addition of 10 ml. of ether, the solution was set aside in a refrigerator overnight. In this manner, there was obtained 52 mg. (74%) of material melting at 236–238°. Recrystallization from the same solvent mixture gave pure cytosine nucleoside **7**, m.p. 239–240°, $[\alpha]^{24}D$ +43.4° (*c* 0.43, water), λ_{max}^{MeOH} 271 mμ (log ε 4.01), ν_{max}^{KBr} 1650 cm.$^{-1}$ (>C=O).

Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.60; H, 5.67; N, 16.19.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl)uracil (9).—To a solution of 340 mg. (0.46 mmole) of the protected nucleoside **5** in 20 ml. of dichloromethane was added 20 ml. of absolute methanol saturated with hydrogen chloride. The solution was kept overnight at room temperature, and the solvent was evaporated under diminished pressure at 40°. The residue was recrystallized from ethanol–dichloromethane to give 265 mg. (81%) of pure **9**,[14] m.p. 329–330°.

Anal. Calcd. for $C_{31}H_{23}N_5O_{15}$: C, 52.76; H, 3.29; N, 9.93. Found: C, 52.64; H, 3.41; N, 9.68.

1-(2-Deoxy-β-D-*ribo*-hexopyranosyl)uracil (11).—A suspension of 250 mg. (0.35 mmole) of the de-ethylated nucleoside **9** in 20 ml. of 0.01 *N* methanolic sodium methoxide was stirred overnight at room temperature. The solution was made neutral by the addition of 0.05 ml. of glacial acetic acid, and the solvent was evaporated at 40° under diminished pressure. The residue was dissolved in water, and the solution was extracted thoroughly with ether. The aqueous layer was stirred for 10 min. with a little Darco G-60 and 2 g. of Rexyn 300 (H-OH) ion-exchange resin,[12] filtered, and evaporated under diminished pressure at 45°. The syrupy material was re-evaporated four times with 10-ml. portions of absolute ethanol, giving 75 mg. (81%) of product melting at 105–110°. Attempted crystallization from 2-propanol gave pure **11** as semiamorphous material: m.p. 110–112°, $[\alpha]^{24}D$ +28.3° (*c* 1.0, water), λ_{max}^{MeOH} 261 mμ (log ε 3.9), ν_{max}^{KBr} 1710 (–NHCO–) and 1680 cm.$^{-1}$ (–NCONH–).

Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.61; H, 5.42; H, 10.74.

Acknowledgment.—The authors thank Drs. G. E. Boxer and M. Zimmerman, Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey, for their valued assistance with the inhibition tests. They are grateful to Dr. T. L. V. Ulbricht, Twyford Laboratories, London, England, for his kindness in carrying out the O.R.D. studies. They thank also Miss Paula M. Parisius, Microanalytic Laboratory (under the direction of Dr. W. C. Alford), Laboratory of Chemistry, National Institutes of Health, Bethesda, Maryland, for the combustion analyses.

(14) The material has an extremely low solubility in the usual organic solvents, including nitromethane; hence, its optical rotation was not determined.

Quinazolines and 1,4-Benzodiazepines. XXVI.[1] 1,2-Dihydroquinazoline 3-Oxides

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Our interest in 2-aminobenzophenone oximes[2] and their transformations led to the finding that the *anti* isomer[3] of 2-amino-5-chlorobenzophenone oxime III would condense with acetone to form the beautiful, crystalline, yellow 1,2-dihydroquinazoline 3-oxide (II).[5] Its infrared spectrum contains a sharp band at 3390 cm.$^{-1}$ attributable to the NH stretching vibration. Its ultraviolet spectrum shows bands at λ_{max} 237 mμ (ε 24,000), 255 (sh) (18,000), 305 (7500), and 390 (4000). This spectrum is strikingly similar to that of the nitrone[6a] IX which has a band at λ_{max} 233 mμ (ε 21,000), 259 (14,000), and 307 (10,000), and does not resemble that of the oxime III.[6b]

