1,3,6-Trihydroxy-2,4,5,7-tetrazanaphthalene. 2-Hydroxy-4,5-dicarbamylpyrimidine was allowed to react with hypobromite as described above for the preparation of 1,3-dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene. The product was obtained, in 74% yield, as a finely divided, light brown crystalline solid, insoluble in boiling water but readily soluble in dilute base. A sample for analysis was taken up in hot dilute ammonium hydroxide and reprecipitated with acetic acid. This was repeated three times. It remained unmelted up to 360°.

Anal. (dried 2 hr. at 100°). Calcd. for $C_6H_4N_4O_3 \cdot H_2O$: C, 36.35; H, 3.04; N, 28.30. Found: C, 36.02; H, 3.20; N, 28.28. (Dried 3 hours at 200°). Calcd. for $C_6H_4N_4O_3$: N, 31.11. Found: N, 29.35.

Acknowledgment. The author is grateful to W. L. Brown, G. Maciak, H. L. Hunter, and R. Hughes for the microanalyses.

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

Esters of Benzilic Acids and Congeners Having Potential Psychotomimetic Activity

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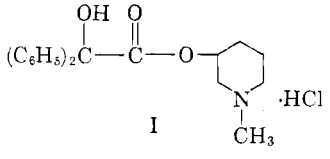
A series of heterocyclic alcoholic esters of benzilic acids and related compounds has been prepared as a part of a study of the structure-activity relationship of certain compounds having hallucinogenic activity.

In 1955, Biel and his co-workers[1] reported the synthesis of a series of disubstituted glycolic acid esters of *N*-alkyl-3-piperidols. Several of these had marked anticholinergic activity; *N*-methyl-3-piperidyl benzilate hydrochloride (I) had 60% of the spasmolytic activity of atropine against actylcholine-induced spasms in the guinea pig ileum.



I

In 1958, Abood, Ostfeld, and Biel[2] reported that compound I produced bizarre psychic effects in a test population of normal human volunteers. The compound is an extremely potent auditory and visual hallucinogen when given in small oral doses. A number of subjects exhibited paranoid and megalomanic delusions; the affective states were reported to range from a feeling of unpleasantness to one of extreme terror. Abood, Ostfeld, and Biel[3] found that the psychotomimetic activity of I was abolished or greatly diminished if the nitrogen-methyl were replaced by ethyl or hydrogen, if the nitrogen were quaternized, or if the hydroxyl group of benzilic acid portion were replaced by hydrogen. The replacement of one of the benzene rings by a cyclohexane or a cyclopentane moiety increased the hallucinogenic activity. These workers made no study of the effects of substitution on the phenyl rings on the potency of the molecule, nor did they report the effects of modifying the hydroxyl group of the benzilic acid portion, other than its replacement by hydrogen.

A number of derivatives and congeners of structure *I* have been prepared in this laboratory, for a further study of structure-activity relationship in this new class of psychotomimetic agents. Attention in the work reported herein has centered chiefly on modifying the acid portion of *I* rather than the amino alcohol portion. A series of esters of disubstituted glycolic acid derivatives has been prepared, and in addition a biologically isosteric α,α-diphenyl propionic acid ester has been prepared. One ester of 2-(1-methyl-4-piperazino) ethanol is listed; with this single exception, the alcoholic portion of the esters if *N*-methyl-3-piperidol.[4] Pharmacological findings will be reported in some detail elsewhere. None of the heterocyclic esters listed has been reported previously in the literature; however, Buehler and his coworkers[5] have reported the preparation of *N*-ethyl-3-piperidyl esters of 2,2′-dimethylbenzilic, 3,3′-dimethylbenzilic, and 4,4′-diphenylbenzilic acids as potential anticholinergic agents.

3,4,3′,4′-Tetramethoxybenzilic acid has apparently never been obtained in an analytically pure state, because of its tendency to undergo decarboxylation during attempted purification. It was possible to convert the crude acid to its methyl ester with diazomethane, and this methyl ester was purified so as to yield a correct analysis.

