# Hydroxylamine Chemistry. V. O-(2-Hydroxyethyl)acetone Oxime *p*-Toluenesulfonate, a Useful Intermediate for the Preparation of Hydroxylamine Derivatives[1]

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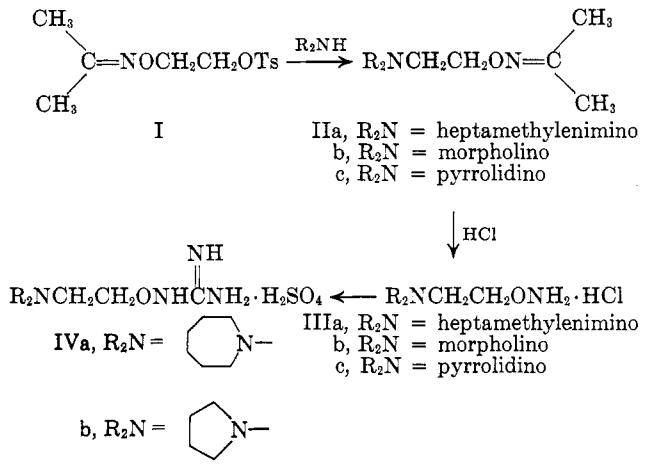
The condensation of O-(2-hydroxyethyl)acetone oxime *p*-toluenesulfonate with various nucleophilic reagents has been studied as a route to the facile introduction of the aminooxyethyl moiety into various substrates. The successful preparations of β-aminooxyethyl derivatives of amines, 2(1H)-pyridone, phenothiazine, and dibenzazepine in high yields are described. In another set of experiments, 10-(aminooxyacetyl)phenothiazine hydrochloride was obtained by the reaction of phenothiazine with isopropylideneaminooxyacetyl chloride, followed by acid-catalyzed removal of the isopropylidene blocking group.

The previous communications of this series[1] have described the preparation of various types of hydroxylamine derivatives and have discussed some of the chemistry peculiar to this class of compounds. As a continuation of this program, we were in need of a general and simple means of effecting the addition of the aminooxyethyl moiety ($H_2NOCH_2CH_2-$) to various substrates. The present study reports the use of O-(2-hydroxyethyl)acetone oxime *p*-toluenesulfonate (I) to achieve this goal.

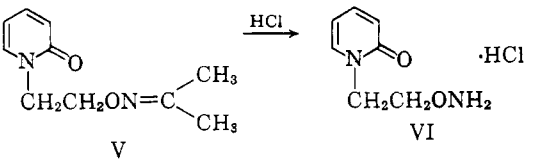
Heretofore, aminooxyethylamines had been prepared *via* the condensation of β-haloethyldialkylamines with the salt of an oxime and subsequent acid hydrolysis of the blocking group.[3,4] The disadvantage of this synthetic route, however, is the fact that a dialkylaminoethyl halide must be prepared each time a different amino function is desired. This difficulty is obviated by the following procedure.




The reaction of O-(2-hydroxyethyl)acetone oxime[5] with *p*-toluenesulfonyl chloride in the cold afforded O-(2-hydroxyethyl)acetone oxime *p*-toluenesulfonate (I) in nearly quantitative yield. Solvolysis of I in an excess of a secondary amine readily afforded the isopropylideneaminooxyethylamines IIa–c in good yields. Hydrochloric acid hydrolysis of IIa–c gave rise to the aminooxy compounds IIIa–c.

In connection with the general problem of introducing aminooxy functions at the site of amino groups in known pharmacologically active materials, we were led to synthesize the hydroxylamine analog of the potent antihypertensive agent [2-(octahydro-1-azocinyl)-ethyl]guanidine sulfate (guanethidine).[6] The reaction of IIIa (as the free base) with 2-methyl-2-thiopseudourea sulfate gave the corresponding guanidine sulfate IVa. Similarly, IVb was prepared from IIIc. Neither analog was observed to effect a lowering of arterial pressure in renal hypertensive rats.[7]

Additionally, we have found that I condensed readily with the anion derived from 2-pyridone to give the isopropylidene derivative V which readily underwent acid hydrolysis, as expected, to the aminooxy counterpart VI.




