pared as reported in the preparation of VI, in 10 ml. of methanol was added in small portions 0.15 g. (3.8 mmoles) of sodium borohydride. When effervescence had ceased, the solution was allowed to stand at room temperature for 2 hr. and then concentrated *in vacuo* to a light brown solid. The material was dissolved in benzene and petroleum ether (b.p. 30–60°) added until a dark brown oil formed. The colorless solution was decanted from the oil and more petroleum ether added until it became turbid. Upon being chilled, the mixture deposited a sandy precipitate that was collected on a filter and washed with petroleum ether; yield 0.40 g. (40%), m.p. 108.5–110.5°. This solid, after two recrystallizations from benzene-petroleum ether, melted at 109–112°; $\lambda_{max(\mu)}^{KBr}$ 3.20 (OH), 5.72 (ester C=O), 8.52, 9.98 (ester C—O—C), 11.92 (*p*-disubstituted phenyl), and no ketone C=O near 5.90.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.4; H, 7.68; N, 5.62. Found: C, 67.3; H, 7.66; N, 5.69.

Methyl 3-{p-[2-(2-chloroethylamino)-1-hydroxyethyl]-phenyl}propionate hydrochloride (IX). Anhydrous hydrogen chloride gas was passed through a solution of 1.0 g. (4 mmoles) of methyl 3-[*p*-(2-aziridinyl-1-hydroxyethyl)-phenyl]propionate (VIII) in 5 ml. of benzene. A brown gum separated upon adding ether to turbidity and chilling. The solution was decanted from the gum and more ether added. After trituration with ether several times and placing in a refrigerator for 1 hr., the gum solidified, yield 1.1 g. (85%) m.p. 133–140°. Recrystallization from 7 ml. of absolute ethanol by adding ether until turbid and chilling yielded 1.0 g., m.p. 139–140°. An analytical sample, m.p. 140–141°, was prepared by a further recrystallization; $\lambda_{max(\mu)}^{KBr}$ 3.00 (OH), 3.60, 4.00 (NH_2^+), 8.61 (ester C—O—C), 9.59 (C—OH), 12.04 (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{14}H_{20}ClNO_3 \cdot HCl$: C, 52.2; H, 6.52; Cl, 22.0; N, 4.35. Found: C, 52.3; H, 6.52; Cl, 21.8; N, 4.53.

Attempts to acid-hydrolyze IX to the corresponding acid were unpromising.

Acknowledgments. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff staff for large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

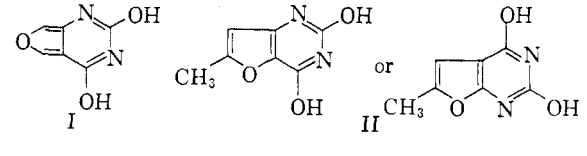
Reaction of Some Heterocyclic *vic*-Dicarboxamides with Alkaline Hypobromite

REUBEN G. JONES

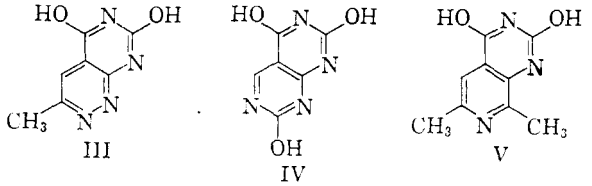
Received January 5, 1960

The reaction of alkaline hypobromite with some heterocyclic 1,2-dicarboxamides has led to the preparation of several bicyclic compounds containing the pyrimidine ring fused to furan, pyridazine, and pyrimidine.

This paper concerns the preparation of the new bicyclic pyrimidine derivatives I to V.[1] These were made and tested as possible chemotherapeutic agents against viruses and cancer because of their structural resemblance to certain of the biologically important purines and pteridines.

