by recrystallization from the same solvent. The infrared spectrum (chf.) had bands at 2.85 and 6.13 μ. Solutions of the compound in ethyl acetate and ethanol showed blue fluorescence. The compound was soluble in dilute acids, but attempts to prepare a hydrochloride were unsuccessful, owing to decomposition.

Anal. Calcd. for $C_{19}H_{20}O_2N_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.45; H, 7.06; N, 8.83.

α-(2-Nitro-4,5-dimethoxyphenyl)-β-(2-pyridyl)-acrylonitrile (Vb).—Condensation of 5.1 g. of 2-nitro-4,5-dimethoxyphenylacetonitrile and 3.5 g. of pyridine-2-aldehyde in the presence of 3 ml. of piperidine, according to procedure A in the preceding experiment, gave 7.1 g. of bright yellow crystals, m.p. 171–175° dec. Recrystallization from ethyl acetate–methanol raised the m.p. to 189–191° dec.

Anal. Calcd. for $C_{15}H_{13}O_4N_3$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.77; H, 4.23; N, 13.28.

Reduction of this compound gave ammonia and viscous oily material which turned dark brown rapidly in the presence of air and did not crystallize.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF THE SCHERING CORPORATION]

Parasympathetic Blocking Agents. III. Phenylglycolic Acid Esters of N-Alkyl-4-piperidinol

BY STEPHEN B. COAN, BERNARD JAFFE AND DOMENICK PAPA

RECEIVED MARCH 21, 1956

Substituted phenylglycolic acid esters of N-alkyl-4-piperidinol and their quaternary salts have been prepared for pharmacological evaluation. Their syntheses and properties are discussed.

In the preceding report[1] the syntheses and pharmacological properties of piperidyl esters of disubstituted acetic acids and their quaternary salts were described. In continuation of this work esters of disubstituted hydroxyacetic acids with the active 4-piperidyl moiety were studied in view of the pronounced antispasmodic or anticholinergic activity of alkamine esters of benzilic acid. The 4-piperidyl esters prepared in this study include those of benzilic, phenylcyclohexyl-glycolic and phenylcyclopentyl-glycolic acids.

Relatively few piperidyl esters of benzilic acid have been reported in the literature. Dawes and Wajda[2a] and Ford-Moore and Ing[2b] described the preparation and properties of the benzilate of 1,2,2,6-tetramethyl-4-piperidinol. Recently Biel and co-workers[3] prepared and reported on the pharmacological properties of N-ethyl-3-piperidyl esters of various glycolic acids; the latter compounds are position isomers of the compounds reported in this paper.

The failure of 1-methyl-4-chloropiperidine to react with disubstituted acetic acids[4] prompted a study of transesterification methods for the preparation of the benzilic acid esters. A modification of the Hill and Holmes procedure,[5] using ethyl benzilate and 1-methyl-4-piperidinol, failed to yield the benzilate ester. The method of Stoll, *et al.*,[6] who transesterified ethyl benzilate with 6-methoxytropinol in the presence of sodium under reduced pressure (method A), although affording moderate yields was inherently restricted to small scale preparations. A modification of the procedure of Ford-Moore, *et al.*[2b] (method B) was successfully applied to large scale syntheses of the benzilate.

In order to prepare the phenylcyclohexylglycolate ester, selective reduction of one ring was attempted, following reported procedures for the partial reduction of polycyclic systems.[7a,b] However, in our hands, attempted selective reduction of the benzilate ester (I) with platinum oxide in acetic acid, ethyl acetate or ethanolic hydrogen chloride invariably gave a mixture of products containing principally starting material. Therefore both the cyclohexyl- and cyclopentylphenyl-glycolates were prepared (in moderate yield) by transesterification of the ethyl ester with 1-methyl-4-piperidinol in the presence of sodium.

Table I summarizes the physical data on the compounds prepared.

Pharmacological studies on the methiodide and methobromide quaternary salts of I will be reported.[8] Data on the remaining compounds will be published elsewhere. In brief, compounds II and III were compared with Pamine[9] and Piptal.[10] In the Shay rat test for measurement of inhibition of gastric acidity and secretion, compounds II and III exhibited the same order of potency as Pamine. It is of interest to note that Piptal, which is little more than a position isomer of II and III, was found to be completely inactive in this test. In dogs, compounds II and III were approximately twice as active as Pamine in inhibiting gastric motility and appeared relatively free of side effects, such as mydriasis, at the effective dose of 1–5 mg./kg.

