Spirans. VI. Azadispirans[1]

LEONARD M. RICE, MEIER E. FREED, AND CHARLES H. GROGAN[2]

The Georgetown University Medical Center, Washington, D. C.

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The synthesis of compounds containing multiple spiro carbon linkages has been investigated. Employing spiro ketones as starting materials, derivatives of 3-azadispiro[5.2.5.2]hexadecane and 2-azadispiro[4.2.5.2]-pentadecane have been prepared. Practical direct methods for the preparation in good over-all yield of the key intermediate, spiro[5.5]undecan-3-one, have been developed.

Earlier papers in this series[3,4] have described the synthesis and pharmacological properties of azaspirans, oxa-, and thiaazaspirans, as well as diazaspirans,[5] all of which contained a single spiro carbon atom. Ring C- and N-substituted spiro compounds were prepared from cyclic *gem*-carboxyacetic and -diacetic anhydrides. In the case of the piperidones, it was more convenient to employ the diester of these acids in lieu of the anhydride. The method is of wide applicability[3-5] for the synthesis of azaspirodiones and azaspirans.

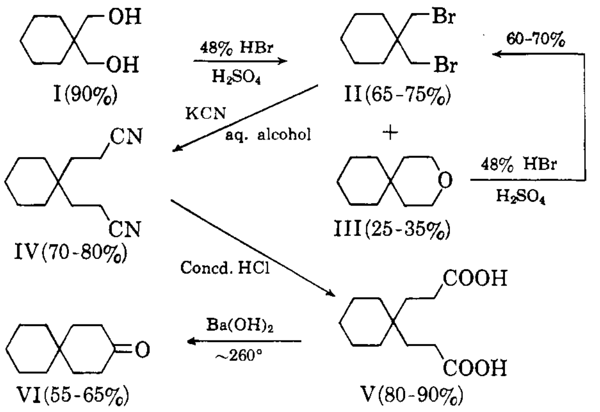
The required cyclic *gem* diacids and diesters employed were obtained from the corresponding cyclic ketones. It was of interest to us, therefore, to ascertain the practicability of preparing molecules containing multiple spiro carbon linkages, starting with spiro ketones.

Our previous papers[3,4] established that ketone functions adjacent to a ring junction did not undergo the double condensation with ethyl cyanoacetate or cyanoacetamide in ammoniacal alcohol to form the dicyanodiacetimide (Guareschi imide[6-8]). Further, the base-catalyzed (piperidine[9]) condensation of cyanoacetate with such hindered ketones frequently gave little or none of the intermediate α-cyano-$\Delta^{1,\alpha}$-cyclic acetic ester. Moderate yields of these esters were obtained in some such cases (α-tetralone and substituted α-tetralones) employing the ammonium acetate–acetic acid method of Cope, *et al.*[10] We therefore chose the nonhindered spiro ketone, spiro[5.5]undecan-3-one, for an investigation of the extension of the synthetic methods to obtain dispiro compounds.

This ketone (VI) was prepared by Burnell and Taylor[11] in low yield by cyanoethylation of cyclohexanone with vinyl cyanide, hydrolysis to cyclohexanone-2,2-bis-β-propionic acid, reduction of the carbonyl group, esterification, Dieckmann cyclization, and hydrolysis–decarboxylation. The cyanoethylation of cyclohexanone gave such low yields of difficultly separable material that we early abandoned this route to VI.

The scheme outlined by Dreiding,[12] who gave no experimental details in his short paper, was investigated. As considerable quantity of the spiro ketone VI was needed, the steps in Scheme I were studied in detail, and procedures which give good yields were developed.

SCHEME I



The diethyl ester of cyclohexane-1,1-diacetic acid[13] was reduced to the diol[14] in 90% yield. Conversion of the glycol I to the dihalide was difficult because of the competitive intramolecular dehydration to the spiro ether, III. In those cases where the dihalide could be obtained by the action of such conventional agents as thionyl bromide, thionyl chloride, phosphorus tribromide, phosphorus pentachloride, or concentrated hydrobromic acid, either alone or with sulfuric acid, the spiro ether III was also obtained in varying amounts. In fact, concentrated hydrobromic acid at 100° for 24 hr. gave the spiro ether III as the sole product. It was found that conversion of the glycol I to the dihalide was best accomplished by heating 4 ml. of 48% hydrobromic acid and 2 ml. of concentrated sulfuric acid/g. of glycol at 100° for 24 hr. Formation of the spiro ether III was limited to 25–35%, and by recycling the latter under identical conditions, the over-all yield of dibromide exceeded 90%. This method was superior to formation of the glycol ditosylate[14] followed by reaction with lithium bromide, since the yield by the latter procedure was lower and entailed an extra step.

