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Synthesis of 5,6-Dimethoxyindole-3-propionic Acids and 6,7-Dimethoxy-3,4-dihydrocarbostyrils, by Reduction of Nitrocompounds

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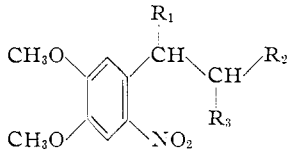
RECEIVED MARCH 5, 1956

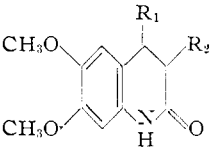
In palladium-catalyzed reductive cyclization of 2-nitrophenylsuccinic and 2-nitrobenzylsuccinic acids and esters, formation of 3,4-dihydrocarbostyrils precludes cyclization to five- or seven-membered lactams. Reductive cyclization of γ-cyano-γ-(2-nitrophenyl)-butyric esters affords indole-3-propionic esters, showing that five-membered rings form in preference to seven-membered rings.

This paper presents results of some further studies in reductive cyclization of nitro-compounds.[1] Cyclizations involving possible formation of five-, six- and seven-membered heterocyclic rings were studied, and some new data bearing upon relative ease of formation of these systems were obtained.

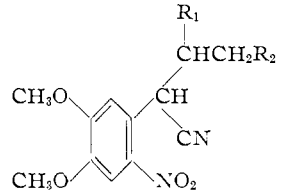
CHART



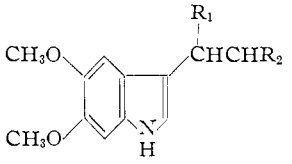
Ia, $R_1 = R_2 = H$; $R_3 = COOEt$
b, $R_1 = H$; $R_2 = CH_2COOEt$; $R_3 = COOEt$
c, $R_1 = R_3 = COOEt$; $R_2 = H$
d, $R_1 = H$; $R_2 = CH_2COOH$; $R_3 = COOEt$
e, $R_1 = R_3 = COOH$; $R_2 = H$



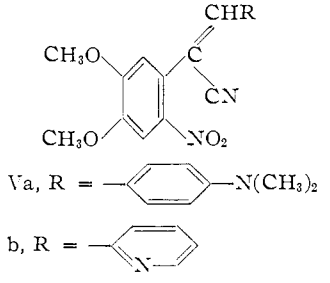
IIa, b, c, d, e



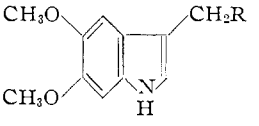
IIIa, $R_1 = H$; $R_2 = CN$
b, $R_1 = H$; $R_2 = COOCH_3$
c, $R_1 = CH_3$; $R_2 = COOEt$



IV (b, c)



Va, R = —C6H4—N(CH3)2
b, R = —C5H4N



VI (a)

Hydrogenation of nitroesters Ia, Ib and Ic in turn in the presence of palladium–charcoal in ethyl acetate at 80° gave in each case a crystalline product in high yield. The infrared spectra of the three compounds (II) all had an intense lactam band at 5.95–5.96 μ, as expected for 3,4-dihydrocarbostyrils. While this absorption reasonably excludes an alternative oxindole (5.80–5.85 μ)[1] structure for IIc, it does not exclude[2] a 2-oxo-2,3,4,5-tetrahydrobenzazepine formula for IIb. However, in view of the recently found rearrangement of seven-membered lactams to 3,4-dihydrocarbostyrils,[2] a seven-membered ring structure for IIb is unlikely. Further evidence for structures IIb and IIc was obtained through reductive cyclization of a nitro-acid ester Id corresponding to Ib and nitro-diacid Ie corresponding to Ic. Lactam-acids were obtained in each case, and these acids gave IIb and IIc, respectively, upon esterification with ethanol. Formation of seven-membered lactam acids from Id and Ie would necessarily involve an unlikely acid–ester exchange in (d) and reversal of the direction of cyclization of the esters. From these results one may conclude that it is not possible to prepare substituted oxindoles or 2-oxo-2,3,4,5-tetrahydrobenzazepines by reductive cyclization when there is also present opportunity for dihydrocarbostyril formation. This conclusion is in accord with previous observations[2–5] on the relative stabilities of these heterocyclic systems. It should also be mentioned that reduction of nitriles corresponding to Ic failed to give indoles or other recognizable products.

