride salt in the usual manner was followed by recrystallization from ethanol-ether to give 1.0 g. (0.0028 mole, 25.5%) of yellow crystals, m.p. 180–182°. Infrared analysis of a Nujol mull of the hydrochloride salt showed double bond absorption (6.10 μ) but no hydroxyl absorption.

Anal. Calcd. for $C_{21}H_{22}ClNO_2$: C, 70.89; H, 6.19; Cl, 9.99; N, 3.94. Found: C, 70.89, 70.91; H, 6.24, 6.15; Cl, 10.09, 9.84; N, 4.07, 4.05.

N-Methyl-3-piperidyl acetate. This compound was prepared in 38% yield by the method employed by Jones and Major[31] for acetyldiethylaminoethanol, b.p. 32–40°/0.2 mm., n_D^{26} 1.4471. The picrate salt, recrystallized from absolute ethanol, gave rise to bright yellow prisms, m.p. 121–123.

Anal. Calcd. for $C_{14}H_{18}N_4O_9$: C, 43.5; H, 4.66; N, 14.5. Found: C, 43.6; H, 4.61; N, 14.3.

N-Methyl-3-piperidyl 3,3-diphenyl-3-hydroxypropionate. This compound was prepared by a modification of the method employed by Hauser and Dunnavant[32] for the condensation of ethyl acetate with benzophenone. To a well stirred suspension of 0.2 mole of freshly prepared sodium amide in 500 ml. of liquid ammonia contained in a 2 l. standard taper round bottom three necked flask equipped with a dropping funnel and a Dry Ice–acetone cold finger condenser and seated in a Dry Ice–acetone bath, was added as rapidly as possible a solution of 15.7 g. (0.1 mole) of freshly distilled *N*-methyl-3-piperidyl acetate in 75 ml. of anhydrous ether. As soon as the last portion of this solution ran into the flask, a solution of 18.2 g. (0.1 mole) of benzophenone in 75 ml. of anhydrous ether was added as rapidly as possible. The resulting grey-black mixture was stirred for 0.5 hr., then an excess of solid ammonium chloride was added. Stirring was continued and the reaction mixture was permitted to come to room temperature, so as to permit removal of the liquid ammonia. Evaporation was completed on a steam bath, leaving a dirty white solid residue. This material was washed thoroughly with water, and the insoluble portion was recrystallized twice from Skelly B to afford 12.4 g. (36.6%) of white rosettes, m.p. 84–85°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.3; H, 7.38; N, 4.14. Found: C, 73.7; H, 7.53; N, 3.93.

The bifumarate salt was prepared and was recrystallized from Skelly B, forming masses of tiny prisms, m.p. 165–167°.

(30) Kindly supplied by Dr. J. H. Biel, Lakeside Laboratories, Inc., Milwaukee, Wis.

(31) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, 49, 1534 (1927).

(32) C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, 25, 1296 (1960).

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 66.0; H, 6.38; N, 3.38. Found: C, 65.6; H, 6.46; N, 3.11.

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Structures Related to Morphine. XIX.[1] Benzomorphans from 3,4-Diethylpyridine

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3,4-Diethylpyridine has been converted to 5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IV) and a diastereoisomer (V) (in low yield) by either the Grewe synthesis or a method based on the Stevens rearrangement. Hofmann cleavage of the methyl ether of IV followed by palladium-charcoal aromatization produced a nitrogen-free compound whose spectral, chemical, and analytical behavior are accommodated by the structure of 1,2-diethyl-7-methoxynaphthalene (X). The analgesic activity (mouse) and physical dependence capacity (monkey) of IV, V, and the *N*-phenethyl analog of IV have been determined.

The use of 3,4-lutidine[2] in the Grewe morphinan synthesis has provided a group of compounds—benzomorphans—possessing interesting central nervous system effects. In this class as a whole it is apparent that a marked separation of analgesic action and morphine abstinence-suppressing ability (often equated with addiction liability)[3] has been achieved with respect to the mouse and monkey species; one member of this group, 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan,[2a,4] has been shown to have clinical utility. The substitution of 3,4-diethylpyridine for 3,4-lutidine as a starting material could be expected to produce homologous benzomorphans such as IV, V, and XI, which are also very close relatives of the powerful analgesic, 3-hydroxy-*N*-methylmorphinan (VI).[5] This report is concerned with the conversion of 3,4-diethylpyridine to 5,9-diethyl-6,7-benzomorphans by the Grewe synthesis or by a more versatile alternative synthesis,[6] the latter based on the Stevens rearrangement of 1-benzyl-1,2,5,6-tetrahydropyridines.

When 3,4-diethylpyridine methobromide or methiodide (II) and *p*-methoxybenzylmagnesium chloride (I) were brought together in the Freund reaction, a good yield of the dihydropyridine derivative (III) resulted. Reduction of III in aqueous methanol with sodium borohydride afforded the tetrahydro compound (IX) which was obtained also, albeit in lower yield, by hydrogenation of III (dilute hydrochloric acid, palladium on barium sulfate). Treatment of IX with hot 48% hydrobromic acid gave 5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (IV) in 10–30% over-all yields, depending on the procedure used for the conversion of III to IX, and about 3% of a diastereoisomer (V) in analogy with the 5,9-dimethyl series.[2]

Compound IV was also prepared in 25% over-all yield[6] by sodium borohydride reduction of II to 3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (VII), isolated as the *p*-methoxybenzyl chloride quaternary (VIII) rearrangement of VIII to IX with phenyllithium[6] and treatment of the crude IX with 48% hydrobromic acid.

The benzomorphan IV was converted to the *N*-phenethyl analog (XI) in the standard way[2] and to 1,2-diethyl-7-methoxynaphthalene by Hofmann degradation of the methiodide of IV methyl ether, and palladium-charcoal aromatization of the product.

Compounds IV and XI are somewhat less potent in mice (subcutaneous administration)[7] than the

(1) Paper XVIII, S. Saito and E. L. May, *J. Org. Chem.*, **26**, 4536 (1961).

(2) (a) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959); (b) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960); (c) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959); (d) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(3) G. A. Deneau and M. H. Seevers, Addendum 1, Minutes of the 21st Meeting of the Committee on Drug Addiction and Narcotics, National Research Council, January 1960, and personal communications.

(4) Generic name phenazocine, trade names Prinadol, Narphen; *cf.* H. F. Fraser and H. Isbell, *Bulletin on Narcotics*, **12**, 15 (1960) for a leading reference.

(5) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955); R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949); O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949). Compound IV is simply the open (at the 6,7-bond of VI) analog of VI. We are of the opinion (*cf.* ref. 2a and 2d) that the 9-ethyl substituent is oriented away from nitrogen (axial for the hydroaromatic ring) in IV and toward it in V. Preliminary NMR data appear to confirm this.

(6) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).