2-Amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucopyranose (VII).—1,6:2,3-Dianhydro-4-*O*-methyl-β-D-mannopyranose (0.1 g.) was sealed in a glass tube with 5.0-ml. of concentrated ammonium hydroxide. The ampoule was heated in a steam bath for 30 hr. Evaporation of the aqueous ammonia at reduced pressure left a residue of 0.1 g. which crystallized. Recrystallization from isopropyl alcohol gave 0.076 g. (68%), m.p. 160–161°, $[\alpha]^{20}D$ −69.6° (*c* 1.2, methanol).

Anal. Calcd. for $C_7H_{13}NO_4$: C, 48.0; H, 7.43; N, 8.0. Found: C, 48.26; H, 7.46; N, 8.20.

2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose (IX).—2-Amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucopyranose (0.45 g.) was refluxed with 25 ml. of 10% hydrochloric acid for 48 hr. The reaction mixture was filtered through a layer of Celite and decolorizing carbon. The colorless filtrate was evaporated under reduced pressure to give 0.57 g. of residue. The residue was dissolved in 6 ml. of anhydrous methanol containing 0.06 g. of sodium. The salt that separated was removed by filtration. To the filtrate was added 0.31 g. of acetic anhydride (1.2 equiv.) with stirring. After standing at room temperature for 40 hr. the reaction mixture was evaporated at 50° at reduced pressure. The residue (0.7 g.) was dissolved in methanol. Ether was added to turbidity. About 0.2 g. of crystalline material separated on standing which had m.p. 209–212° dec. after a second recrystallization.

The mother liquor from the crystallization (0.5 g.) was chromatographed on a column of silicic acid. An additional 34 mg. of IX was separated which, after recrystallization from methanol–ether, had m.p. 218–219° dec. The compound showed mutarotation from $[\alpha]^{20}D$ +83° to $[\alpha]^{20}D$ +70° (after 16 min.) to $[\alpha]^{20}D$ +47° (after 24 hr. in water, *c* 0.85).[17]

Anal. Calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.95. Found: C, 45.81; H, 7.13; N, 6.05.

Also isolated from the column chromatography was 10 mg. of crystals which, after recrystallization from methanol–ether, had m.p. 207–209°. The mixture melting point with authentic 2-acetamido-2-deoxy-D-glucopyranose[18] was not lowered.

Acknowledgment.—The author thanks Dr. Roger W. Jeanloz for the infrared spectra of 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose.

(17) Jeanloz and Gansser[9] reported m.p. 211–215° dec. and mutarotation from $[\alpha]^{24}D$ +79° (after 16 min.) to $[\alpha]^{22}D$ +69° (after 24 hr.) (*c* 1.02, water).

(18) Y. Inonye, K. Onodera, S. Kitaoka, and S. Hirano, *J. Am. Chem. Soc.*, **78**, 4722 (1956).

2-Deoxy Sugars. XI. Additional Pyrimidine Nucleosides Containing 2-Deoxy-D-*arabino*-hexopyranose and 2-Deoxy-D-*ribo*-hexopyranose[1]

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The discovery[3] that 1-(2-deoxy-β-D-*arabino*-hexopyranosyl)thymine ("2-deoxyglucosylthymine")[4] is a powerful and specific inhibitor of a pyrimidine nucleoside phosphorylase, obtained from Ehrlich's ascites tumor cells, prompted us to investigate the preparation of additional pyrimidine nucleosides containing 2-deoxyhexoses.