In contrast with homoveratronitrile, which reacts readily with two moles of acrylonitrile,[6] it was found that 2-nitro-4,5-dimethoxyphenylacetonitrile reacted with one mole of acrylonitrile and methyl acrylate in the presence of Triton B and gave compounds IIIa and IIIb, respectively. Similarly, reaction of 2-nitrohomoveratronitrile with ethyl crotonate under forcing conditions gave IIIc. The different behavior of homoveratronitrile and its 2-nitro derivative in these reactions probably is due to increased steric hindrance after introduction of the nitro group. While reduction

(1) G. N. Walker, THIS JOURNAL, **77**, 3844 (1955).
(2) H. A. Lloyd, L. U. Matternas and E. C. Horning, *ibid.*, **77**, 5932 (1955).
(3) H. A. Lloyd and E. C. Horning, *ibid.*, **76**, 3651 (1954).
(4) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *ibid.*, **75**, 5305 (1953).
(5) P. L. Julian and H. C. Printy, *ibid.*, **75**, 5301 (1953).
(6) E. C. Horning, M. G. Horning, M. S. Fish and M. W. Rutenberg, *ibid.*, **74**, 773 (1952).

experiments with IIIa were unpromising, compounds IIIb and IIIc were converted[1] easily to indoles IVb and IVc. These compounds were characterized by preparation of corresponding acid hydrazides and, in the case of IIIb, by hydrolysis to β-(5,6-dimethoxyindole-3)-propionic acid. It is noteworthy that the alkoxycarbonyl group does not interact with the amino group of (presumed) intermediate 2-aminoindoles[1] during cyclization of IIIb and IIIc.

Some further examples of reductive cyclization of benzylidene 2-nitrophenylacetonitriles[1] were studied. Compound Va was transformed into indole VIa, but no well-defined product could be isolated after reduction of Vb, perhaps because of instability.

Experimental[7,8]

β-(2-Nitro-4,5-dimethoxyphenyl)-propionic Acid.—A solution of 6.0 g. of β-(3,4-dimethoxyphenyl)-propionic acid[9] in 20 ml. of glacial acetic acid was treated slowly with 8 ml. of concd. nitric acid with ice-cooling to prevent the temperature from rising above 40°. After 1.5 hr. standing at 10°, the solution was diluted with ice-water. The product was collected, washed with water and triturated with methanol. There was obtained 6.1 g. of yellow crystals, m.p. 183–185°, not raised by recrystallization from the same solvent.

Anal. Calcd. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13. Found: C, 51.75; H, 5.36.

The corresponding **ethyl ester Ia** was prepared by esterification of 5.9 g. of the acid with 190 ml. of absolute ethanol containing 10 ml. of concd. sulfuric acid (3 hr. reflux). Isolation of the neutral product in the usual way gave 5.5 g. of yellow needles, m.p. 82–84°.

Anal. Calcd. for $C_{13}H_{17}O_6N$: C, 55.11; H, 6.05. Found: C, 55.5; H, 6.01.

Monoethyl Ester of 2-Nitro-4,5-dimethoxybenzylsuccinic Acid (Id).—Stobbe condensation of veratraldehyde with ethyl succinate and hydrogenation of the half-ester were carried out as described previously.[10] A solution of 26 g. of crude monoethyl ester of 3,4-dimethoxybenzylsuccinic acid in 100 ml. of glacial acetic acid was treated at ice temperature with 40 ml. of concd. nitric acid, and the solution was kept overnight at 0°. The product was isolated as described in the preceding experiment. Recrystallization from methanol gave 27 g. (90%) of yellow crystals, m.p. 143–147°, raised to 150–151.5° on further recrystallization.

Anal. Calcd. for $C_{15}H_{19}O_8N$: C, 52.78; H, 5.61. Found: C, 52.59; H, 5.65.