The dinitrile IV was obtained smoothly from the dibromide II on treatment with alcoholic KCN. Hydrolysis of the dinitrile to the dipropionic acid V was best accomplished with concentrated hydrochloric acid. Dieckmann cyclization of diethyl cyclohexane-1,1-bis-β-propionate afforded the keto ester in 51% yield according to Burnell and Taylor.[11] Our best yield by their procedure was 60%. The additional hydrolysis–decarboxylation step cut the yield of spiro ketone VI to less than 50%. Pyrolysis of the barium salt of the dipropionic acid V consistently gave the spiro ketone in

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[1] Supported by the Geschickter Fund for Medical Research, Inc.

[2] Author to whom inquiries should be addressed at the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda 14, Md.

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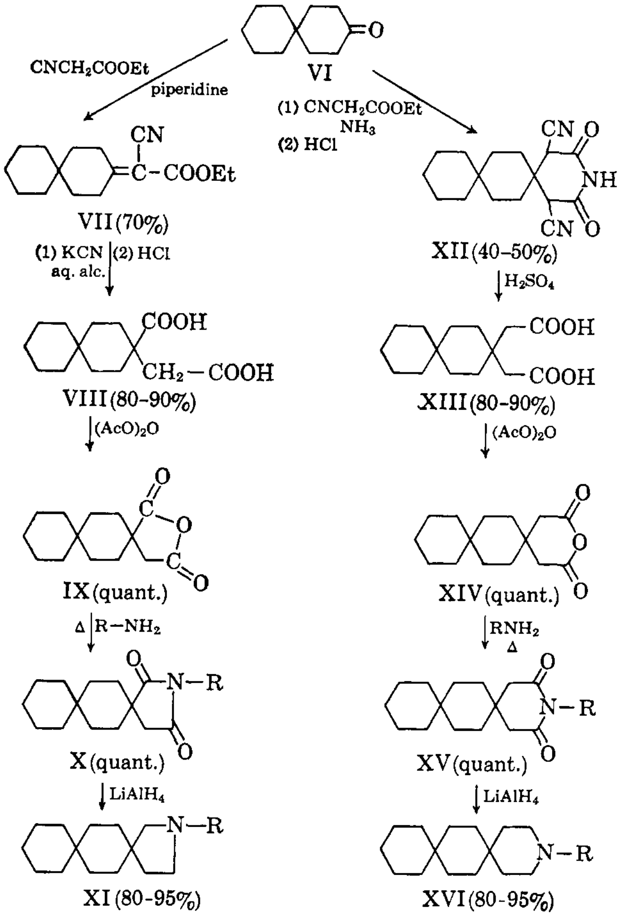
SCHEME II



55–65% yield. Unchanged acid, carried into the receiver by the extensive frothing, when separated and recycled increased the over-all yield to around 90%.

The formation of dispiro compounds was next investigated according to Scheme II. The spiro ketone VI readily condensed with ethyl cyanoacetate in ammoniacal alcohol to give the Guareschi imide XII. This was hydrolyzed by 60–70% sulfuric acid to spiro[5.5]undecane-3,3-diacetic acid (XIII). The piperidine-catalyzed condensation of VI with ethyl cyanoacetate proceded readily to give VII, which, after addition of alkali metal cyanide and hydrolysis with concentrated hydrochloric acid, gave spiro[5.5]undecane-3-carboxy-3-acetic acid (VIII).

The spiro *gem*-carboxyacetic and -diacetic acids were dehydrated with acetic anhydride to their anhydrides IX and XIV which on reaction with ammonia and primary amines and cyclization at 180–240° formed the dispiroimides X and XV. Reduction of the dispiroimides X and XV afforded the azadispirans XI and XVI in excellent yield. The azadispirans were stable, colorless oils which could be distilled *in vacuo* without decomposition.