Acknowledgment.—The authors wish to express their appreciation to Mr. Edwin Conner for the micro-analyses herein reported and to Dr. William Govier, Dr. Frank Roth, Mr. A. Makovsky and

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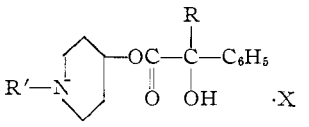
(9) Registered Trade Mark of the Upjohn Co. for scopolamine methobromide.

(10) Registered Trade Mark of Lakeside Laboratories for 1-ethyl-3-piperidyl benzilate methobromide, a sample of which was generously supplied by Dr. J. Biel.

TABLE I



No.	R	R′	X	M.p., °C., cor.	Formula	Analyses, % Calcd. C	Calcd. H	Found N	Found C	Found H	Found N
I	Phenyl	CH_3	....	162.5–163.0	$C_{20}H_{23}NO_3$	73.82	7.12	4.30	73.53	7.00	4.09
II	Phenyl	CH_3	CH_3I	199.5–200.0	$C_{21}H_{26}INO_3$	[a]	..	2.99	[a]	..	3.34
III	Phenyl	CH_3	CH_3Br	237.0–238.0	$C_{21}H_{26}BrNO_3$	60.00	6.23	3.33	60.14	6.24	3.43
IV	Phenyl	C_2H_5	....	87.0– 87.5	$C_{21}H_{25}NO_3$	74.31	7.42	4.13	74.44	7.35	4.26
V	Phenyl	C_2H_5	CH_3I	167.0–168.0	$C_{22}H_{28}INO_3$	54.88	5.86	2.91	54.52	6.00	2.68
VI	Cyclohexyl	CH_3	....	180–183[b]	$C_{20}H_{29}NO_3$	72.47	8.81	4.22	72.24	8.81	4.10
VII	Cyclohexyl	CH_3	CH_3I	163–165	$C_{21}H_{33}INO_3$	53.16	7.01	..	53.37	6.98	..
VIII	Cyclopentyl	CH_3	....	178–180[b]	$C_{19}H_{27}NO_3$	71.89	8.57	4.41	72.20	9.00	4.40
IX	Cyclopentyl	CH_3	CH_3I	184.5–185.0	$C_{20}H_{30}INO_3$	52.17	6.78	..	51.80	6.65	..

[a] *Anal.* Calcd: I, 27.17. Found: I, 26.77. [b] Boiling point at 1 mm.

Miss Eileen Eckhardt for the pharmacological data.

Experimental

Preparation of the Piperidinols. N-Ethylchelidamic Acid.—A stirred suspension of 500 g. (2.6 moles) of chelidamic acid in 2.5 l. of water was neutralized to *p*H 8 with 20% sodium hydroxide solution. To the alkaline solution was added 400 ml. of 33% aqueous ethylamine (3.0 moles) and the mixture heated at 80–90° for 3 hours. The mixture was poured onto ice, acidified with concentrated hydrochloric acid, and the precipitate which formed was filtered and recrystallized from hot water yielding 350 g. (1.66 moles, 64%), m.p. 208–210° dec.

Anal. Calcd. for $C_9H_9NO_5$: N, 6.63. Found: N, 6.91.

N-Ethyl-4-pyridone.—Four hundred grams (1.9 moles) of N-ethylchelidamic acid was heated over a free flame in a 2.0-liter flask until the evolution of CO_2 ceased. The dark residue was distilled at 1 mm. pressure and redistilled, collecting 86 g. (0.7 mole, 36.8%), b.p. 185–187° (1 mm.). (The pyridone solidified in the receiver.)

Anal. Calcd. for C_7H_9NO: N, 11.38. Found: N, 11.00.

N-Ethyl-4-piperidinol.—A solution of 86 g. (0.7 mole) of N-ethyl-4-pyridone in 400 ml. of ethanol was hydrogenated at 2000 lb. and 125° in the presence of 40 g. of Raney nickel. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was distilled *in vacuo* yielding 76 g. (0.59 mole, 85%), b.p. 105–110° (15 mm.), $n^{33}D$ 1.4769.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.83. Found: N, 10.96.

N-Methyl-4-piperidinol was prepared by substituting methylamine for ethylamine in the above synthesis which is a modification of that described by Riegel, *et al.*,[11] b.p. 101–103° (16 mm.) (reported b.p. 116–118° (36 mm.)).