The diethyl ester Ib was prepared by esterification of the acid-ester in the usual way. A quantitative yield of neutral orange oil was obtained.

α-Methoxycarbonyl-β-(3,4-dimethoxyphenyl)-succinonitrile.—A suspension of 19.5 g. (0.075 mole) of ethyl veratrylidenecyanoacetate and 11.5 g. (0.177 mole) of potassium cyanide in 75 ml. of methanol was boiled for 10 minutes. The cooled solution was diluted with 100 ml. of water and was acidified at ice temperature with hydrochloric acid. The product was extracted with ether, and the ether solution was washed with dilute hydrochloric acid and water. Extraction with 3 portions of 5% sodium hydroxide solution and acidification of the alkaline solutions (hydrochloric acid) gave product which was free from neutral impurities. This material was extracted again with ether. The ether solution was washed with three portions of water and dried over magnesium sulfate. Evaporation of the ether gave 17.5 g. (85%) of oil which crystallized slowly. Recrystallization from methanol gave colorless crystals, m.p. 95–103°, evidently a mixture of stereoisomers. The infrared spectrum (chf.) had peaks at 4.44 and 5.68 mμ.

Anal. Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.30; H, 5.14. Found: C, 61.40; H, 5.32.

Evidently ester exchange (methyl for ethyl) accompanied this reaction, which is reported[11] to lead to loss of the α-alkoxycarbonyl group when carried out in ethanol.

α-Ethoxycarbonyl-β-(2-nitro-4,5-dimethoxyphenyl)-succinonitrile.—A solution of 3.0 g. of dicyano ester from the preceding experiment in 10 ml. of acetic acid was treated with 5 ml. of concd. nitric acid at ice temperature. After 15 minutes the product was isolated as usual. Trituration with methanol gave 2.3 g. of yellow crystals, m.p. 151–157°. Recrystallization from methanol raised the m.p. to 157–158°.

Anal. Calcd. for $C_{14}H_{13}O_6N_3$: C, 52.67; H, 4.10; N, 13.16. Found: C, 52.64; H, 4.22; N, 13.15.

Hydrogenation of this nitro-dicyano ester in the presence of 10% palladium–charcoal in ethyl acetate at 80° gave viscous oil which turned dark rapidly in air and afforded no crystalline product.

2-Nitro-4,5-dimethoxyphenylsuccinic Acid (Ie).—Hydrolysis of 35 g. of α-carbomethoxy-β-(3,4-dimethoxyphenyl)-succinonitrile with 300 ml. of concd. hydrochloric acid and 100 ml. of water (refluxed 3.5 hr.), according to an earlier procedure,[11] gave 23 g. (70%) of crude **3,4-dimethoxyphenylsuccinic acid**, m.p. 100–122°. Recrystallization from ethyl acetate gave 14.5 g. of colorless, anhydrous crystals, m.p. 172–174°, in agreement with the reported[11] value. The infrared spectrum (Nujol) had an intense double peak at 5.79 and 5.87 μ.

A solution of 6.8 g. of 3,4-dimethoxyphenylsuccinic acid in 25 ml. of acetic acid was treated with 13 ml. of concd. nitric acid in 2 portions, while swirling the mixture in an ice-bath. The temperature rose to 35°. The re-cooled dark red solution was poured immediately into 200 ml. of ice-water, and this solution was kept at 0° for several hours, during which time the product separated as yellow crystals. The material was collected, washed with a small portion of cold water and air-dried. The yield of yellow crystals, m.p. 195–198° dec., was 6.0 g. (75%). Recrystallization from ethyl acetate–methanol raised the m.p. to 202–204° dec.

Anal. Calcd. for $C_{12}H_{13}O_8N$: C, 48.16; H, 4.38; N, 4.68. Found: C, 47.88; H, 4.38; N, 4.53.

Compound Ic was prepared by esterification of this nitrodiacid in the usual way, or better by esterification of 3,4-dimethoxyphenylsuccinic acid followed by nitration as described under α-ethoxycarbonyl-β-(2-nitro-4,5-dimethoxyphenyl)-succinonitrile. An 80% yield of neutral, bright yellow oil was obtained by the second method.