Likewise, the condensation of the anion of phenothiazine with I in dimethylformamide afforded 10-[2-(isopropylideneaminooxy)ethyl]phenothiazine (VII) in excellent yield. Alternatively, VII was produced, albeit in only 7% yield, when 10-phenothiazineethanol was treated with sodium in dioxane, ethereal chloramine, and acetone, in that order. The independently prepared samples were found to be identical and served to confirm a normal solvolytic course in the first reaction sequence.[8]

Hydrolysis of VII with 8 *N* aqueous hydrochloric acid resulted in tar formation; if, however, the hydrolysis was effected in 8 *N* hydrochloric acid–ethanol, 10-(2-aminooxyethyl)phenothiazine hydrochloride (VIII) was readily obtained (see Scheme I).

In another set of experiments, exposure of phenothiazine to a refluxing benzene solution of isopropylideneaminooxyacetyl chloride (IX) resulted in the ready evolution of hydrogen chloride and afforded 10-(isopropylideneaminooxyacetyl)phenothiazine (X) in excellent yield. Mild acid hydrolysis of X, which consisted of short reaction times, made it possible to remove the iso-

(1) For paper IV of this series, see E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964); earlier papers of this series are cited in ref. 6.

(2) Department of Chemistry, The Ohio State University, Columbus 10, Ohio.

(3) Ciba Ltd., British Patent 842,968 (Aug. 4, 1960).

(4) D. O. Holland and F. A. Robinson, *J. Chem. Soc.*, 182 (1948).

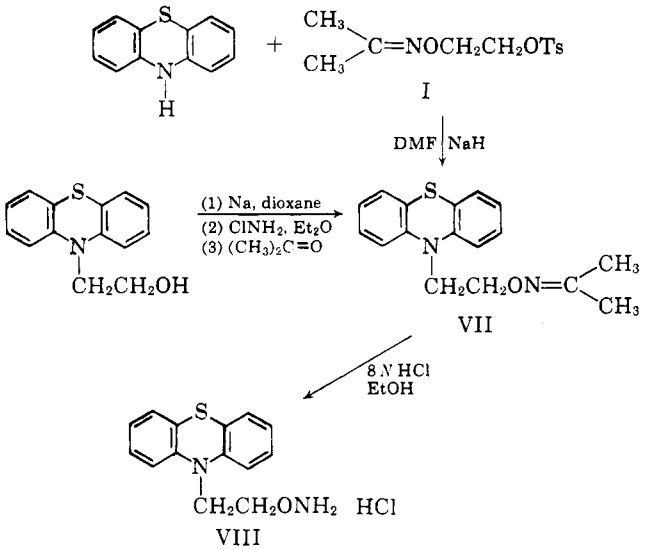
(5) G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4223 (1959).

(6) R. P. Mull, M. E. Egbert, and M. A. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

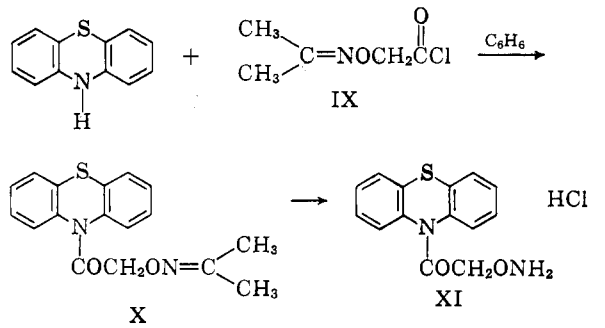
(7) The author is indebted to W. A. Freyburger of these laboratories for these results.

(8) It is worthy of note that VII was not obtained from the condensation of 10-(2-chloroethyl)- or 10-(2-toxyloxyethyl)phenothiazines with sodio acetone oxime.