An extension of previous methods of synthesis of azaspirans and azaspirodiones[3-5] diazaspirans and diazaspirodiones[5] employing spiro ketones as starting materials has shown that the method is applicable to the synthesis of compounds containing multiple spiro carbon linkages. Repetition of Schemes I and II starting with the *gem*-spiro acids, VIII and XIII, should afforded trispiro compounds. In view of the clear-cut nature of the method we see no immediate reasons why the sequence could not be extended to obtain compounds with any desired number of spiro carbon linkages.

Experimental

All melting points were obtained either with a Fisher-Johns block-type or Thomas-Hoover capillary-type apparatus and are corrected. Elemental microanalyses were performed by Shwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

1,1-Bis(β-bromoethyl)cyclohexane (II).—A solution of 80 g. (0.465 mole) of 1,1-bis(β-hydroxyethyl)cyclohexane (I) in 320 ml. of 48% aqueous HBr was precooled to 10–20° and 160 ml. of concentrated H_2SO_4 was added portionwise with shaking and cooling. The resultant clear solution was heated at 100° in an oil bath for 24 hr., cooled, diluted with 2 l. of water, and extracted three times with 300 ml. of ether. The ether extract was washed twice with water, once with 10% $NaHCO_3$, and once with saturated NaCl solution, and dried overnight over anhydrous Na_2SO_4. The ether was stripped off and the residue was distilled to yield two fractions at 10 mm., one boiling below 150° and the other above 150°. Vacuum distillation of the higher boiling fraction gave 99 g. of product, 71%, b.p. 100–102° (0.1 mm.), $n^{22}\mathrm{D}$ 1.5362.

Anal. Calcd. for $C_{10}H_{18}Br$: C, 40.28; H, 6.08; Br, 53.64. Found: C, 40.50; H, 6.01; Br, 53.40.

3-Oxaspiro[5.5]undecane (III).—Fractionation of the fraction, b.p. < 150° (10 mm.), obtained from the preparation of II, gave III, 20 g. (28%, b.p. 82–85° (10 mm.).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.2; H, 11.8. Found: C, 77.16; H, 11.92.

The same spiro ether III was obtained nearly quantitatively by heating 75 g. of the glycol I with 320 ml. of 48% aqueous HBr at 100° for 24 hr.

1,1-Bis(β-bromoethyl)cyclohexane (II) from 3-Oxaspiro[5.5]-undecane (III).—When 77 g. of III was treated with 48% aqueous HBr–concentrated H_2SO_4 as in the preparation of II from I, 100 g. of the dibromide II and 20 g. of III were obtained.

1,1-Bis(β-cyanoethyl)cyclohexane (IV).—A solution of 284 g. (0.95 mole) of the dibromide II dissolved in 1 l. of alcohol was added rapidly with stirring to a solution of 180 g. of KCN in 1 l. of 80% alcohol. The mixture was refluxed for 24 hr., cooled, and poured into 4 l. of ice–water. The crude product solidified, was washed copiously with water, and was air-dried. On distillation there was obtained 138 g., 76%, of product, b.p. 150–155 (0.1 mm.). It melted at 51–52° on recrystallization from alcohol–water.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.58; H, 9.41; N, 14.63.

Cyclohexane-1,1-bis-β-propionic Acid (V).—The dinitrile IV, 138 g. (0.72 mole), was refluxed with 1 l. of concentrated HCl for 24 hr. On cooling the product crystallized. The crude product was suitable for the subsequent pyrolysis to spiro[5.5]-undecan-3-one. The pure acid was obtained by dissolving the crude material in boiling $NaHCO_3$, decolorizing with Norit A, filtering, and acidifying with HCl. It melted at 89–90° on recrystallization from benzene–hexane. Hydrolysis with 25–50% H_2SO_4 or with alkali did not give as good yields nor was as convenient as hydrolysis with HCl.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.96; H, 8.64.