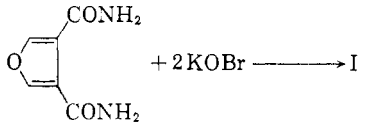


I II



III IV V

The compounds were obtained from appropriate 1,2-dicarboxamides by reaction with alkaline hypobromite under the conditions described by Baxter and Spring.[1] This Hofmann reaction on 1,2-dicarboxamides appears to be a rather general method for the synthesis of the 2,4-dihydroxypyrimidine ring system.[1]



The yields of compounds III, IV, and V were quite satisfactory (70 to 80%), but the yield of compound II was only 20 to 25% and the yield of I was 5 to 8%. One experiment was carried out in which 3,4-thiophenedicarboxamide was allowed to react with hypobromite. A crude product was obtained, but it could not be purified.

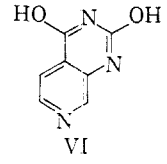
From each of the reactions leading to II, III, IV, and V, two isomeric products would appear to be possible. In each case, however, only one compound was isolated. The assignment of structure V is based on analogy with compound VI, which is the exclusive product from the reaction of 3,4-pyridinedicarboxamide with hypobromite.[2] The isomeric 2,3-pyridinedicarboxamide reacts with hypobromite to give exclusively compound VII.[3] By analogy with this latter reaction structures III and

(1) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 229 (1945). This reference gives the earlier literature on these reactions.

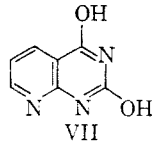
(2) S. Gabrial and J. Cohnan, *Ber.*, **35**, 2831 (1902).

(3) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).

IV have been assigned, but it is to be emphasized that these structure assignments are only tentative. In the case of compound II both possible structures are shown.



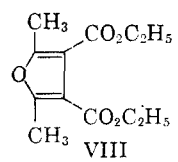
VI



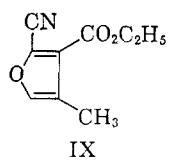
VII

Compounds I and IV retained water of crystallization. From I the water was removed readily by heating at 150°, but from IV the water was only partially removed by heating at 200° for three hours.

Preparation of the starting dicarboxamides deserves some comment. 3,4-Furandicarboxamide, 5-methyl-2,3-furandicarboxamide, 3,4-thiophenedicarboxamide, 2,6-dimethyl-3,4-pyridinedicarboxamide, and 6-methyl-3,4-pyridazinedicarboxamide were all obtained in excellent yields (80 to 98%) by simply allowing the corresponding diethyl esters to stand at room temperature in methanol saturated with ammonia. 2-Hydroxy-4,5-pyrimidinedicarboxamide was prepared with concentrated aqueous ammonia. It would appear to be unnecessary to prepare 3,4-furandicarboxamide by going through the acid chloride as recommended by Stork.[4] Earlier workers have experienced great difficulty in trying to prepare amides by reaction of ammonia with diethyl 2,5-dimethyl-3,4-furandicarboxylate[5,6] (VIII) and ethyl 2-cyano-4-methyl-3-furancarboxylate[5] (IX), and Bilton and Linstead[5] have stated: "the resistance to amide formation appears to be a general property of furan esters. . . ." More likely the resistance to amide formation in these cases is due to steric hinderance. The very appreciable steric effects of the methyl groups on the reactions of VIII and the related monomethyl compound with hydrazine have been noted previously.[7] The present preparation of 2,6-dimethyl-3,4-pyridinedicarboxamide in 80% yield by reaction of the diethyl ester in methanolic ammonia at room temperature contrasts sharply with the 54% yield obtained by Mumm and Hüneke[8] by heating the ester in ethanolic ammonia for eight hours at 150°.

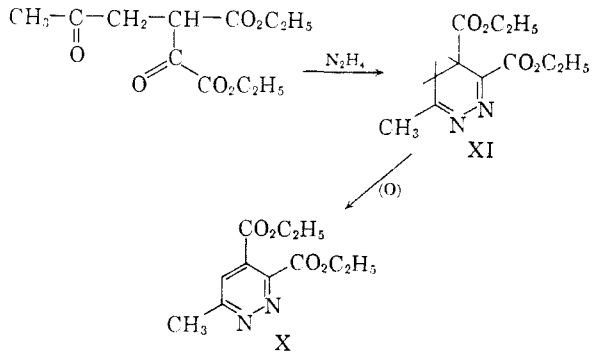


VIII



IX

Diethyl 6-methyl-3,4-pyridazinedicarboxylate (X), from which was prepared III *via* the diamide, is a new compound. It was obtained by the accompanying reactions starting from ethyl 2-ethoxalyl-4-ketovalerate.[9] Compound XI was obtained in good yield, but its oxidation to X by either the permanganate[10] or nitrous acid[11] method was only moderately satisfactory.