Preparation of the Glycolic Esters. Ethyl Phenylcyclohexylglycolate.—Prepared in 50% yield from ethyl benzoylformate and cyclohexyl bromide according to the procedure of Smith, *et al.*,[12] b.p. 167–169° (6 mm.), $n^{25}D$ 1.5125 (reported b.p. 172–173° (10 mm.)).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.73; H, 8.44.

Ethyl Phenylcyclopentylglycolate.—Following the described analogous procedure[9] on a 0.25 *M* scale, the ester was obtained in 40% yield, b.p. 122° (1 mm.), $n^{25}D$ 1.5071.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.30; H, 8.36.

Preparation of the Basic Esters. 1-Methyl-4-piperidyl Benzilate. Method A.—A mixture of 11.5 g. (0.1 mole) of 1-methyl-4-piperidinol and 300 mg. of freshly cut sodium in a 100-ml. distilling flask was warmed on a steam-bath until the sodium had completely dissolved. To the solution was added 38 g. (0.15 mole) of ethyl benzilate and the flask was fitted with a still-head, receiver and a capillary inlet. The flask and contents were placed in an oil-bath previously heated to 125–140° and vacuum was applied, adjusting the pressure to 25–35 mm. After 24–36 hours at the aforementioned temperature and pressure, the pressure was lowered to 1–2 mm. The distillate consisting of unreacted starting material was discarded.

The viscous residue was dissolved in 5% aqueous hydrochloric acid and the acid mixture was thoroughly extracted with ether. The aqueous layer was neutralized with dilute sodium hydroxide solution and the oil which separated quickly solidified. The crude ester was removed by filtration and recrystallized from benzene–ligroin (30–50°), yield 9.0 g. (28%), m.p. 161–162°.

Method B.—In a 1.0-liter wide-mouthed round-bottom flask was placed 151 g. (1.0 mole) of N-methyl-4-piperidinol hydrochloride and 271 g. (1.02 moles) of diphenylchloroacetyl chloride.[13] The mixture was heated in a bath at 140–160° under an atmosphere of nitrogen. During the initial esterifying process, the internal temperature rose about 10° higher than the bath temperature and hydrogen chloride was copiously evolved. The viscous melt was poured into 2.0 liters of hot water and the resultant solution was held at 85° for 30 minutes. The aqueous solution was cooled and made alkaline with ammonium hydroxide solution. The gummy precipitate was taken up in benzene which was subsequently extracted with dilute sodium hydroxide and water. The benzene solution was concentrated to a low volume, chilled and filtered. The basic ester was recrystallized from benzene–ligroin (30–50°), yield 195 g. (60%), m.p. 161.5–162.5°.

1-Ethyl-4-piperidyl Benzilate.—According to method B, from 15 g. (0.09 mole) of 1-ethyl-4-piperidinol and 24 g. (0.09 mole) of diphenylchloroacetyl chloride, there was obtained 11 g. (0.032 mole, 36%), m.p. 87.0–87.5° after recrystallization from ligroin (30–50°).

1-Methyl-4-piperidyl Phenylcyclohexylglycolate.—According to method A, 22 g. (0.2 mole) of 1-methyl-4-piperidinol, 17 g. (0.065 mole) of ethyl phenylcyclohexylglycolate and 300 mg. of sodium afforded an alkali-insoluble, noncrystallizable oil. The oil was separated from the alkaline mixture by extraction with ether. The ether solution was dried over anhydrous potassium carbonate, filtered and concentrated to a residue. The residue was distilled *in vacuo* yielding 8 g. (24%), b.p. 178–183° (1 mm.), $n^{25}D$ 1.5239.

1-Methyl-4-piperidyl Phenylcyclopentylglycolate.—According to method A, 15 g. (0.13 mole) of 1-methyl-4-piperidinol, 12 g. (0.05 mole) of ethyl phenylcyclopentylglycolate and 300 mg. of sodium yielded a viscous oil, yield 3.1 g. (20%), b.p. 178–180° (1 mm.), $n^{30}D$ 1.5120.