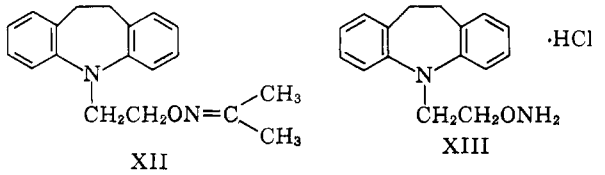
SCHEME I




propylidene blocking group without cleaving the susceptible amide link; 10-(aminooxyacetyl)phenothiazine hydrochloride (XI) was thus readily obtained.




Although the anion of phenothiazine was readily generated at 50–60° with sodium hydride in dimethylformamide, the analogous conversion of dibenzazepine to its anion required a temperature of 140°. Alkylation of I with the dibenzazepine anion afforded 5-[2-(isopropylideneaminooxy)ethyl]dibenzazepine (XII) as a noncrystallizable oil. Hydrolysis of XII in 8 *N* hydrochloric acid–ethanol yielded 5-(2-aminooxyethyl)dibenzazepine hydrochloride (XIII).




The aminooxy derivatives VIII, XI, and XIII proved to be light-sensitive substances and were rapidly converted to violet-colored solids on exposure to light. Attempts to methylate VIII by various procedures were unsuccessful and generally afforded uncharacterizable tarry products.

## Experimental[9]

**O-(2-Hydroxyethyl)acetone Oxime *p*-Toluenesulfonate (I).**—To a rapidly stirred slurry of 75.5 g. (0.644 mole) of O-(2-hydroxyethyl)acetone oxime[5] and 139 g. (0.73 mole) of *p*-toluenesulfonyl chloride cooled to 0° was added dropwise 95 g. (1.20 moles) of pyridine over a 30-min. period. The mixture was stirred an additional 1.5 hr. at 0° after completing the addition and was then poured into 1 l. of water containing crushed ice. After remaining in the refrigerator for 1 hr., the mixture (the organic phase had crystallized) was extracted with three 500-ml. portions of ether. The combined organic phases were washed with 500 ml. of cold, dilute sulfuric acid containing ice chips, 500 ml. of ice–water, 500 ml. of cold, dilute potassium hydroxide containing ice chips, and 500 ml. of ice–water in that order. The ethereal solution was dried, filtered, and evaporated to give 164 g. (94.4%) of a colorless liquid which crystallized, m.p. 34–39°. Four recrystallizations of this material from ether–hexane gave the pure tosylate as white needles, m.p. 39.5–41.0°.

*Anal.* Calcd. for $C_{12}H_{17}NO_4S$: C, 53.11; H, 6.32; N, 5.16. Found: C, 53.18; H, 6.32; N, 5.10.

**N-[2-(Isopropylideneaminooxy)ethyl]hexamethylenimine Hydrochloride (IIa).**—I (5.40 g., 2.0 moles) was dissolved in 496 g. (5.0 moles) of freshly redistilled (b.p. 135–137°) hexamethylenimine with magnetic stirring. After 0.5 hr. a very exothermic reaction commenced which required considerable ice-bath cooling to abate. The mixture was allowed to stand overnight at room temperature. Ether (2 l.) and a slurry of 175 g. (2.08 moles) of sodium bicarbonate in 1. of water was added and, after thorough shaking, the layers were separated. The aqueous phase was extracted with two additional 1-l. portions of ether. The combined ethereal layers were dried, filtered, and evaporated. The residual brown liquid was distilled to give 356 g. (90.0%) of colorless liquid, b.p. 120–125° (14 mm.), $n^{26}D$ 1.4706. A sample of this material was converted to its hydrochloride with ethereal hydrogen chloride to give IIa as fine white platelets from ethanol–ether, m.p. 104–105°.

*Anal.* Calcd. for $C_{11}H_{23}ClN_2O$: C, 56.27; H, 9.87; N, 11.93. Found: C, 56.44; H, 9.75; N, 11.80.