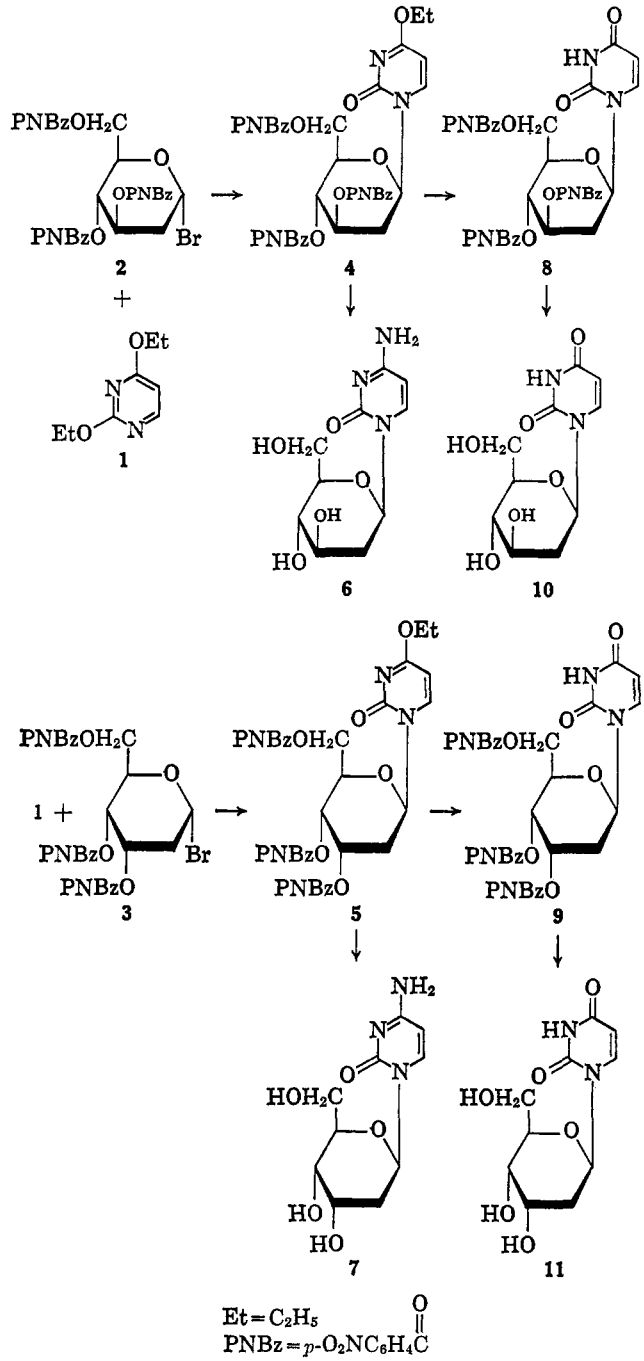
(1) Presented before the Division of Carbohydrate Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965. This work was supported in part by U. S. Public Health Service Grant No. CA07514, from the National Cancer Institute.

(2) (a) Predoctoral research assistant. (b) Postdoctoral research associate, Georgetown University, 1963–1965.

(3) P. Langen and G. Etzold, *Biochem. Z.*, **339**, 190 (1963).

(4) W. W. Zorbach and G. J. Durr, *J. Org. Chem.*, **27**, 1474 (1962).

SCHEME I



The presently described study provides for a further extension of our work dealing with the direct synthesis of 2-deoxyglycosides employing stable, crystalline 2-deoxy-*O*-*p*-nitrobenzoylglycosyl halides. An added advantage of this methodology, adequately demonstrated in the present study, is that nitrobenzoylation has conferred crystalline character on *all* nucleoside intermediates[5] which could, therefore be characterized by elemental analysis.

The coupling (see Scheme I) of 2,4-diethoxypyrimidine (1) with 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-

(5) The use of nitrobenzoylated halides led to crystalline intermediates in the synthesis of (a) 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)thymine [W. W. Zorbach and S. Saeki, *ibid.*, **29**, 2018 (1964)], and also (b) of 1-(2-deoxy β-D-*arabino*-hexopyranosyl)-5-fluorocytosine [G. J. Durr, *J. Med. Chem.*, **8**, 140 (1965)].