Chemical transformations were also consistent with structure II. Methylation of II yielded a monomethyl derivative which was identical with the product obtained by the reaction of the crude *anti*-oxime V with acetone. This proved that methylation had occurred at position 1 and that the product had structure VI. Comparison of the ultraviolet spectra of II and VI showed, furthermore, that no fundamental structural changes had occurred during the methylation. The N-oxide character of the oxygen in II was demonstrated by its removal with phosphorus trichloride[7] to give VII. The 1,2-dihydroquinazoline VII could be reduced with sodium borohydride to form the tetrahydroquinazoline derivative X which was obtained as the crystalline hydrochloride. The same hydrochloride was also obtained by condensing 2-amino-5-chlorobenzhydrylamine XI with acetone followed by salt formation. Oxidation of the analog IV, formed similarly from the oxime III and acetaldehyde, gave the known 2-methylquinazoline 3-oxide VIII.[2a] Further investigation of the formation of II showed that it was formed only from the *anti*-oxime III.[8] Heating solutions of the *syn* isomer I in acetone with or without an acidic catalyst resulted in the formation of only traces of dihydroquinazoline II. However, it was found that II could be formed in high yield from the *syn*-oxime I, if a trace of cupric sulfate was added to the reaction mixture. Since it has been observed that cupric ion will accelerate the isomerization of oximes of phenyl 2-pyridyl

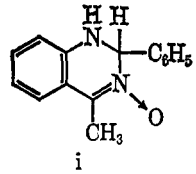
(1) Paper XXV: L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, **8**, 815 (1965).

(2) (a) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960); (b) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); (c) J. G. Pritchard, G. F. Field, K. Koch, G. Reymond, L. H. Sternbach, V. Toome, and S. Traiman, unpublished results.

(3) The *anti* isomer is defined as that isomer in which the hydroxyl group is *anti* to the phenyl ring bearing the 2-amino group. See also ref. 2a, footnote 9, and ref. 4, footnote 19.

(4) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

(5) (a) This compound was first prepared by Mr. C. Mason. (b) M. Busch, F. Straetz, P. Unger, R. Reichold, and B. Eckardt [*J. prakt. Chem.*, **150**, 1 (1937)] have observed that the treatment of 2-aminoacetophenone oxime with benzaldehyde yielded a condensation product to which they assigned structure i, since it could be nitrosated to