EXPERIMENTAL

Diethyl 6-methyl-4,5-dihydro-3,4-pyridazinedicarboxylate. A solution of 24.5 g. (0.10 mole) of ethyl 2-ethoxalyl-4-ketovalerate[9] in 500 ml. of 95% ethanol was cooled in an ice bath and to it was added, with rapid stirring, a solution of 5.0 g. (0.10 mole) of hydrazine hydrate in 50 ml. of ethanol. After addition was complete, the solution was allowed to stand at room temperature for about 1 hr. and then was evaporated under reduced pressure to a volume of about 50 ml. The solution was diluted with 300 ml. of water and extracted with three 100-ml. portions of ether. After the ether extract had been dried with magnesium sulfate, it was evaporated, finally under reduced pressure, leaving an oil that crystallized after standing. The product was washed with petroleum ether (b.p. 60–68°) and air dried to yield 20 g. (84%) of soft white crystals. A sample recrystallized from petroleum ether melted at 86–87°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.22; H, 6.73; N, 11.54.

Diethyl 6-methyl-3,4-pyridazinedicarboxylate. To a solution of 345 g. (1.40 moles) of distilled ethyl 2-ethoxalyl-4-ketovalerate[9] in 3 l. of alcohol was added, with stirring and cooling during 1.5 hr., a solution of 70 g. (1.40 moles) of hydrazine hydrate in 1 l. of alcohol. The resulting solution was allowed to stand overnight and was then evaporated under reduced pressure to a sirup. This was warmed on the steam bath under reduced pressure for 0.5 hr. to remove all the alcohol. After cooling, the crude diethyl 6-methyl-4,5-dihydro-3,4-pyridazinedicarboxylate partially crystallized.

The crude product (315 g.) was dissolved in 2.75 l. of acetone and the solution was rapidly stirred while a hot solution of 65 g. of potassium permanganate in 900 ml. of water was added during 1 hr. The mixture was cooled and kept saturated with carbon dioxide by continuous addition of small pieces of solid carbon dioxide.

The resulting mixture was filtered on a large suction funnel and the manganese dioxide cake was washed by suspension in 1 l. of acetone. The total filtrate was evaporated under reduced pressure on the steam bath to remove acetone. The residue was extracted with ether and the ether solution was dried and evaporated. The product was distilled under reduced pressure to yield 35 g. of forerun, b.p. 112–115° (0.6

(4) G. Stork, *J. Am. Chem. Soc.*, **67**, 884 (1945).
(5) J. A. Bilton and R. P. Linstead, *J. Chem. Soc.*, 922 (1937).
(6) R. Seka, *Ber.*, **57**, 1864 (1924).
(7) R. G. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
(8) O. Mumm and H. Hüneke, *Ber.*, **50**, 1568 (1917).
(9) R. G. Jones, *J. Am. Chem. Soc.*, **77**, 4069 (1955).
(10) C. Paal and J. Ubber, *Ber.*, **36**, 497 (1903).
(11) C. Paal and C. Koch, *Ber.*, **36**, 2538 (1903).

mm.) which was shown to be diethyl 5-methyl-2,3-furandicarboxylate, and 128 g. of diethyl 6-methyl-3,4-pyridazinedicarboxylate. This was recrystallized by dissolving it in 100 ml. of ether, diluting with 200 ml. of petroleum ether (b.p. 60–68°), and keeping it in the refrigerator overnight. The yield was 114 g. (37%). A sample for analysis was recrystallized again from petroleum ether (b.p. 60–68°), long white needles, m.p. 53–53.5°.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.27; H, 5.77.

6-Methyl-3,4-pyridazinedicarboxylic acid. The diethyl ester, 12 g. (0.5 mole), was hydrolyzed by warming with a solution of 5 g. of sodium hydroxide in 50 ml. of water. The resulting solution was acidified with 12 ml. of 12*N* hydrochloric acid and cooled in the refrigerator to yield 8.75 g. (95%) of the acid. It was recrystallized from water, m.p. 235–237° dec.