**4-[2-(Isopropylideneaminooxy)ethyl]morpholine Hydrochloride (IIb).**—A 5.4-g. (0.020-mole) sample of I was dissolved in 15 ml. of morpholine and the resulting solution was allowed to stand at room temperature for 4.5 days. The major portion of the morpholine was removed under reduced pressure, and the residue was treated with 50 ml. of ether and 25 ml. of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with two 30-ml. portions of ether. The combined organic layers were dried, filtered, and evaporated. The residual oil was distilled to give 2.80 g. (75.8%) of colorless liquid, b.p. 114–116° (14 mm.), $n^{27.5}D$ 1.4665. The base was converted to its hydrochloride in the usual manner to afford IIb as shiny white plates from ethanol–ether, m.p. 133–134°.

*Anal.* Calcd. for $C_9H_{19}ClN_2O_2$: C, 48.53; H, 8.60; N, 12.58. Found: C, 48.11; H, 8.52; N, 12.69.

**N-[2-(Isopropylideneaminooxy)ethyl]pyrrolidine Hydrochloride (IIc).**[10]—From 815 g. (3.0 moles) of I and 535 g. (7.5 moles) of pyrrolidine, when allowed to react according to the procedure for IIa, there was obtained 425 g. (83.5%) of colorless liquid, b.p. 113–114° (27–28 mm.), $n^{19}D$ 1.4650. A sample of this material was converted to its hydrochloride in the usual manner to yield IIc as white plates from ethanol–ether, m.p. 128–129°.

*Anal.* Calcd. for $C_9H_{19}ClN_2O$: C, 52.29; H, 9.26; Cl, 17.15; N, 13.55. Found: C, 51.96; H, 9.14; Cl, 17.58; N, 13.56.

**N-[2-(Aminooxy)ethyl]hexamethylenimine Dihydrochloride (IIIa).**—A solution of 234.7 g. (1.18 moles) of IIa (as the base) in 500 ml. of water and 500 ml. of concentrated hydrochloric acid was steam distilled for 0.5 hr. The solvent was removed under reduced pressure. Ethanol (200 ml.) was added and also evaporated. The residue was taken up in ethanol and treated with ether. The crystalline material which formed was filtered and dried. There was obtained 269 g. (98.6%) of white solid, m.p. 138–141° dec. Four recrystallizations of this material from ethanol–ether afforded pure IIIa, m.p. 152–154° dec.

*Anal.* Calcd. for $C_8H_{20}Cl_2N_2O$: C, 41.56; H, 8.72; N, 12.12. Found: C, 41.33; H, 8.53; N, 11.96.

A sample of the dihydrochloride was dissolved in water and the solution was made basic with concentrated ammonium hydroxide. After three chloroform extractions, the combined organic layers were dried, filtered, and evaporated. The residual liquid was distilled to give the colorless base, b.p. 115–116° (13 mm.), $n^{25}D$ 1.4850.

(9) Melting points are corrected while boiling points are uncorrected. Infrared spectra supported the assigned structures in all cases. The microanalyses were performed by the Physical and Analytical Chemistry Department of The Upjohn Company.

(10) The author is indebted to L. L. Skaletzky for these data.

**4-[2-(Aminooxy)ethyl]morpholine Dihydrochloride (IIIb).**—Hydrochloric acid hydrolysis of 18.7 g. (0.10 mole) of IIb according to the above procedure yielded 21.5 g. (98.3%) of white solid, m.p. 181–187° (gas evolution). Pure IIIb was obtained as shiny white platelets from aqueous ethanol, m.p. 189–191° (gas evolution).

*Anal.* Calcd. for $C_6H_{16}Cl_2N_2O_2$: C, 32.89; H, 7.36; N, 12.79. Found: C, 32.78; H, 7.25; N, 12.89.

**1-[2-(Aminooxy)ethyl]pyrrolidine Dihydrochloride (IIIc).**[10]—Hydrochloric acid hydrolysis of 425 g. (2.05 moles) of IIc according to the procedure for IIIa gave 470 g. (92.5%) of white solid, m.p. 145–150°. Pure IIIc was obtained as shiny white plates from isopropyl alcohol, m.p. 152–153°.

*Anal.* Calcd. for $C_6H_{16}ClN_2O$: C, 35.48; H, 7.94; N, 13.80. Found: C, 35.24; H, 7.84; N, 13.66.