i

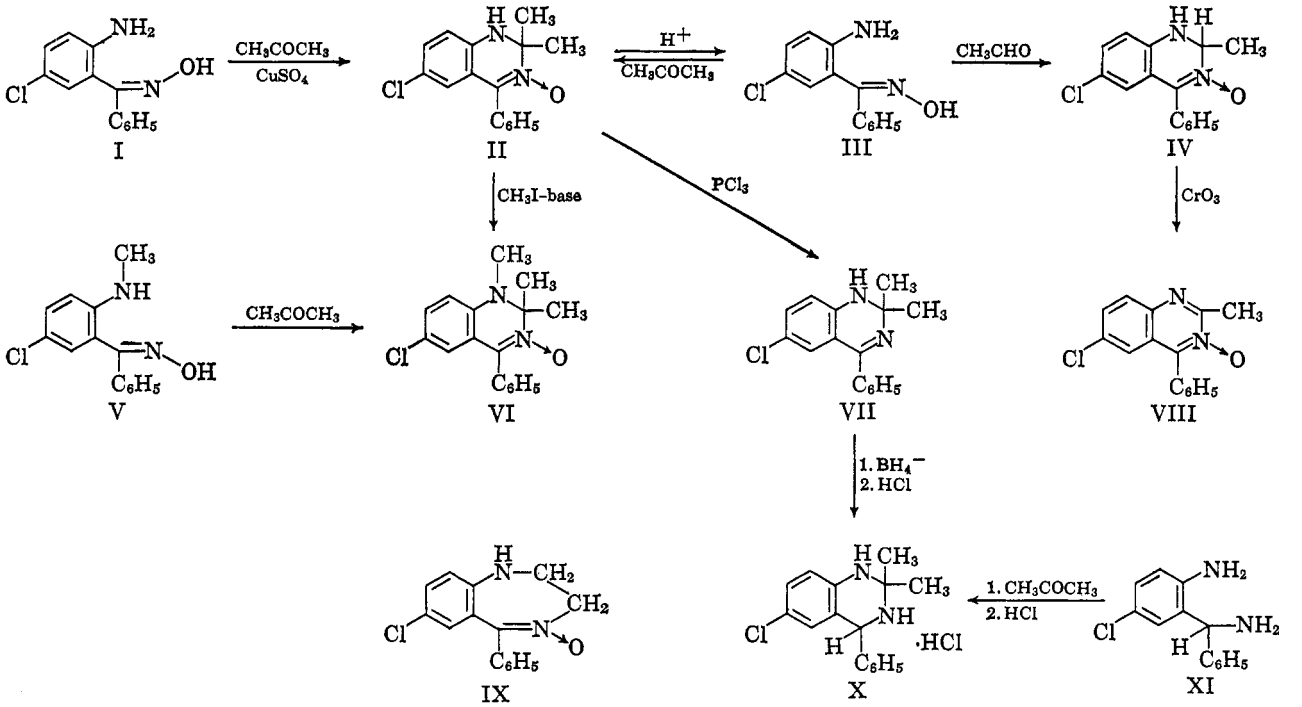
yield a mononitroso derivative. (c) Since the completion of our work, a paper [A. Kövendi and M. Kircz, *Chem. Ber.*, **98**, 1049 (1965)] has appeared in which a number of condensation products of 2-aminoacetophenone oxime with various aldehydes was described. The 1,2-dihydroquinazoline 3-oxide structure of these products was substantiated by oxidation to the corresponding quinazoline 3-oxides of known structure.

(6) (a) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **28**, 2459 (1963). See also, M. S. Kamlet and L. A. Kaplan, *ibid.*, **22**, 576 (1957), for discussion of the ultraviolet spectra of phenyl-substituted nitrones. (b) S. C. Bell, G. L. Conklin, and S. J. Childress, *ibid.*, **29**, 2368 (1964).

(7) E. Ochiai, *ibid.*, **18**, 353 (1953); J. Hammer and A. Macaluso, *Chem. Rev.*, **64**, 491 (1964).

(8) The possibility that hydroxylamine was transferred from the benzophenone oxime to acetone prior to ring closure was eliminated when treatment of acetone oxime and 2-amino-5-chlorobenzophenone in acetone solution under identical conditions failed to yield any II.

CHART I



ketone,[9] the catalytic effect of cupric ion is probably due to a similar effect in our case. Thus 1,2-dihydroquinazoline 3-oxides similar to II become readily accessible from the mixture of isomers formed in the oximation of 2-aminobenzophenones.

Hydrolysis of II with 3 *N* hydrochloric acid at room temperature gave the *anti* isomer of 2-amino-5-chlorobenzophenone oxime III. This reaction, in conjunction with the formation of II from the *syn* isomer using a cupric sulfate catalyst, provides a very convenient method for the preparation of the thermodynamically less stable *anti* isomer III which, in the normal oximation, is obtained as the minor reaction product.[10] We have extended this conversion to other 2-aminobenzophenone oximes, such as the 2-amino-5-nitrobenzophenone oxime[11] and 2-amino-5-trifluoromethylbenzophenone oxime.[4]

Experimental Section[12]

6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-Oxide (II). A. From 2-Amino-5-chlorobenzophenone *anti*-Oxime (III).—A solution of 10 g. (40.5 mmoles) of crude 2-amino-5-chlorobenzophenone *anti*-oxime (III)[13] in 100 ml. of acetone containing 2 drops of glacial acetic acid was heated under reflux for 20 min. The reaction mixture was cooled to 0° and 7.3 g. (63%) of a yellow solid was collected by filtration, m.p 220–228° dec.

An analytical sample was obtained as yellow rods, m.p. 221–222° from methylene chloride–acetone.

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27. Found: C, 67.27; H, 5.35.