Spiro[5.5]undecan-3-one (VI).—Cyclohexane-1,1-bis-β-propionic acid (V) 120 g. (0.53 mole), was mixed with 10 g. of barium hydroxide in 500-ml. flask equipped with an 8-in. column. On heating, some water distilled above the melting point of the acid and active pyrolysis started at 260°. The pressure was reduced to 200 mm. and gradually to 10 mm. as the reaction proceeded. Regardless of painstaking effort, some froth invariably passed into the receiver. When no more distillate was obtained, the distillate was dissolved in 500 ml. of ether and washed with water and 10% $NaHCO_3$. From the bicarbonate wash, after boiling, filtering, acidifying with HCl, and cooling, was obtained 40 g. of the starting acid. The ether solution was washed with saturated NaCl solution and dried overnight over anhydrous Na_2SO_4, the ether was stripped off, and the residue was distilled to give VI, 52 g., 60%, b.p. 110–112° (3.5–4 mm.) or 88–91° (1.5 mm.), $n^{22}\mathrm{D}$ 1.4916. The spiro ketone is a colorless oil with characteristic odor which is not sweetish like cyclohexanone or cyclopentanone but more piquant like 4-cyclohexylcyclohexanone.[3,4]

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.26; H, 10.78.

1,5-Dicyano-3-azadispiro[5.2.5.2]hexadecane-2,4-dione (the Guareschi Imide, XII).—Spiro[5.5]undecan-3-one, 33.2 g. (0.2 mole), and 47.5 g. (0.42 mole) of ethyl cyanoacetate were placed in a 500-ml. thick-walled flask. The mixture was cooled to 0° and 100 ml. of ethanol saturated with anhydrous ammonia at 0° was added. After mixing and wedging the stopper in, the mixture was stored at 0–5° for 1 week. The precipitated ammonium salt of the Guareschi imide was filtered, dissolved in boiling water, filtered, and acidified with HCl. The Guareschi imide was filtered, washed with water, and dried. It melted at 230–233° and on recrystallization from alcohol–water at 232–233°; there was obtained 24 g., 40%.

Anal. Calcd. for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.27; H, 7.09; N, 14.04.

Spiro[5.5]undecane-3,3-diacetic Acid (XIII).—The dried imide XII, 24 g., was dissolved with the aid of heat in 100 ml. of concentrated H_2SO_4 in a 1-l. flask and allowed to stand overnight. Water (85 ml.) was added portionwise with shaking through an efficient condenser and the mixture was refluxed for 24 hr. The reaction mixture was diluted with two volumes of water, cooled, and filtered; the residue was dissolved in boiling $KHCO_3$, decolorized with charcoal, filtered, acidified with HCl, and cooled overnight. The product was filtered and washed with water. There was obtained 19.5 g., m.p. 221–223° and 221–222° on recrystallization from benzene–petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.81; H, 9.25.

Spiro[5.5]undecane-3,3-diacetic Anhydride (XIV).—Refluxing 19 g. of the acid XIII with four times its weight of acetic anhydride for 4 hr. and removal of the acetic anhydride at the water pump gave XIV, 17 g., m.p. 126–128° and 126–127° on recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.90; H, 8.79.

3-Azadispiro[5.2.5.2]hexadecane-2,4-dione (XV, R = H).—The imide was obtained quantitatively on heating the anhydride XIV, 9 g. (0.036 mole), with an excess of concentrated aqueous ammonia and cyclization at 240°. It melted at 239–240° on recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.32; H, 9.35; N, 5.56.

3-Azadispiro[5.2.5.2]hexadecane (XVI, R = H).—Reduction of 5 g. (0.02 mole) of the dispiroimide XV (R = H) with 5 g. of lithium aluminum hydride in absolute ether gave 3.3 g., 75% of the title base. This was converted to the hydrochloride by adding 5 ml. of saturated alcoholic HCl to the base in ether. The **hydrochloride** melted at 357–359° dec. and at 358–360° dec. on recrystallization from alcohol–ether.

Anal. Calcd. for $C_{15}H_{28}ClN$: Cl, 13.75. Found: Cl, 13.75.

The **picrate** was formed in methanol and melted at 221–223° unchanged on recrystallization.

Anal. Calcd. for $C_{21}H_{30}N_4O_7$: N, 12.44. Found: N, 12.65.

3-(3-Dimethylaminopropyl)-3-azadispiro[5.2.5.2]hexadecane-2,4-dione (XV, R = Dimethylaminopropyl).—The anhydride XIV, 8.5 g. (0.034 mole), was treated with a 10% molar excess of 3-dimethylaminopropylamine and cyclized 1 hr. at 180°. The imide was obtained quantitatively and melted at 46–49° and at 55–56° on recrystallization from acetone–water.