The free base was obtained by treating the dihydrochloride with an excess of 15 *M* ammonium hydroxide and extracting three times with ether which was dried over magnesium sulfate. The ether was removed and the 1-[2-(aminooxy)ethyl]pyrrolidine was distilled under reduced pressure, b.p. 91.5° (15 mm.).

**1-[2-(Hexahydro-1H-azepin-1-yl)ethoxy]guanidine Hydrogen Sulfate (IVa).**—A solution of 15.8 g. (0.10 mole) of N-[2-(aminooxy)ethyl]hexamethylenimine and 13.9 g. (0.10 mole) and 2-methyl-2-thiopseudourea sulfate in 65 ml. of water was refluxed for 4 hr. The solution was concentrated to one-half of its original volume and treated with an equal volume of ethanol. After cooling, the white crystals were removed by filtration and dried to give 12.8 g. (86.0%) of product, m.p. 215° (with prior sintering at 180°). Three recrystallizations of this material from aqueous ethanol gave pure IVa as white needles, m.p. 255–256°.

*Anal.* Calcd. for $C_9H_{22}N_4O_5S$: C, 36.23; H, 7.43; N, 18.78. Found: C, 36.26; H, 7.49; N, 18.56.

**1-[2-(Pyrrolidinyl)ethoxy]guanidine Hydrogen Sulfate (IVb).**—Treatment of 13.0 g. (0.10 mole) of 1-[2-(aminooxy)ethyl]pyrrolidine according to the above procedure afforded 10.6 g. (78.2%) of product, m.p. 240–243° dec. Three recrystallizations of this material from aqueous ethanol gave pure IVb as clusters of white needles, m.p. 246–247° dec.

*Anal.* Calcd. for $C_7H_{18}N_4O_5S$: C, 31.10; H, 6.71; N, 20.73. Found: C, 31.28; H, 6.50; N, 20.52.

**1-[2-(Isopropylideneaminooxy)ethyl]-2(1H)-pyridone Hydrochloride (V HCl).**—A solution of 11.7 g. (0.10 mole) of 2-pyridone sodium[11] and 27.1 g. (0.10 mole) of I in 150 ml. of absolute ethanol was refluxed for 6 hr. The cooled mixture was filtered to remove the precipitated sodium *p*-toluenesulfonate and the filtrate was concentrated under reduced pressure. The residue was treated with a 1:1 ethanol–ether mixture, filtered, and concentrated. The dark brown residue was distilled *in vacuo* to give 8.2 g. (42.4%) of colorless liquid, b.p. 125–133° (0.25 mm.), $n^{24}D$ 1.5316. The hydrochloride was prepared in the usual manner to give pure V HCl as white beads from ethanol–ether, m.p. 115–116°.

*Anal.* Calcd. for $C_{10}H_{15}ClN_2O_2$: C, 52.06; H, 6.55; N, 12.15. Found: C, 51.96; H, 6.85; N, 12.13.

**1-(2-Aminooxyethyl)-2(1H)-pyridone Hydrochloride (VI).**—When 13.4 g. (0.069 mole) of V HCl was hydrolyzed according to the procedure of IIIa, there was obtained 12.7 g. (97.0%) of white solid, m.p. 186–190° dec. Pure VI was obtained as fluffy white crystals from ethanol–ether, m.p. 197–198° dec.

*Anal.* Calcd. for $C_7H_{11}ClN_2O_2$: C, 44.10; H, 5.82; N, 14.70. Found: C, 44.36; H, 5.86; N, 14.79.