B. From 2-Amino-5-chlorobenzophenone *syn*-Oxime (I).—A mixture of 10 g. (40.5 mmoles) of the *syn*-oxime of 2-amino-5-chlorobenzophenone (I), 100 ml. of acetone, and 0.5 g. of finely ground cupric sulfate pentahydrate was heated under reflux for 2 hr. The mixture containing the crystalline precipitated reaction product was cooled to room temperature and the product was isolated by filtration. It was suspended in 75 ml. of water, filtered, and washed with water to remove copper sulfate. The yield was 9.7 g (80%) of yellow prisms, m.p. 200–220°. Under the same conditions, rather crude mixtures of the *syn*- and *anti*-oximes gave comparable yields. From analogous reactions in which the copper sulfate was omitted or replaced with acetic acid or sulfuric acid, the starting oxime I could be recovered in approximately 70% yield.

1,2-Dihydro-2,2-dimethyl-4-phenylquinazoline 3-Oxide.—This compound was obtained by a procedure similar to the one described above in 37% crude yield, m.p. 192–197°, and recrystallized from acetone to give pale yellow prisms, m.p. 206–208.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.35; H, 6.06.

1,2-Dihydro-2,2-dimethyl-6-nitro-4-phenylquinazoline 3-Oxide.—This compound was obtained similarly in 73% yield, and recrystallized from acetone to give yellow prisms, m.p. 200–205°.

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09. Found: C, 64.78; H, 5.10.

1,2-Dihydro-2,2-dimethyl-4-phenyl-6-trifluoromethylquinazoline 3-Oxide.—This compound was obtained as above and recrystallized from isopropyl alcohol to give yellow needles, m.p. 224–226°.

Anal. Calcd. for $C_{17}H_{15}F_3N_2O$: C, 63.74; H, 4.73; Found: C, 63.61; H, 4.90.

6-Chloro-1,2-dihydro-1,2,2-trimethyl-4-phenylquinazoline 3-Oxide (VI). A. From 5-Chloro-2-methylaminobenzophenone Oxime (V).—A mixture of 10 g. of 5-chloro-2-methylaminobenzophenone oxime (mixture of isomers),[2c] 0.1 g. of cupric sulfate pentahydrate, 100 ml. of acetone, and 100 ml. of chloro-

(9) E. G. Vassian and R. K. Murmann, *J. Org. Chem.*, **27**, 4309 (1962).

(10) An alternative conversion of the *syn* isomer I to the *anti* isomer III by refluxing the former with formic acid followed by alkaline hydrolysis of the quinazoline 3-oxide which is formed is considerably more difficult to perform. See K. v. Auwers and O. Jordan, *Ber.*, **57**, 800 (1924), and ref. 2a.

(11) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(12) All melting points are corrected. The infrared and ultraviolet absorption spectra of the compounds described were determined to establish structural changes. Identity was proved by mixture melting point and comparison of infrared spectra. The ultraviolet spectra were determined in isopropyl alcohol using a Cary Model 14 spectrophotometer. The n.m.r. spectra were determined using a Varian A-60 instrument. Alumina refers to Woelm alumina, activity I, and petroleum ether to a fraction of b.p. 40–60°.

(13) The ultraviolet and n.m.r. spectra indicated that the starting *anti*-oxime contained approximately 30% of the *syn* isomer. This material was obtained from the crude oximation mixture of 2-amino-5-chlorobenzophenone (*cf.* ref. 2a). The *syn*-oxime was removed by crystallization from ethanol and the material remaining in the mother liquors was recrystallized repeatedly from benzene to yield the material used in this experiment.

form was refluxed overnight while the condensate was passed through a Soxhlet extractor containing anhydrous sodium sulfate. The cupric sulfate was removed by filtration and the solvents were evaporated *in vacuo*. The residue was crystallized from ethyl acetate. Recrystallization from petroleum ether and from ethanol–water gave an analytical sample as yellow rods of m.p. 115–116°; λ_{max} 237 mμ (ε 20,000), 255 (sh) (17,000), 311 (6500), and 390 (5500).