3,4-Dihydro-6,7-dimethoxycarbostyril (IIa).—Hydrogenation (40 lb.) of 1.8 g. of Ia in the presence of 1.0 g. of 10% palladium–charcoal in 100 ml. of ethyl acetate (or acetic acid) at 80° for 2 hr. gave 1.2 g. of slightly purple crystals, m.p. 134–136°, after trituration with ethyl acetate. Recrystallization from ethyl acetate gave colorless crystals, m.p. 135–136°. The infrared spectrum (chf.) had moderate peaks at 2.92, 3.12 and 6.15 μ, and a very intense peak at 5.96 μ.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.8; H, 6.32. Found: C, 64.1; H, 6.41.

3-Carbethoxymethyl-3,4-dihydro-6,7-dimethoxycarbostyril (IIb).—A solution of 6.0 g. of Ib in 200 ml. of ethyl acetate containing 3 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for 2 hr. Filtration of the catalyst and evaporation of the solvent gave 4.6 g. (97%) of light purple crystals, m.p. 113–118°. Recrystallization from cyclohexane–ethyl acetate gave colorless crystals, m.p. 117–118°. The infrared spectrum (chf.) had weak bands at 2.95 and 3.12 μ, a moderately strong peak at 6.16 μ and intense peaks at 5.79 and 5.96 μ (doublet).

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53. Found: C, 61.35; H, 6.40.

Hydrogenation of 11.0 g. of monoethyl ester of 2-nitro-4,5-dimethoxybenzylsuccinic acid (Id) in the presence of 1.2 g. of 10% palladium–charcoal and 100 ml. of acetic acid at 80° for 2 hr. and trituration of the crude product (ethyl

(7) Melting points are corrected.

(8) Analyses by Dr. William C. Alford and his staff. Spectra furnished by Mrs. Iris Siewers, Mr. and Mrs. H. Franklin Byers and Miss Catherine Monaghan.

(9) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1080 (1907).

(10) E. C. Horning and G. N. Walker, THIS JOURNAL, **74**, 5147 (1952).

(11) T. Richardson, R. Robinson and E. Seijo, *J. Chem. Soc.*, 835 (1937).

acetate) afforded 6.3 g. of somewhat discolored crystals, m.p. 227–230° dec. This acid IId was very insoluble in organic solvents and could not be purified completely. Esterification of 5 g. of the acid with ethanol in the presence of sulfuric acid and recrystallization of the neutral product from cyclohexane–ethyl acetate gave 2.7 g. of colorless crystals, m.p. 117–118.5°. The mixed m.p. with IIb was not depressed, and the infrared spectra of the samples were identical.

3,4-Dihydro-4-ethoxycarbonyl-6,7-dimethoxycarbostyril (IIc).—Hydrogenation (40 lb.) of 2.2 g. of Ic in the presence of 2 g. of 10% palladium–charcoal and 200 ml. of ethyl acetate at 80° for 2 hr. gave 1.5 g. (87%) of colorless crystals, m.p. 191–192°, after recrystallization from ethyl acetate. The infrared spectrum (chf.) had moderate peaks at 2.93, 3.12 and 6.18 μ and intense peaks (doublet) at 5.80 and 5.95 μ.

Anal. Calcd. for $C_{14}H_{17}O_5N$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.40; H, 6.17; N, 5.08.

Hydrogenation (40 lb.) of 3.0 g. of Ie in the presence of 2.5 g. of 10% palladium–charcoal and 100 ml. of acetic acid at 80° for an hour gave discolored crystals, trituration of which with ethyl acetate afforded 2.0 g. of IIe, m.p. 198–207° dec. Recrystallization from methanol–ethyl acetate gave IIe hydrate, m.p. 215–218° dec., after drying at 80° *in vacuo*. The infrared spectrum (Nujol) had peaks at 2.81, 5.86 and 5.97 μ.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.53; H, 5.62; N, 5.20. Found: C, 54.17; H, 5.45; N, 5.34.