**10-[2-(Isopropylideneaminooxy)ethyl]phenothiazine (VII). A. From Phenothiazine.**—To a stirred suspension of 2.4 g. (0.10 mole) of sodium hydride in 200 ml. of anhydrous purified dimethylformamide, protected by an atmosphere of nitrogen, was added in two portions 19.9 g. (0.10 mole) of phenothiazine. After warming to 50–60° for 2 hr. with stirring, the reaction mixture was cooled in ice and a solution of 27.1 g. (0.10 mole) of I in 50 ml. of dimethylformamide was added dropwise below 10°. The solution was heated at 60–70° for 2 hr. and was stirred overnight at room temperature. The major portion of the solvent was removed under reduced pressure, and the residue was poured into 500 ml. of cold water. The mixture was extracted with three 200-ml. portions of methylene chloride; the combined organic layers were dried, filtered, and evaporated. The resulting brown oil was chromatographed on Woelm neutral alumina [elution with hexane–acetone (19:1)] and 26.3 g. (88.3%) of pale yellow crystals, m.p. 66–67°, resulted. Recrystallization from hexane afforded pure VII as fine white needles, m.p. 68–69°.

*Anal.* Calcd. for $C_{17}H_{16}N_2OS$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.13; H, 5.80; N, 9.24; S, 10.79.

**B. From 10-Phenothiazineethanol.**—A solution of 60.8 g. (0.25 mole) of 10-phenothiazineethanol[12] in 250 ml. of anhydrous purified dioxane was treated with 5.75 g. (0.25 g.-atom) of sodium metal, and the mixture was heated under reflux with stirring until the sodium had dissolved (about 4 hr.). After the solution had cooled to room temperature, 250 ml. of a cold (−50 to −40°) ether solution containing approximately 0.25 mole of chloramine[13] was added in several portions. After the addition was completed, the mixture was cooled in ice to prevent the ether from boiling. After 10 min., the ice bath was removed, and the reaction mixture was stirred overnight at room temperature. The deep purple mixture was filtered and the major portion of the solvent mixture was removed under reduced pressure. The residue was treated with 500 ml. of anhydrous ether, and the mixture was refiltered. The filtrate was treated with a slight excess of ethanolic hydrogen chloride. After several minutes, the supernatant liquid was decanted from the black oil which had separated. The black oil was treated with 600 ml. of 20% sodium hydroxide solution, and the aqueous phase was extracted with three 300-ml. portions of methylene chloride. The combined organic layers were washed with 300 ml. of water, dried, filtered, and evaporated to give a very dark gum. This material was chromatographed on Florisil[14] (elution with hexane–acetone, 19:1) and yielded 5.55 g. (7.45%) of a light orange solid, m.p. 64.5–66°. Recrystallization of this material from hexane gave fine, white needles, m.p. 67–68°, identical in all respects with the sample prepared in A.

**10-(2-Aminooxyethyl)phenothiazine Hydrochloride (VIII).**—A mixture of 6.0 g. (0.020 mole) of VII, 75 ml. of 8 *N* hydrochloric acid, and 50 ml. of ethanol was heated under reflux until solution was effected (about 3 hr.). The solution was steam distilled for 1 hr., then evaporated to dryness. The purple gummy solid was taken up in alcohol and filtered through charcoal; the filtrate was treated with ether and cooled. The white solid was separated by filtration and dried to give 3.75 g. (63.5%) of the hydrochloride, m.p. 158° dec. Pure VIII was obtained as shiny white platelets from ethanol–ether, m.p. 161° dec. The product turned light violet on exposure to light and air.

*Anal.* Calcd. for $C_{14}H_{15}ClN_2OS$: C, 57.03; H, 5.13; N, 9.50. Found: C, 57.06; H, 4.96; N, 9.41.

**10-Isopropylideneaminooxyacetylphenothiazine (X).**—To a hot mixture of 10.0 g. (0.050 mole) of practical grade phenothiazine in 50 ml. of sodium-dried benzene was added, in one portion, a solution of 7.5 g. (0.050 mole) of isopropylideneaminooxyacetyl chloride (IX)[15] in 20 ml. of sodium-dried benzene. The solution was heated under reflux for 2 hr. The solvent was evaporated under reduced pressure and the residual oil was treated with 40 ml. of absolute ethanol and cooled. The pale yellow solid which formed was separated by filtration and dried to yield 14.2 g. (91.1%) of product, m.p. 115–116°. Three recrystallizations of this material from absolute ethanol gave analytically pure X as colorless plates, m.p. 115–116°.