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70. Found: C, 67.80; H, 5.67.

B. From 6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-Oxide (II).—A suspension of 114.8 g. (0.4 mole) of 6-chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide (II) in 3.5 l. of dry tetrahydrofuran was cooled to 5° with an ice bath, and 50 g. of potassium *t*-butoxide was added; the stirring and cooling were continued for 15 min. and then the mixture was filtered through Celite. The filtrate was concentrated *in vacuo*, and the residue was crystallized from hexane to give 53 g. (44%) of crude product, m.p. 105–108°. Recrystallization from ethanol–water and then from cyclohexane gave 37.5 g., m.p. 109–112°.

6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline (VII).—To a solution of 5 g. (17.4 mmoles) of II in 100 ml. of chloroform was added 2 ml. (23 mmoles) of phosphorus trichloride diluted with 20 ml. of chloroform. The mixture was heated under reflux for 30 min. and poured into 100 ml. of 1.2 *N* sodium hydroxide. The chloroform phase was separated, washed with 50 ml. of 10% sodium bicarbonate solution and 50 ml. of brine, and dried over sodium sulfate. This solution was filtered through 50 g. of alumina and the alumina was washed with 100 ml. of methylene chloride. The eluate was concentrated *in vacuo* and the residue was crystallized from hexane to give 2.5 g. (53%) of the product melting at 140–144°. An analytical sample, prepared by repeated crystallization from ethanol–water and from hexane–ether, formed yellow needles, m.p. 142–144.5°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: C, 70.60; H, 5.58. Found: C, 70.72, H, 5.89.

6-Chloro-1,2,3,4-tetrahydro-2,2-dimethyl-4-phenylquinazoline Hydrochloride (X). A. From 6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline (VII).—To a solution of 5 g. (18.5 mmoles) of VII in 400 ml. of methanol, cooled with an ice bath, was added 2.5 g. of sodium borohydride. The cold mixture was stirred for 6 hr., neutralized with acetic acid, and concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of methylene chloride; the solution was washed with 100 ml. of water and dried over sodium sulfate. Concentration *in vacuo* left 5.34 g. of a pale yellow oil which had an infrared spectrum identical with that obtained in B. A solution of 2.73 g. of this oil in 10 ml. of methanol was treated with 1 ml. of 10 *N* methanolic hydrogen chloride and 80 ml. of ether. This procedure gave 1.9 g. of product, m.p. 220–240° dec.

B. From 2-Amino-5-chlorobenzhydrylamine (XI).[14]—A solution of 20 g. of 2-amino-5-chlorobenzhydrylamine (made from the corresponding dihydrochloride[15]) in 200 ml. of acetone containing 5 drops of glacial acetic acid was refluxed for 8 hr., and then it was evaporated *in vacuo*. The residue was extracted with hot hexane, which was filtered and evaporated to give 23 g. of an orange oil. This oil was dissolved in the calculated amount of 1 *N* methanolic hydrogen chloride and diluted with ether to give 24.2 (91%) of orange crystalline monohydrochloride, m.p. 225–230°. Additional crystallizations from methanol–acetone gave bright yellow rhombs, m.p. 230–243°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2$: C, 62.14; H, 5.86; Cl, 22.93. Found: C, 62.09; H, 5.88; Cl, 22.73.

6-Chloro-1,2-dihydro-2-methyl-4-phenylquinazoline 3-Oxide (IV).—A solution of 50 g. of crude 2-amino-5-chlorobenzophenone *anti*-oxime[16] in 250 ml. of methanol was cooled with an ice bath to 5°. To this solution was added 5 ml. of acetic acid and 20 ml. of acetaldehyde (exothermic reaction). The mixture was filtered after standing in the ice bath for 1 hr. The precipitate was collected and recrystallized from isopropyl alcohol–water to give 16.6 g. (30%) of product, m.p. 170–174°. An analytical sample prepared by three recrystallizations from isopropyl alcohol formed yellow needles and melted at 174–176°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80. Found: C, 66.42; H, 4.98.