Anal. Calcd. for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.49; H, 9.96; N, 8.11.

The **hydrochloride** was formed by bubbling HCl gas through an ether solution of the base and melted at 200–201° on recrystallization from methanol–ether.

Anal. Calcd. for $C_{20}H_{35}ClN_2O_2$: Cl, 9.56. Found: Cl, 9.30.

The **methiodide** was formed by refluxing the base with an excess of methyl iodide in acetone, adding an equal volume of ethyl acetate, and cooling. It melted at 292–294° dec.

Anal. Calcd. for $C_{21}H_{37}IN_2O_2$: I, 26.64. Found: I, 26.72.

3-(3-Dimethylaminopropyl)-3-azadispiro[5.2.5.2]hexadecane (XVI, R = Dimethylaminopropyl).—Reduction of 9.4 g. (0.028 mole) of the preceding imide with 8 g. of lithium aluminum hydride in absolute ether gave 7.5 g., 87%, of the title compound, b.p. 135–145° (0.08 mm.).

Anal. Calcd. for $C_{20}H_{38}N_2$: C, 78.36; H, 12.50. Found: C, 78.57; H, 12.83.

The **dihydrochloride** was prepared by bubbling gaseous HCl through an ether solution of the base. It melted at 322–323° dec.

Anal. Calcd. for $C_{20}H_{40}Cl_2N_2$: Cl, 18.69. Found: Cl, 18.46.

The **dimethiodide** was formed by refluxing the base in isopropyl alcohol with an excess of methyl iodide and diluting with an equal volume of ethyl acetate. It melted at 285–286° dec.

Anal. Calcd. for $C_{22}H_{44}I_2N_2$: I, 42.99. Found: I, 43.04.

Ethyl-2 Cyano-2-(spiro[5.5]undecyliden-3-yl)acetate (VII).—Spiro[5.5]undecan-3-one, 34.1 g. (0.2 mole), was mixed with 24 g. (slight excess) of ethyl cyanoacetate and 0.5 ml. of piperidine. The mixture was allowed to stand for five days with heating to 100° daily. It was poured into 1 l. of water, acidified with 1 ml. of concentrated HCl, and extracted three times with ether. The ether extract was washed with water and dried over Na_2SO_4, the ether was stripped off, and the residue was distilled *in vacuo* to yield 37.7 g., 70%, of product, b.p. 138–142° (0.2 mm.), m.p. (from ethanol–water) 54–55°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.61; H, 9.10; N, 5.70.

Spiro[5.5]undecane-3-carboxy-3-acetic Acid (VIII).—The ester VII, 30.8 g. (0.12 mole), was dissolved in 250 ml. of alcohol and a solution of 20 g. of KCN in 50 ml. of water was added. After standing for 5 days, the mixture was stripped of all solvents to a dry powder. This was placed in a 1-l. boiling flask; 200 ml. of concentrated HCl was added portionwise through the condenser and then refluxed for 48 hr. It was diluted with an equal volume of water and cooled overnight; the crystalline product was filtered and washed with water. The crude product, 27 g., 88%, m.p. 183–185°, was dissolved in boiling $KHCO_3$, decolorized with charcoal, filtered and reprecipitated with concentrated HCl to yield 26.5 g., m.p. 185–186°, unchanged on recrystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.35; H, 8.90.

Spiro[5.5]undecane-3-carboxy-3-acetic Acid Anhydride (IX).—Refluxing 26 g. of the acid VIII with 60 ml. of acetic anhydride for 2 hr., stripping off one-half of the acetic anhydride, and cooling gave 19 g. of the anhyride, m.p. 140–142° and 141–142° on recrystallization from ethyl acetate. Additional less pure material was obtained by stripping the acetic anhydride to dryness.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.17; H, 8.53. Found: C, 71.11; H, 8.64.

2-(3-Morpholinopropyl)-2-azadispiro[4.2.5.2]pentadecane-1,3-dione (X, R = morpholinopropyl).—This imide was obtained quantitatively on reaction of 6.5 g. (0.028 mole) of the anhydride IX with a slight excess of 3-morpholinopropylamine and cyclization at 180° for 1 hr. It melted at 109–110° on recrystallization from acetone–water.