*Anal.* Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.42; H, 5.26; N, 8.62.

**10-(Aminooxyacetyl)phenothiazine Hydrochloride (XI).**[16]—A mixture of 3.1 g. (0.01 mole) of X, 20 ml. of water, 25 ml. of acetic acid, and 1.0 ml. (0.012 mole) of concentrated hydrochloric acid was heated on the steam bath for 15 min., then evaporated to dryness under reduced pressure. Recrystallization of the solid residue from 95% ethanol–ether gave 1.1 g. (35%) of pure product which decomposed at 198°.

*Anal.* Calcd. for $C_{14}H_{13}ClN_2O_2S$: C, 54.45; H, 4.24; Cl, 11.48; N, 9.07; S, 10.38. Found: C, 54.40; H, 4.18; Cl, 11.64; N, 8.88; S, 10.73.

**5-[2-(Isopropylideneaminooxy)ethyl]dibenzazepine (XII).**—To a stirred suspension of 2.4 g. (0.10 mole) of sodium hydride in 200 ml. of anhydrous purified dimethylformamide protected by an atmosphere of nitrogen was added 19.5 g. (0.10 mole) of dibenz-

(11) C. Rath, *Ann.*, **489**, 107 (1931).

(12) R. Dahlbom, *Acta Chem. Scand.*, **6**, 310 (1952).

(13) G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1939). The author is indebted to D. B. Hooker for preparing the chloramine.

(14) Florisil is a magnesia silica gel adsorbent manufactured by the Floridin Co., Tallahassee, Fla.

(15) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. DaVanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962).

(16) The author is indebted to E. L. Schumann for these data.

azepine.[17] The mixture was refluxed with stirring for 1 hr. and then cooled in ice while a solution of 27.1 g. (0.10 mole) of I in 50 ml. of dimethylformamide was added dropwise below 10°. The solution was stirred at 60–70° for 2 hr. and allowed to stand overnight at room temperature. The major portion of the solvent was removed under reduced pressure and the residue was poured into 500 ml. of cold water. The insoluble material was extracted with three 200-ml. portions of methylene chloride; the combined organic layers were dried, filtered, and evaporated. The resulting dark oil was chromatographed on Woelm neutral alumina (elution with hexane) to give 17.85 g. (60.7%) of XII as a colorless, noncrystallizable oil.

(17) W. Schindler and F. Hafliger, U. S. Patent 2,764,580 (Sept. 25, 1956).

**5-(2-Aminooxyethyl)dibenzazepine Hydrochloride (XIII).**—A mixture of 17.7 g. (0.060 mole) of XII, 75 ml. of 8 *N* hydrochloric acid, and 75 ml. of ethanol was refluxed for 1 hr. and steam distilled for 1 hr. The solution was concentrated under reduced pressure and the dark residue was dissolved in ethanol. The ethanolic solution was filtered through a pad of charcoal, and the almost colorless filtrate was treated with ether and cooled. The crystalline product was filtered and dried to give 11.4 g. (65.5%) of off-white solid, m.p. 184.5–187° dec. Three recrystallizations of this material from ethanol–ether afforded pure XIII as shiny, white platelets, m.p. 188–189° dec.

*Anal.* Calcd. for $C_{16}H_{19}ClN_2O$: C, 66.08; H, 6.59; N, 9.64. Found: C, 65.93; H, 6.60; N, 9.48.

# The Reaction between β-Keto Esters and Arylamines in the Presence of Polyphosphoric Acid. II.[1] Ethyl Acetoacetate and Its α-Alkyl Derivatives and Arylamines