The general method for preparation of the substituted benzilic esters 1–9 (Table II) was as fol-

(1) J. H. Biel, E. P. Sprengeler, H. A. Leiser, J. Horner, A. Drukker, and H. Friedman, *J. Am. Chem. Soc.*, **77**, 2250 (1955).

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

(3) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Arch. Int. Pharmacodynam.*, **120**, 186 (1959).

(4) Generously supplied by Dr. John H. Biel, Lakeside Laboratories, Milwaukee.

(5) C. A. Buehler, H. A. Smith, D. M. Glenn, and K. V. Nayak, *J. Org. Chem.*, **23**, 1432 (1958).

TABLE I

METHYL ESTERS OF BENZILIC ACIDS

$(RC_6H_4)_2C(OH)COOCH_3$

No.	R′	B.P. or M.P.[a]	n_D^t	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
1	2,2′-Dichloro	65–67[b]	—	$C_{15}H_{12}O_3Cl_2$	57.8	3.86	22.9	58.1	3.96	23.2
2	3,3′-Dichloro	172–180 (0.5 mm.)	1.5854 (23°)	$C_{15}H_{12}O_3Cl_2$	57.8	3.86	22.9	57.9	4.08	22.6
3	2,2′-Dimethyl	83–85[c]	—	$C_{17}H_{18}O_3$	75.6	6.68		75.8	6.82	
4	3,3′-Dimethyl	63–65[d]	—	$C_{17}H_{18}O_3$	75.6	6.68		75.1	6.54	
5	3,4,3′,4′-Tetramethoxy	132–133[e]	—	$C_{19}H_{22}O_7$	63.0	6.08		63.3	6.13	
6	3,4,3′,4′-Bis-methylenedioxy	130–131[c]	—	$C_{17}H_{14}O_7$	62.0	4.26		62.5	4.36	

[a] All melting points uncorrected. [b] From aqueous methanol. [c] From Skelly-C. [d] From Skelly-B. [e] From Skelly-C-benzene.

lows: treatment of the appropriately substituted benzyldehyde with potassium cyanide; oxidation of the resulting crude benzoin; and rearrangement of the benzil thus formed to the benzilic acid. All of the amino alcohol esters (1–14) were obtained by transesterification of the corresponding methyl ester. Those methyl esters which are new compounds are listed in Table I. When hydrohalide salts of an amino ester proved to be hygroscopic, the bifumarate salt was prepared for pharmacological evaluation.

EXPERIMENTAL

Benzoin condensations. One mole of freshly distilled aromatic aldehyde was dissolved in 150 ml. of 95% ethanol in a round bottom flask, and a solution of 15 g. of potassium cyanide in 120 ml. of water was added. The mixture was refluxed 1 hr., then an additional 15 g. of solid potassium cyanide was added and refluxing was continued for 1.5 hr. The mixture was permitted to cool and was diluted with water to a total volume of 1 l. After standing 15–20 min., the upper aqueous layer was decanted and discarded and the lower heavy, oily layer was washed twice with water. This crude benzoin was oxidized to the benzil without further purification.

Benzils. Method A. The crude benzoin was refluxed with an excess of Fehling's solution for 15 hr. The resulting mixture of cuprous oxide and benzil was collected on a suction filter, washed with copious amounts of water, and air dried. This material was transferred to the extraction thimble of a Soxhlet apparatus and was extracted to exhaustion with acetone. In most instances, the benzil precipitated from the acetone solution on cooling; if not, the solvent was removed by distillation. The crude benzils were recrystallized from ethanol, ethanol-chloroform, or ethanol-benzene.

Method B. The crude benzoin derived from 1 mole of aromatic aldehyde was placed in a 1-l. Erlenmeyer flask and to it was added cautiously in 50 ml. portions a total of 350 ml. of concd. nitric acid. After all of the nitric acid had been added, the mixture was heated on a steam bath until no more brown fumes were evolved. The solid crude benzil was collected on a suction filter, washed with copious amounts of water, dried, and recrystallized as in Method A.