(14) This experiment was performed by Dr. G. A. Archer.

(15) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1961 (1962).

6-Chloro-2-methyl-4-phenylquinazoline 3-Oxide (VIII).—To a solution of 0.36 g. (1.2 mmoles) of sodium dichromate dihydrate in 10 ml. of acetic acid was added 1 g. (3.66 mmoles) of the dihydroquinazoline IV. The solution, which turned green immediately, was diluted in 100 ml. of methylene chloride and filtered through 25 g. of alumina. The residue, obtained after evaporation of the methylene chloride, was crystallized from ether–petroleum ether to yield 0.65 g. (60%) of VIII, m.p. 154–156° (sintering at 145°).[2a]

Attempted Reaction of Acetone Oxime with 2-Amino-5-chlorobenzophenone.—A solution of 10 g. (43.2 mmoles) of 2-amino-5-chlorobenzophenone and 5 g. of acetone oxime in 100 ml. of acetone and 0.5 ml. of acetic acid was heated under reflux for 3.5 hr. Thin layer chromatography of the reaction mixture on silica gel G plates developed with 5% methanol in chloroform indicated that no dihydroquinazoline (II) was present.

Hydrolysis of 6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-Oxide (II) to 2-Amino-5-chlorobenzophenone *anti*-oxime (III).—A suspension of 10 g. of II in 100 ml. of 3 *N* hydrochloric acid was stirred at room temperature for 2 hr. The white solid was separated by filtration and resuspended in 100 ml. of water. This suspension was neutralized with solid sodium carbonate and filtered. The solid was washed with 100 ml. of water and recrystallized from benzene to give 6.9 g. (80%) of crude 2-amino-5-chlorobenzophenone *anti*-oxime, m.p. 120–129°. A solution of 2 g. of the crude oxime in 100 ml. of ether was washed with 50 ml. of 10% sodium bicarbonate solution, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from benzene to give 1.3 g. of pure III, m.p. 129–132.5°. This product was identical with the *anti*- (β-) oxime described in the literature.[2a] By this process, 1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide gave a 53% yield of 2-aminobenzophenone *anti*-oxime[16] and 6-trifluoromethyl-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide gave a 40% yield of 2-amino-5-trifluoromethylbenzophenone *anti*-oxime.[4]

2-Amino-5-nitrobenzophenone *anti*-Oxime from 1,2-Dihydro-2,2-dimethyl-6-nitro-4-phenylquinazoline 3-Oxide.—To a solution of 5.0 g. of 1,2-dihydro-2,2-dimethyl-6-nitro-4-phenylquinazoline 3-oxide in 100 ml. of boiling ethanol was added 2 ml. of concentrated hydrochloric acid, the mixture was refluxed for 5 min., and 100 ml. of cold water was added. After the mixture had stood for *ca.* 30 min., the precipitate was collected and washed with 50 ml. of water in two portions. Recrystallization from aqueous ethanol gave 2.3 g. (53%) of product, m.p. 200–203° (depressed on admixture of the *syn* isomer). After recrystallization from ethanol the oxime formed orange prisms, m.p. 197–203° dec.[2c]

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.72; H, 4.28. Found: C, 61.04; H, 4.27.

Acknowledgment.—We thank Dr. A. Steyermark, Mr. S. Traiman, Dr. V. Toome, and Dr. E. Billeter, respectively, for the microanalyses, the infrared spectra, the ultraviolet spectra, and the n.m.r. spectra. We also thank Mr. T. Flynn and Mr. R. DiMaio for their skillful technical assistance.

(16) K. v. Auwers and F. v. Meyerburg, *Ber.*, **24**, 2303, 2305, 2370 (1891).

Alkylation of Benzophenone with Aminoalkyl Halides in Liquid Ammonia

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Schlenk and Weikel[1] showed in 1911 that benzophenone forms a disodio derivative in ether and that

(1) W. Schlenk and T. Weikel, *Chem. Ber.*, **44**, 1182 (1911).