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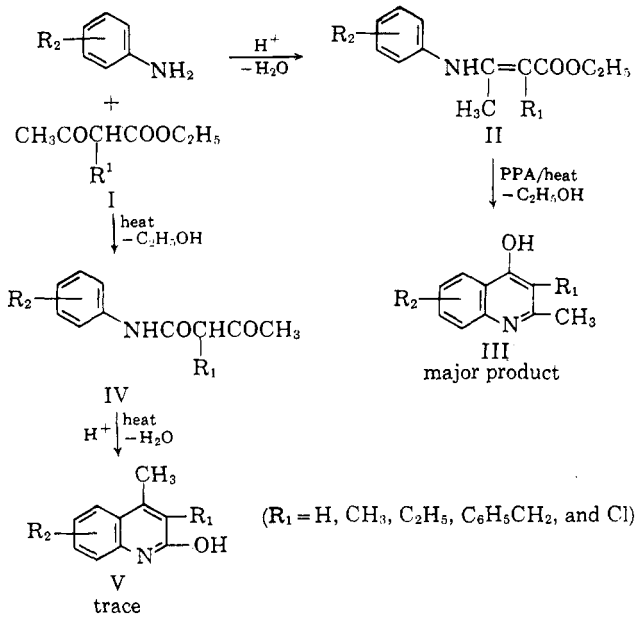
4-Hydroxyquinaldines have been synthesized directly from ethyl acetoacetate, or its α-alkyl derivatives and arylamines using polyphosphoric acid. The intermediate acetoacetanilides and ethyl β-arylaminocrotonates have been prepared and cyclized to hydroxyquinolines with polyphosphoric acid. The isomeric 5- and 7-substituted 4-hydroxyquinaldines derived from *meta*-substituted arylamines have been separated.

Recently the first direct synthesis of 4-hydroxy- and 2-hydroxyquinolines by the Conrad–Limpach[2] and Knorr[3] reactions, respectively, from arylamines and ethyl benzoylacetate has been effected using polyphosphoric acid (PPA).[1a]

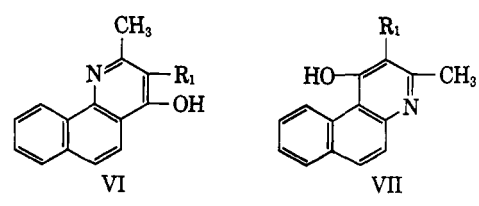
The condensation of a variety of arylamines with a number of other β-keto esters I in the presence of polyphosphoric acid has now led to the preparation of 4-hydroxyquinaldines III, the yields of which were generally higher than those obtained by the two-stage Conrad–Limpach reaction. Small amounts of the isomeric 2-hydroxylepidines V were isolated in some instances. The intermediate ethyl β-arylaminocrotonates II were not isolated. Cyclization of the crotonates with polyphosphoric acid gave higher yields of III than when heated in Dowtherm.




(R1 = H, $CH_3$, $C_2H_5$, $C_6H_5CH_2$, and Cl)

4-Nitroarylamines condensed readily with β-keto esters in the presence of polyphosphoric acid to give high yields of the 6-nitro-4-hydroxyquinaldines, the structures of which were proved by their reduction and deamination to the corresponding 4-hydroxyquinaldines. Arylamines containing a nitro group *ortho* or *meta* to the amino group, even in the presence of activating methoxy, or methyl groups in the molecule, failed to condense with β-keto esters in the presence of polyphosphoric acid.

The 1- and 2-naphthylamines reacted with β-keto esters to give the corresponding 4-hydroxy-7:8-benzoquinaldines VI and 4-hydroxy-5:6-benzoquinaldines VII, respectively.




(R1 = H, $CH_3$, and $C_2H_5$)

Mixtures of the isomeric 5- and 7-substituted 4-hydroxyquinaldines were formed when *meta*-substituted arylamines were used. The proportions of the 5- and 7-isomers were found to depend on the nature of the *meta* substituent. When the latter was a methoxy group the 7-isomer predominated, while with a methyl,

(1) (a) Part I: B. Staskun and S. S. Israelstam, *J. Org. Chem.*, **26**, 3191 (1961); (b) A. K. Mallams and S. S. Israelstam, *Chem. Ind.* (London), 952 (1963).

(2) M. Conrad and L. Limpach, *Ber.*, **20**, 944 (1887); **21**, 523, 1649 (1888); **24**, 2990 (1891).

(3) L. Knorr, *Ann.*, **236**, 69 (1886); *Ber.*, **17**, 540 (1884).