Preparation of the Quaternary Salts.—The quaternary methiodides were prepared by treating the basic ester with an excess of methyl iodide generally in refluxing ether solution. The quaternary methobromides were prepared both

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by *trans*-halogenation of the iodide in methanol solution with freshly prepared silver bromide and by bubbling anhydrous methyl bromide into a benzene solution of the basic ester. The salts were purified by recrystallization from methanol–ether.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Synthesis of Some 6-N-Substituted Amido Derivatives of 4,6-Diaminoquinaldine and a Study of their *in vitro* Antibacterial Activity[1,2]

BY CHIN-TZU PENG AND T. C. DANIELS

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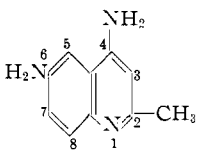
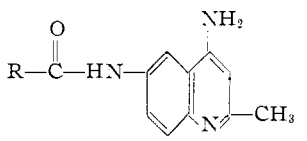
Two series of acylamino and N-substituted carbamylamino derivatives of 4,6-diaminoquinaldine were prepared and tested as antibacterials. Some correlation between the chemical structure and the bacteriostatic activity of these compounds was observed.

The antibacterial activity reported for Surfen (bis-4-amino-2-methyl-6-quinolylurea)[3] and its low toxicity for tissues prompted an interest in the preparation of related derivatives for study as antibacterial agents. According to recent biochemical studies on the mode of action of suramin,[4] Antrycide[5] and other trypanocidal agents,[4,5] the activity does not depend upon the symmetry or the bis-molecular character of the active compound. The Surfen-type compounds[6] have a bis-molecular structure and it was of interest to ascertain whether the unsymmetrical analogs would have comparable activity.

The 4,6-diaminoquinaldine (I) was employed as the basic moiety for the synthesis of a wide variety of acyl and N-substituted carbamyl derivatives (II). The diamine base was condensed in acetic acid with acyl chlorides to form the 6-N-substituted amide derivatives and condensed in acetone with isocyanates or isothiocyanates to yield substituted ureas.



I R = alkyl, aralkyl, and aryl amino-



II

By analogy to the aminoquinolines,[7] 4-aminoquinaldine should be more basic than the isomeric 6-aminoquinaldine, nevertheless, acylation of the diamine base yielded exclusively the 6-N-substituted derivative. This confirms the findings of Pratt and Archer.[8] Our attempt to selectively benzoylate the 4-amino group of I by the Schotten–Baumann reaction was unsuccessful. However, both 4- and 6-amino groups were acylated when compound I was heated under reflux with acetic anhydride (or benzoyl chloride) and sodium acetate.

The substituted ureides were prepared by condensing I with isocyanates or isothiocyanates in dry acetone. When the condensation of *o*-nitrophenyl isocyanate with I was carried out in dry purified dioxane, two compounds were isolated. The close similarity of their absorption spectra in the region of 210–500 mμ suggested that the two compounds were positional isomers, *i.e.*, the 4- and 6-N-substituted derivatives of I. Based on structural considerations, particularly in relation to the resonance and basicity of these isomers, the compound having an absorption band at a longer wave length (265 mμ) and showing a greater solubility in dilute hydrochloric acid was tentatively designated as the 6-N-substituted derivative. This structure was confirmed by the following synthesis: (1) the condensation of *o*-nitrophenylcarbamyl chloride with I, and (2) the reaction of *o*-nitrophenyl isocyanate with the monohydrochloride of I in aqueous dioxane. Other methods for the preparation of this compound, such as the amination of 1-(*o*-nitrophenyl)-3-(4-chloro-6-quinaldyl)-urea and of 1-(*o*-nitrophenyl)-3-(4-methoxy-6-quinaldyl)-urea, led only to decomposition products. It is reported[9] that in acetone the condensation of *p*-nitrophenyl isocyanate with I yields the corresponding 6-N-substituted derivative; a repetition of the experiment using *o*-nitrophenyl isocyanate also gave exclusively 1-(*o*-nitrophenyl)-3-(4-amino-6-quinaldyl)-urea. The selective affinity of the substituent group for the 6-amino group of I when the condensation was carried out in acetone may be due to a dipole–dipole interaction of the solvent acetone molecules with the contributing quinonoid form of the 4-aminoquinaldine moiety, thereby leaving the 6-amino group more available for reaction.

The pK_a values of a number of the amides and ureas (Table III) were measured in order to determine the effect of the substituent groups on the basicity of the compounds. These data show that the compounds having an intact 4-amino group are more basic than those congeners with the 4-amino group either replaced or substituted.

(1) Abstracted from a thesis submitted by C. T. Peng in partial fulfillment of the requirements for Doctor of Philosophy in Pharmaceutical Chemistry, June, 1953.

(2) Presented in summary before the Division of Medicinal Chemistry at the 123rd National Meeting of American Chemical Society, Los Angeles, Calif., March, 1953.

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