Anal. Calcd. for $C_7H_6N_2O_4$: N, 15.38. Found: N, 15.55.

6-Methyl-3,4-pyridazinedicarboxamide. To 400 ml. of methanol saturated with ammonia was added 47.6 g. (0.2 mole) of diethyl 6-methyl-3,4-pyridazinedicarboxylate. The flask was tightly stoppered and allowed to stand at room temperature for 3 days. The crystalline precipitate of diamide was collected and air dried, yield 35 g. (97%). A sample was recrystallized from aqueous alcohol, m.p. 245–246°.

Anal. Calcd. for $C_7H_8N_4O_2$: N, 31.10. Found: N, 31.10.

2,6-Dimethyl-3,4-pyridinedicarboxamide.[8] A solution of 70 g. of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate[8] in 500 ml. of methanol saturated with ammonia was allowed to stand in a stoppered flask for 3 days. The mixture was evaporated under reduced pressure and the white crystalline residue of diamide was washed with ether, yield 42 g. (81%), m.p. 213–214° (lit.,[8] m.p. 220°).

2-Hydroxy-4,5-pyrimidinedicarboxamide. To 300 ml. of concd. aqueous ammonia was added 48 g. (0.20 mole) of diethyl 2-hydroxy-4,5-pyrimidinedicarboxylate.[12] The resulting solution was allowed to stand in a stoppered flask for 2 days during which time a mass of large crystals separated. The mixture was chilled and the crystalline product was collected. It was the ammonium salt of 2-hydroxy-4,5-pyrimidinedicarboxamide, yield 32 g. (80%). A sample was recrystallized from dilute ammonium hydroxide solution; it did not melt but decomposed above 300°.

Anal. Calcd. for $C_6H_9N_5O_3$: N, 35.17. Found: N, 34.53.

The ammonium salt, 30 g., was ground to a fine powder and suspended in 100 ml. of 20% acetic acid. The suspension was heated on the steam bath for 2 hr., cooled, and the 2-hydroxy-4,5-pyrimidinedicarboxamide collected, yield 24.3 g. (89%). A sample was recrystallized from water in which it was somewhat soluble. It had no sharp melting point but decomposed above 300°.

Anal. Calcd. for $C_6H_6N_4O_3$: N, 30.76. Found: N, 30.64.

2-Methyl-4,5-furandicarboxamide. A solution of 45.2 g. (0.20 mole) of diethyl 2-methyl-4,5-furandicarboxylate[9] in 150 ml. of methanol, to which had been added 40 g. of ammonia, was kept in a stoppered flask for 3 days. The mass of white crystalline precipitate was collected by filtration and air dried, yield 30 g. (89%). A sample was recrystallized from aqueous ethanol, m.p. 257–258°.

Anal. Calcd. for $C_7H_8N_2O_3$: N, 16.68. Found: N, 16.79.

3,4-Furandicarboxamide.[4] A solution of 63.6 g. (0.30 mole) of diethyl 3,4-furandicarboxylate[13] in 500 ml. of methanol saturated with ammonia was allowed to stand at room temperature in a stoppered flask for 4 days. A mass of white crystalline precipitate had separated. To the mixture was added another 50 ml. of liquid ammonia and it was allowed to stand an additional 4 days. The finely divided white precipitate was collected and air dried, yield 45 g. (97%). A sample for analysis was recrystallized three times from water in which it was very sparingly soluble.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 47.24; H, 3.92; N, 18.04.

3,4-Thiophenedicarboxamide. A solution of 20 g. (0.10 mole) of dimethyl 3,4-thiophenedicarboxylate[13] in 250 ml. of methanol saturated with ammonia was allowed to stand in a stoppered flask for 5 days. The methanol was evaporated under reduced pressure and the residual crystalline diamide was washed with ether, yield 16.7 g. (98%). A sample was recrystallized from water, m.p. 237–239°.

Anal. Calcd. for $C_6H_6N_2O_2S$: N, 16.46. Found: N, 16.46, 16.50.