Anal. Calcd. for $C_{21}H_{34}N_2O_3$: C, 69.58; H, 9.45; N, 7.73. Found: C, 69.32; H, 9.50; N, 8.00.

The **hydrochloride**, obtained by passing HCl through an ether solution of the base, melted at 247–248°.

Anal. Calcd. for $C_{21}H_{35}ClN_2O_3$: Cl, 8.89. Found: Cl, 8.86.

The **methiodide**, obtained by refluxing the base with excess methyl iodide in ethyl acetate for 30 min. and cooling, melted at 240–241°.

Anal. Calcd. for $C_{22}H_{37}IN_2O_3$: I, 25.16. Found: I, 25.42.

2-(3-Morpholinopropyl)-2-azadispiro[4.2.5.2]pentadecane (XI, R = Morpholinopropyl).—Reduction of 9 g. (0.025 mole) of the preceding imide with lithium aluminum hydride in absolute ether and distillation gave 7 g., 84%, of the title compound, b.p. 158–165° (0.18 mm.).

Anal. Calcd. for $C_{21}H_{38}N_2O$: C, 75.39; H, 11.45; N, 8.37. Found: C, 75.35; H, 11.67; N, 8.50.

The **dimethiodide**, obtained by refluxing the base in 1:1 ethanol–acetone with an excess of methyl iodide for 2 hr., cooling, and adding ethyl acetate, melted at 253–254° dec. on recrystallization from methanol–ether.

Anal. Calcd. for $C_{23}H_{44}I_2N_2O$: I, 41.04. Found: I, 41.07.

The **dihydrochloride**, formed from a solution of the base in ether and gaseous HCl, melted at 292–293° on recrystallization from methanol–ether.

Anal. Calcd. for $C_{21}H_{40}Cl_2N_2O$: Cl, 17.40. Found: Cl, 17.48.

2-Allyl-2-azadispiro[4.2.5.2]pentadecane-1,3-dione (X, R = Allyl).—This imide was obtained quantitatively on reaction of excess allylamine with the anhydride IX, 5 g. (0.02 mole), and cyclization at 180° for 1 hr. It melted at 101–102° on recrystallization from acetone–water.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.18; H, 9.14; N, 5.29.

2-Allyl-2-azadispiro[4.2.5.2]pentadecane (XI, R = Allyl).—Reduction of the preceding imide, 5.5 g., dissolved in benzene, with lithium aluminum hydride in ether, gave 4 g., 84%, of the title base, b.p. 90–95° (0.08 mm.).

Anal. Calcd. for $C_{17}H_{29}N$: C, 82.52; H, 11.81; N, 5.66. Found: C, 82.82; H, 11.87; N, 5.73.

The **hydrochloride**, prepared in the usual way, melted at 203–204° on recrystallization from acetone–ether.

Anal. Calcd. for $C_{17}H_{30}ClN$: Cl, 12.49. Found: Cl, 12.21.

The **methiodide**, prepared in the usual way, melted at 169–170° on recrystallization from acetone–ether.

Anal. Calcd. for $C_{18}H_{32}IN$: I, 32.60. Found: I, 32.83.

2-Methyl-2-azadispiro[4.2.5.2]pentadecane-1,3-dione (X, R = Methyl).—The methyl imide, obtained quantitatively by reaction of the anhydride IX, 5 g. (0.02 mole), with excess aqueous methylamine and cyclization at 180° for 1 hr., melted at 108–109° on recrystallization from acetone–water.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.49; H, 9.62; N, 5.88.

2-Methyl-2-azadispiro[4.2.5.2]pentadecane (XI, R = Methyl).—Reduction of the preceding imide, 5 g., in benzene with an ether solution of lithium aluminum hydride gave the title base, 3.8 g., 86%, b.p. 85–90° (0.12 mm.).

Anal. Calcd. for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33. Found: C, 81.11; H, 12.59; N, 6.03.

The **hydrochloride**, prepared from HCl and the base in ether, melted at 256–257°.

Anal. Calcd. for $C_{15}H_{28}ClN$: Cl, 13.75. Found: Cl, 13.63.