Esterification of 0.7 g. of the lactam-acid with ethanol and sulfuric acid gave 0.6 g. of neutral, colorless crystals, m.p. 185–189°, raised to 191–192° by recrystallization from methanol or ethyl acetate. The mixed m.p. with IIc was not depressed, and the infrared spectra of the samples were identical.

Ethyl β-Cyano-β-(2-nitro-4,5-dimethoxyphenyl)-propionate. (A) **Alkylation.**—A mixture of 42 g. of homoveratronitrile, 55 g. of ethyl bromoacetate, 12 g. of sodium amide and 300 ml. of dry xylene was stirred and refluxed for 3 hr. The cooled suspension was treated with water, and the neutral product was isolated as usual. Distillation *in vacuo* gave 6.5 g. of yellow oil, b.p. 190–203° (1.5 mm.). (B) **Nitration.**—A solution of 5.5 g. of material from (A) in 16 ml. of glacial acetic acid was chilled in ice and treated with 9 ml. of concd. nitric acid. When reaction was complete (5 minutes), the solution was diluted with ice-water. The gummy product was extracted with ether–ethyl acetate. The organic solution was washed with dilute sodium hydroxide solution and water and was dried over magnesium sulfate. Evaporation of the solvents gave viscous oil which crystallized slowly in the presence of methanol. Trituration with this solvent gave 1.1 g. of yellow crystals, m.p. 115–118°. Recrystallization from methanol raised the m.p. to 120–122°.

Anal. Calcd. for $C_{14}H_{16}O_6N_2$: C, 54.54; H, 5.23. Found: C, 54.36; H, 5.28.

Hydrogenation of 0.9 g. of this nitro-cyano ester gave only 0.2 g. of crystalline material, m.p. 145–172°, evidently a mixture.

α-(2-Nitro-4,5-dimethoxyphenyl)-glutaronitrile (IIIa).—A boiling solution of 4.1 g. of 2-nitro-4,5-dimethoxyphenylacetonitrile[1] and 6 g. of acrylonitrile in 80 ml. of methanol was treated with 1.8 ml. of 30% Triton B solution. The dark solution was distilled on a steam-cone for an hour until 60 ml. of methanol had been collected. The cooled residue was treated with water and extracted with 300 ml. of ether. The ether solution was washed with 5% sodium hydroxide solution and water and was dried over magnesium sulfate. Evaporation of the ether and trituration of the residue with the same solvent gave 2.1 g. (41%) of product, m.p. 136–140°. Recrystallization from methanol gave yellow crystals, m.p. 140–142°.

Anal. Calcd. for $C_{13}H_{13}O_4N_3$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.96; H, 4.91; N, 15.34.

Hydrogenation of this nitro-dinitrile resulted in formation of ammonia, but a crystalline product could not be isolated.

Methyl β-(5,6-Dimethoxyindole-3)-propionate (IVb). (A) **Methyl γ-Cyano-γ-(2-nitro-4,5-dimethoxyphenyl)-butyrate (IIIb).**—Reaction of 12.8 g. of 2-nitro-4,5-dimethoxyphenylacetonitrile and 12.0 g. of methyl acrylate in the presence of 5.5 ml. of 30% Triton B and 200 ml. of methanol, as described in the preceding experiment, gave 14.9 g. of neutral, red oil which did not crystallize, but was suitable for further work. (B) **Reduction.**—A solution of 10.4 g. of crude product from (A) in 200 ml. of ethyl acetate containing 4 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for 3 hr. Four moles of hydrogen was absorbed, and ammonia was formed. The mixture was filtered, and most of the solvent was evaporated as rapidly as possible on a steam-cone. The residue crystallized rapidly on cooling. Trituration with ethyl acetate afforded 4.6 g. (52%) of slightly discolored crystals, m.p. 106–109.5°. Recrystallization from methanol gave colorless crystals, m.p. 107.5–109.5°. The infrared spectrum (chf.) had peaks at 2.88, 5.80 and 6.14 μ.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.61; N, 5.32.