Benzilic acids. A modification of the method of Ford-Moore[6] was found to be of general utility. An 8.5-g. sample of potassium hydroxide was dissolved with heating in 65 ml. of 1-butanol, and the boiling solution was added to 0.05 mole of the purified benzil contained in a 200-ml. round bottom flask fitted with a condenser. The resulting mixture was refluxed vigorously for 10 min., then it was cooled to room temperature. The potassium salt of the benzilic acid precipitated from solution, and it was collected on a suction filter and washed with two portions of cold 1-butanol, then with several portions of dry ether. The crude potassium benzilate was dissolved in 200–300 ml. of water; the solution was filtered, and was extracted three times with ether. Air was bubbled through the aqueous solution for some minutes to remove the dissolved ether; an excess of concd. hydrochloric acid was then added to precipitate the benzilic acid. The acids often separated as gums, but on standing for some time, they crystallized. The crude acid was collected on a suction filter, dried, and was converted to its methyl ester without purification.

9-Hydroxyfluorene-9-carboxylic acid (Esters 10 and 11). This compound was prepared from phenanthrenequinone in 34% yield by the method of Staudinger.[7]

α,α-Diphenyl propionic acid (Ester 12). This compound was prepared by the method of Wegmann and Dahn[8] in 42% yield.

Diphenyl methoxyacetic acid (Ester 13). This acid was prepared in the form of its methyl ester. Diphenyl bromoacetyl bromide was prepared according to the method of Klingler[9] and the crude product was recrystallized several times from Skelly A. A 46.5-g. sample (0.13 mole) of the purified product was placed in a 1-l. round bottom flask equipped with a condenser and a calcium chloride tube. Anhydrous methanol (600 ml.) was added, and the mixture was refluxed 5 hr. The solvent was removed under reduced pressure on a steam bath and the residue of amber-colored oil was distilled, b.p. 124–127 (0.3 mm.).[10] The yield was 17.5 g. (40%) of a water-white, viscous liquid.

O-Acetyl N-methyl-3-piperidyl benzilate (Ester 14). A 2.5-g. sample (0.0069 mole) of *N*-methyl-3-piperidyl benzilate hydrochloride[1] was refluxed 1 hr. with 10 ml. of freshly distilled acetic anhydride, and the reaction mixture was permitted to stand overnight. The resulting clear liquid was poured into 100 ml. of distilled water to destroy the excess acetic anhydride. Ice was added, and an excess of concd. ammonia water was then added to precipitate the acetylated crude product as a white, flocculent solid. The mixture was extracted twice with ether, and the ethereal solutions were combined and dried with anhydrous magnesium sulfate. The bifumarate salt of the ester was prepared from this solution.

2-(1-Methyl-4-piperazino)ethanol (Ester 11). This amino alcohol was prepared by an unpublished method devised

(6) A. H. Ford-Moore, *J. Chem. Soc.*, 1947, 952.

(7) H. Staudinger, *Ber.*, 39, 3062 (1906).

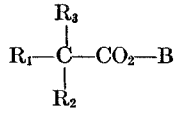
(8) J. Wegmann and H. Dahn, *Helv. Chim. Acta*, 29, 425 (1946).

(9) H. Klingler and G. Nickell, *Ann.*, 390, 365 (1912).

(10) H. Klingler, *Ann.*, 390, 371 (1912) b.p. 191–192 (19 mm.).