The **methiodide**, prepared in ethyl acetate, melted at 294–295°.

Anal. Calcd. for $C_{16}H_{30}IN$: I, 34.93. Found: I, 34.98.

Preparation of Acetoxybenzyl Bromides

D. L. Fields, J. B. Miller, and D. D. Reynolds

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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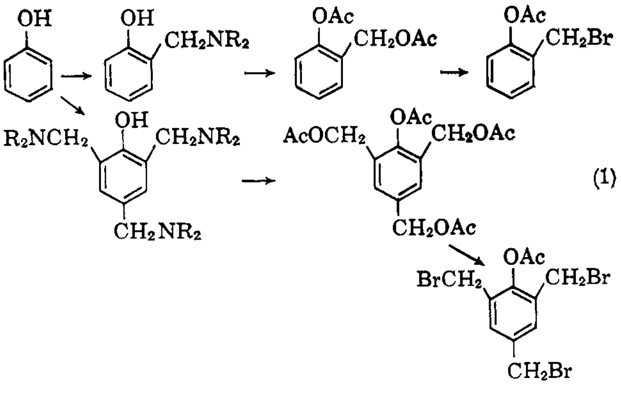
A three-step synthesis of acetoxybenzyl bromides from the corresponding phenols is described. The procedure gives high yields and can be used for large-scale preparations. All of the mono-, di-, tri-, and tetrabromomethylhydroquinone diacetates are described, together with some similar derivatives of catechols and phenols.

Although chloromethylation[1] of mildly activated aromatic compounds is a valuable synthetic tool, it has had very limited application in the alkylation of phenols and phenolic acetates. In general, phenols are so highly activated that the reaction cannot be controlled and diarylmethanes as well as polymers result. Bromomethylation has been effected under the same general conditions as chloromethylation but in even poorer yields.[2]

We describe here a three-step synthesis applicable to phenols which affords bromomethyl derivatives, usually in good yields. The three steps, as typified in eq. 1, are the Mannich-type condensation, acetolysis of the Mannich base, and treatment of the resulting acetoxymethyl acetate with hydrogen bromide in acetic acid. The bromomethylphenol product is acetylated, which is often advantageous since esters of halomethylphenols are much less prone to polymerize than the parent phenol.

In the present study, we have been primarily concerned with derivatives of hydroquinone and catechol, although two examples using phenol (eq. 1) are included to illustrate better the scope of the reaction.



(1)

Mannich Condensation.—The characterizations and structures of the Mannich bases derived from hydroquinone and catechol are summarized in Tables I and II, respectively. Aminomethylhydroquinones, Ia, Ic, Ie, and If (Table I), were prepared by varying the stoichiometry and reaction conditions in direct condensations of hydroquinone with formaldehyde and morpholine.

Morpholinomethylhydroquinone (Ia) was isolated in 65% yield by allowing equimolar amounts of starting materials to react at 25° for 8 hr.

At reaction temperatures below 80°, 2,5-bis(morpholinomethyl)hydroquinone (Ic) was obtained in greater than 70% yield even when greater than the stoichiometric quantity of 2 molar equiv. of amine and formaldehyde per molar equivalent of hydroquinone was used.

A higher reaction temperature and a longer reaction time (*e.g.*, 140°, 20 hr.) were necessary for the production of tris- and tetrakis(morpholinomethyl)hydroquinone, Ie and If, respectively.[3] Purification of Ie (m.p. 168–169°) by fractional crystallization from trace amounts of Ic and If was difficult, but material of sufficient purity (m.p. 150–160°) for subsequent reactions was readily obtained by this method.

2,6-Bis(morpholinomethyl)hydroquinone (Id) was prepared by the procedure of Burke, *et al.*,[4] from 4-benzyloxyphenol. Conversion of Id to Ie by their method did not seem to offer any particular advantage over the more direct route described here, nor was the purity of their product (m.p. 159–160°) significantly better.

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(1) R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

(2) G. Darzens, *Compt. rend.*, **208**, 818 (1939).

(3) Previously prepared by W. J. Burke, J. L. Bishop, and J. A. Warburton, *J. Org. Chem.*, **27**, 4003 (1962).

(4) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bills, *ibid.*, **26**, 4669 (1961).