The corresponding **acid hydrazide** was prepared by refluxing the ester (1.4 g.) with anhydrous hydrazine (10 ml.) for an hour. The cooled solution was diluted with water (100 ml.) and was chilled. After several hours, the product was collected, washed with cold water and air-dried. The yield of crystals, m.p. 143–147°, was 1.1 g. Recrystallization from ethyl acetate–methanol gave colorless crystals, m.p. 145–147°. The infrared spectrum (chf.) had peaks at 2.88, 6.00 and 6.15 μ.

Anal. Calcd. for $C_{13}H_{17}O_3N_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.54; H, 6.38; N, 16.02.

The corresponding **acid** was obtained by hydrolysis of the ester (0.5 g.) with 5% sodium hydroxide solution (40 ml.) (refluxed 1 hr.), followed by slow acidification at ice temperature. Recrystallization from benzene gave the **hydrate** as cream-colored, fine crystals, m.p. 124–126°, after drying at 80° *in vacuo*. The infrared spectrum (chf.) had peaks at 2.85, 5.85 and 6.12 μ.

Anal. Calcd. for $C_{13}H_{17}O_5N$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.71; H, 6.24; N, 5.23.

β-(5,6-Dimethoxyindole-3)-butyric Acid Hydrazide (IVc, Hydrazide). (A) **Condensation.**—A mixture of 3.2 g. of 2-nitro-4,5-dimethoxyphenylacetonitrile, 5 g. of ethyl crotonate and 2 ml. of 30% Triton B was heated on a steam-cone for 1 hr. and stirred occasionally. The cooled material was treated with water, and the neutral product was isolated by extraction with ether, as described in preceding experiments. There was obtained 3.4 g. of deep-red, viscous oil. (B) **Reduction.**—The crude product of (A) was hydrogenated as described in the preceding experiment. Ammonia was formed. The product, isolated as described for IVb, consisted of viscous, yellow oil which turned dark gradually upon exposure to air and resisted efforts to cause crystal formation. (C) **Hydrazine.**—Crude product (B) was taken up in 20 ml. of anhydrous hydrazine, and the solution was refluxed for 1 hr. The cooled solution was diluted with 80 ml. of water. Refrigeration brought about slow crystallization (5 days). The material was collected, washed with a small portion of cold water, air-dried and triturated with ethyl acetate. There was obtained 0.8 g. of colorless powder, m.p. 166–168°. The m.p. and crystallinity were not improved by recrystallization from ethyl acetate–methanol. The infrared spectrum (Nujol) had peaks at 3.00 and 6.10–6.15 μ (doublet).

Anal. Calcd. for $C_{14}H_{19}O_3N_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.74; H, 6.70; N, 15.29.

3-(*p*-Dimethylaminobenzyl)-5,6-dimethoxyindole (VIa). (A) **Condensation.**—A solution of 5.8 g. of 2-nitro-4,5-dimethoxyphenylacetonitrile, 6.0 g. of *p*-dimethylaminobenzaldehyde, 60 ml. of methanol and 3 ml. of piperidine was warmed on a steam-cone for 20 minutes. The crystals which separated (10 minutes) were pressed dry on a filter and were triturated with methanol. There was obtained 4.6 g. of orange crystals, m.p. 178–180°. The m.p. was not improved by recrystallization.

Anal. Calcd. for $C_{19}H_{19}O_4N_3$: C, 64.58; H, 5.42. Found: C, 65.07; H, 5.48.

(B) **Reduction.**—A mixture of 4.0 g. of product from (A) 3 g. of 10% palladium–charcoal and 200 ml. of ethyl acetate was shaken under hydrogen (40 lb.) at 80° for 4 hr. Five moles of hydrogen was absorbed, and ammonia was formed. Filtration of the catalyst, evaporation of the solvent and trituration of the residue with methanol gave 2.6 g. (74%) of colorless crystals, m.p. 140.5–144°, raised to 144–145°

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 $C_{19}H_{22}O_2N_2$: 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 $C_{16}H_{13}O_4N_3$: 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.