TABLE II

SALTS OF BENZILIC ESTERS AND CONGENERS



No.	R_1	R_2	R_3	B	Method of Prepn. of Benzil	Salt Prepd.	M.P.[b]	Yield,[h] %	Formula	Analysis	Calcd.	Found
1	2-Cl_6H_4	2-ClC_6H_4	OH	*N*-Methyl-3-piperidyl	B	HCl	237–238 dec.[c]	21	$C_{20}H_{22}O_3NCl_3$	N	3.25	3.14
										Cl	24.4	23.7
2	3-ClC_6H_4	3-ClC_6H_4	OH	*N*-Methyl-3-piperidyl	B	HCl	181–182[c]	30	$C_{20}H_{22}O_3NCl_3$	N	3.25	3.0
										Cl	24.4	24.0
3	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	180–183[c]	32	$C_{26}H_{31}O_7N$	C	66.8	67.0
										H	6.68	6.98
										N	2.99	2.71
4	3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	193–194[d]	73.5	$C_{22}H_{28}O_3NCl$	N	3.60	3.75
										Cl	9.10	8.94
5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	211–214 dec.[c]	33	$C_{22}H_{28}O_3NCl$	N	3.60	3.75
										Cl	9.10	9.51
6	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	188–190[c]	10	$C_{26}H_{31}O_9N$	C	62.3	62.5
										H	6.19	6.43
										N	2.79	3.10
7	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	OH	*N*-Methyl-3-piperidyl	A	Bifumarate	191–193[d]	16.1	$C_{28}H_{35}O_{11}N$	C	61.7	61.6
										H	6.48	6.57
										N	2.56	2.86
8	3,4-$(OCH_2O)_2$-C_6H_3	3,4-$(OCH_2O)_2C_6H_3$	OH	*N*-Methyl-3-piperidyl	A	HCl	236–238 dec.[e]	40	$C_{22}H_{24}O_7NCl$	N	3.13	3.11
										Cl	7.88	7.55
9	4-$C_6H_5C_6H_4$	4-$C_6H_5C_6H_4$	OH	*N*-Methyl-3-piperidyl	A	HCl	221–223 dec.[f,a]	25	$C_{32}H_{32}O_3NCl$	N	2.73	3.02
										Cl	6.90	7.30
10	see footnote[a]			*N*-Methyl 3-piperidyl	—	HCl	255–256 dec.[c]	26.7	$C_{20}H_{24}O_3NCl$	N	3.89	3.78
										Cl	9.89	9.51
11	see footnote[a]			2-(1-Methyl-4-piperazino) ethyl	—	2HCl	221–224 dec.[c]	42.4	$C_{21}H_{26}O_3N_2Cl_2$	N	6.58	6.27
										Cl	16.69	16.30
12	C_6H_5	C_6H_5	CH_3	*N*-Methyl-3-piperidyl	—	Bifumarate	156–158[g]	13.6	$C_{25}H_{28}O_6N$	C	68.7	69.1
										H	6.4	6.8
										N	3.2	3.3
13	C_6H_5	C_6H_5	CH_3O	*N*-Methyl-3-piperidyl	—	HCl	109–111[d]	22	$C_{21}H_{26}O_3NCl$	N	3.72	3.55
										Cl	9.45	9.12
14	C_6H_5	C_6H_5	Acetyl	*N*-Methyl-3-piperidyl	—	Bifumarate	205–207[f]	45	$C_{26}H_{29}O_8N$	C	64.7	64.5
										H	6.0	6.35
										N	2.9	3.36

[a] The acid portion is 9-hydroxyfluorene-9-carboxylic acid. [b] All melting points uncorrected. [c] From absolute ethanol-ether. [d] From 1-butanol-ether. [e] From aqueous ethanol. [f] From 1-butanol. [g] From 1-butanol-Skelly C. [h] Yield of salt based on the amount of methyl ester taken for transesterification.

by Leiser and Biel.[11] To 100.2 g. (1.0 mole) of *N*-methyl piperazine dissolved in 1 l. of anhydrous methanol was added dropwise and with stirring a solution of 44 g. (1.0 mole) of ethylene oxide in 100 ml. of dry toluene. The mixture was stirred for an additional 3 hr. and was permitted to stand overnight. The solvents were removed by distillation, and the residue was fractionated, the liquid boiling at 90–92 (3.0 mm.) being collected. The yield was 91 g. (63%).

Methyl esters. All of the methyl esters except methyl α,α-diphenylmethoxyacetate were prepared by treating an ethereal solution or suspension of the acid with an eightfold 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 methyl ester was purified by recrystallization or distillation to give an almost quantitative yield. See Table I.