4,6-Dihydroxy-2-oxa-5,7-diazaindene. A hypobromite solution was made by dissolving 61.6 g. (1.1 moles) of potassium hydroxide in 160 ml. of water, adding 400 g. of crushed ice, and then stirring in 32 g. (0.20 mole) of bromine. To the resulting pale yellow solution was added all at once 15.4 g. (0.10 mole) of 3,4-furandicarboxamide. With stirring almost all the solid went into solution. The mixture was kept in the refrigerator overnight but did not appear to undergo any change. It was allowed to stand at room temperature for 2 days during which time some white crystalline solid separated. The mixture was heated on the steam bath for 1 hr. and acidified with 70 ml. of acetic acid. After 5 days at room temperature a little tan crystalline solid had separated. This was collected, dissolved in 50 ml. of hot, dilute ammonium hydroxide solution, and reprecipitated with acetic acid as a white crystalline solid, yield 1.4 g. (8.2%). In another experiment the yield was 4.7%. It did not melt below 300°.

Anal. (dried 2 hr. at 125°). Calcd. for $C_6H_4N_2O_3 \cdot H_2O$: C, 42.45; H, 3.53; N, 16.50. Found: C, 42.68; H, 3.67; N, 16.64, 16.70. (Dried 3 hr. at 150°). Calcd. for $C_6H_4N_2O_3$: N, 18.42. Found: N, 18.37.

4,6-Dihydroxy-2-methyl-1-oxa-5,7-diazaindene or 5,7-dihydroxy-2-methyl-1-oxa-4,6-diazaindene. Finely powdered 2-methyl-4,5-furandicarboxamide was allowed to react with potassium hypobromite as described above for the preparation of 4,6-dihydroxy-2-oxa-5,7-diazaindene. The crude product was purified by dissolving it in dilute ammonium hydroxide solution and precipitating with acetic acid. The yields in two experiments were 25% and 20%. A sample for analysis was recrystallized from water.

Anal. (dried 2 hr. at 100°). Calcd. for $C_7H_6N_2O_3$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.47; H, 3.89; N, 16.66.

1,3-Dihydroxy-5,7-dimethyl-2,4,6-triazanaphthalene. 2,6-Dimethyl-3,4-pyridinedicarboxamide was allowed to react with hypobromite as described above for the preparation of 4,6-dihydroxy-2-oxa-5,7-diazaindene. After standing overnight in the refrigerator, the mixture containing a large quantity of white precipitate was heated on the steam bath for 1 hr. The solid dissolved. The solution was acidified with acetic acid, and the resulting white crystalline precipitate was collected and air dried, yield 75%. An analytical sample was recrystallized from glacial acetic acid, m.p. 355–357°.

Anal. (dried 1 hr. at 100°). Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.73; N, 21.98. Found: C, 56.59; H, 5.05; N, 22.02.

1,3-Dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene. 3-Methyl-5,6-pyridazinedicarboxamide (0.1 mole) was added all at once to a hypobromite solution prepared as described under 4,6-dihydroxy-2-oxa-5,7-diazaindene. The solid quickly dissolved. After standing in the refrigerator overnight, the solution was heated on the steam bath for 1 hr. and then acidified with acetic acid. A crystalline precipitate separated slowly. The mixture was kept in the refrigerator overnight; then the product was collected and air dried, yield 79%. In another experiment the reaction mixture was neither cooled nor heated prior to acidification, but was allowed to stand at room temperature for 12 hr. The yield of 1,3-dihydroxy-7-methyl-2,4,5,6-tetrazanaphthalene was only 22%. An analytical sample was recrystallized from water.

Anal. (dried 2 hr. at 100°). Calcd. for $C_7H_8N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 46.89; H, 3.15; N, 31.64.

(12) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).

(13) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

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.

INDIANAPOLIS 6, IND.

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

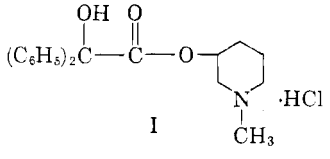
Esters of Benzilic Acids and Congeners Having Potential Psychotomimetic Activity

JOSEPH G. CANNON

Received December 18, 1959

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).