Transesterifications. The methyl ester of the carboxylic acid (0.02 mole) was placed together with an equimolecular portion of the amino alcohol in a 1-l. three necked flask seated in a mantle, and equipped with a Hershberg stirrer and a Dean-Stark moisture determination apparatus topped with a condenser and a calcium chloride tube. Dry *n*-heptane (600 ml.) and 100 mg. of solid sodium methoxide were added to the flask, and the contents were heated and stirred. After an hour's refluxing, an additional 100 mg. of sodium methoxide was added. From time to time, the contents of the Dean-Stark apparatus were drained and discarded, and fresh portions of *n*-heptane were added to the flask so as to maintain the original volume. After 8 hr. refluxing, an additional 50 mg. portion of sodium methoxide was added. Refluxing was continued for a total of 15 hr.; the reaction mixture was then cooled and transferred to a separatory funnel. The organic mixture was extracted repeatedly with water until the washings were approximately *p*H 7. The solvent was removed from the organic solution under reduced pressure from a steam bath; the residue of crude heterocyclic ester was dissolved in ether and this solution was dried over anhydrous magnesium sulfate and filtered. The salt of the ester was prepared from this solution.

Hydrochlorides of the heterocyclic esters. A saturated solution of anhydrous hydrogen chloride in anhydrous ether was added to the dried ethereal solution of the crude amino ester until no more precipitation occurred. The crude hydrochloride was collected on a suction filter, washed with anhydrous ether, and recrystallized.

Bifumarates of the heterocyclic esters. An excess of recrystallized, dried fumaric acid was stirred with 1.5 l. of anhydrous ether for 1 hr., so as to prepare a saturated solution. This solution was filtered through a gravity filter directly into a 3-l. Erlenmeyer flask containing 0.01–0.05 mole of crude amino ester dissolved in 500 ml. of dried ether. The resulting clear solution was placed in a refrigerator for several days, during which time the bifumarate salt slowly crystallized from solution. It was collected on a suction filter and recrystallized.

Acknowledgment. This investigation was supported in part by a grant from Lakeside Laboratories, Milwaukee, Wisconsin, and in part by a grant from the Institute of Mental Health, National Institutes of Health.

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(11) H. A. Leiser and J. H. Biel, Lakeside Laboratories, Milwaukee. Personal communication. J. Cymerman-Craig R. J. Harrisson, M. E. Tate, R. H. Thorp, and R. Ladd [*Australian J. Chem.*, 9, 89 (1956)] prepared this compound from 1-(2-hydroxyethyl)piperazine by a Leuckart Reaction. b.p. 88° (3 mm.).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Amebicides. I. Some 1-(1,4-Dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-pyridinium Betaines

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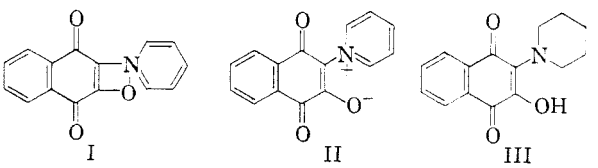
The reaction of 2,3-dichloro-1,4-naphthoquinone with pyridine has been extended to various 2-, 3-, and 4-substituted pyridines and corresponding 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-substituted pyridinium betaines were obtained when acetic acid was used as the solvent for the reaction. The reduction of some of these betaines to 2-hydroxy-3-piperidino-1,4-naphthoquinones is described. The amebicidal activities of these compounds are summarized.

A study and use of the reaction between 2,3-dichloro-1,4-naphthoquinone and pyridine as reported by Ullman and Ettisch,[3] was undertaken in order to obtain a number of pyridinium compounds of a heretofor unstudied group for evaluation as antitubercular and amebicidal agents.[4] Ullmann and Ettisch reported the isolation of 3-hydroxy-1,4-naphthoquinone-2-pyridinium anhydride (I) from the reaction of pyridine and 2,3-dichloro-1,4-naphthoquinone in refluxing alcohol. We prefer to use structure II, 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium betaine, to represent this type of compound.



When we attempted to extend the reaction by the use of 4-(1-octyl)pyridine, a dark red oil was obtained, which was converted with much difficulty to a reddish-purple solid. However, when the initial reaction between 4-(1-octyl)pyridine and 2,3-dichloro-1,4-naphthoquinone was performed in

(1) Research Fellows of Research Corporation, 1950–52.
(2) Research Fellows of Parke, Davis & Co., 1950–53.
(3) F. Ullmann and M. Ettisch, *Ber.*, **54B**, 259 (1921).
(4) Price Truitt, Burl Bryant, William E. Goode, and B. Arnwine, *J. Am. Chem. Soc.*, **74**, 2179 (1952).