D-*arabino*-hexosyl bromide (**2**)[6a] and with 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide (**3**)[6b] was carried out according to the procedure of Hilbert and Jansen[7] under room-temperature conditions.[5b] The resulting, fully protected nucleosides **4** and **5** were treated with methanolic ammonia,[7] leading directly to the cytosine nucleosides **6** and **7**, both of which were crystalline. Alternatively, **4** and **5** were de-ethylated, giving the nitrobenzoylated uracil nucleosides **8** and **9**. Methoxide-catalyzed deacylation of **8** gave the previously reported[8] 1-(2-deoxy-β-D-*arabino*-hexopyranosyl)uracil (**10**) as crystalline material. Similar treatment of **9** gave 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)-uracil (**11**) also in crystalline form. The β configuration is assigned tentatively to the nucleosides **6**, **7**, **10**, and **11**, based on O.R.D. studies, which disclosed a positive Cotton effect in each case.[9]

Screening tests recently have shown that "2-deoxyglucosyluracil" (**10**), as well as "2-deoxyglucosylthymine," is an inhibitor of a pyrimidine nucleoside phosphorylase.[10] In terms of the carbohydrate component, the structural requirements for inhibition of the enzyme appear to be highly specific. While "2-deoxyglucosylthymine" is a powerful inhibitor, the corresponding β-D-glucopyranoside is without effect.[3] Also ineffective as an inhibitor is 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)thymine ("2-deoxyallosylthymine"),[5a,11] whose structure differs from "2-deoxyglucosylthymine" only with respect to a reversal of configuration of the hydroxyl group about C-3 of the sugar portion. The corresponding uracil nucleoside **11** also was without effect; both cytosine nucleosides **6** and **7** gave negative results in the inhibition tests.[10]

Experimental Section

All melting points were determined using a Kofler hot stage.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-*arabino*-hexosyl)-4-ethoxy-2(1*H*)-pyrimidinone (4).—To 10.8 g. (69.3 mmoles) of 2,4-diethoxypyrimidine was added 2.23 g. (3.31 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexosyl bromide (**2**).[6a] The mixture was stirred for 3 hr. after which time it solidified. It was allowed to stand overnight at room temperature, and the solid material was crushed and stirred thoroughly in 250 ml. of dry ether. The insoluble material was filtered off, washed with four 10-ml. portions of ether, and dissolved in 200 ml. of dry dichloromethane. The volume of the solution was diminished to about 90 ml. by boiling, and 40 ml. of ether was added to incipient turbidity. The solution was kept in a refrigerator overnight and the separated material was filtered off. The crystalline, protected nucleoside was washed four times with small portions of ether, giving 1.41 g. (58%) of pure **4**, m.p. 271–272.5°, $[\alpha]^{20}D$ −6.6° (*c* 0.5, dichloromethane).

Anal. Calcd. for $C_{33}H_{27}N_5O_{15}$: C, 54.02; H, 3.71; N, 9.55. Found: C, 53.86; H, 3.83; N, 9.27.

1-(2-Deoxy-β-D-*arabino*-hexopyranosyl)cytosine (6).—A solution of 840 mg. (1.19 mmoles) of the protected nucleoside **4** in 40 ml. of absolute methanol saturated with ammonia was heated in a pressure flask at 75° for 7 hr. The solvent was evaporated under diminished pressure, the residue was dissolved in 10 ml. of water, and the solution was extracted four times with 20-ml. portions of ether. The aqueous solution was evaporated under diminished pressure at 40°, and the crystalline residue was recrystallized from absolute ethanol–ether. Three additional recrystallizations from the same solvent gave 138 mg. (47%) of the nucleoside **6**, m.p. 236–237.5°, $[\alpha]^{24}D$ +21° (*c* 0.528, water), λ_{max}^{MeOH} 271 mμ (log ε 3.98), ν_{max}^{KBr} 1670 cm.$^{-1}$ (–NHCO–). The nucleoside **6** traveled as a single spot when chromatographed on paper by an ascending technique and employing 2-propanol–saturated aqueous ammonium sulfate–water (28:2:70).

Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.64; H, 5.88; N, 16.18.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzyl-β-D-*arabino*-hexosyl)-uracil (8).—To a solution of 1.41 g. (1.92 mmoles) of the protected nucleoside **4** in 100 ml. of dichloromethane was added 25 ml. of 20% (w./w.) methanolic hydrogen chloride. The solution was kept overnight at room temperature, the solvent was evaporated under diminished pressure at 40°, and the residue was re-evaporated three times with 10-ml. portions of absolute ethanol. The residue was dissolved in 130 ml. of dry dichloromethane, stirred with a little Celite 535, and filtered. The filtrate was diminished in volume to about 100 ml. by boiling, and 90 ml. of dry ether was added to incipient turbidity. The solution was kept in a refrigerator overnight and the separated material was filtered off, giving 1.26 g. (94%) of de-ethylated nucleoside **8**. An additional recrystallization from dichloromethane gave dimorphic material: m.p. 143–150°, recrystallizing between 168–173° and melting at 260–263°; $[\alpha]^{24}D$ −8.2° (*c* 0.502, CH_2Cl_2).

Anal. Calcd. for $C_{31}H_{23}N_5O_{15}$: C, 52.77; H, 3.29; N, 9.92. Found: C, 52.79; H, 3.41; N, 10.08.

1-(2-Deoxy-β-D-*arabino*-hexopyranosyl)uracil (10).—A suspension of 1.26 g. (1.79 mmoles) of de-ethylated nucleoside **8** in 100 ml. of absolute methanol saturated with ammonia was stirred overnight. The solvent was removed at 40° under diminished pressure, and the dry residue taken up in 50 ml. of water. After being extracted with ten 50-ml. portions of ether, the aqueous layer was stirred with Darco G-60 and Rexyn 300 (H-OH) ion-exchange resin[12] and filtered, and the filtrate was evaporated under diminished pressure at 40°. The residue was re-evaporated several times with small amounts of absolute ethanol, giving hygroscopic material melting at 95–140°. Crystallization from absolute ethanol gave 176 mg. (38%) of **10**, m.p. 168–169° and also 196–197.5°, $[\alpha]^{24}D$ +5.6 (*c* 0.445, water), λ_{max}^{MeOH} 260 mμ (log ε 3.98), ν_{max}^{KBr} 1680 [RN(C=O)NH–] and 1720 cm.$^{-1}$ [–NHC(=O)–].

Anal.[13] Calcd. for $C_{10}H_{14}N_2O_6$: N, 10.85. Found: N, 10.96.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl)-4-ethoxy-2(1*H*)-pyrimidinone (5).—To 1.38 g. (8 mmoles) of 2,4-diethoxypyrimidine (**1**) was added 675 mg. (1 mmole) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide (**3**).[6b] The mixture was stirred with exclusion of moisture for 2 hr., after which time it solidified. The mixture was kept overnight at room temperature, and the solid was crushed and extracted five times with 30-ml. portions of ether. The residue (410 mg.) was recrystallized from ether–dichloromethane, giving 360 mg. (50%) of pure **5**, m.p. 295–296°, $[\alpha]^{24}D$ +36.4° (*c* 0.8, CH_2Cl_2).

Anal. Calcd. for $C_{33}H_{27}N_5O_{15}$: C, 54.02; H, 3.71; N, 9.55. Found: C, 54.27; H, 3.72; N, 9.38.

1-(2-Deoxy-β-D-*ribo*-hexopyranosyl)cytosine (7).—A suspension of 200 mg. (0.27 mmole) of the completely protected nucleoside **5** in 20 ml. of anhydrous methanol saturated with ammonia was heated in a pressure bottle at 80° for 8 hr. The solution was kept overnight at room temperature, and the solvent was evaporated under diminished pressure at 40°. The residue was dissolved in water and the solution was extracted thoroughly with ether to remove the *p*-nitrobenzamide. The aqueous layer was evaporated under diminished pressure at 50°, and the residue was dissolved in 5 ml. of 90% aqueous ethanol. After the

(6) (a) W. W. Zorbach and G. Pietsch, *Ann. Chem.*, **655**, 26 (1962); (b) W. W. Zorbach and W. Bühler, *ibid.*, **670**, 116 (1963).

(7) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **58**, 60 (1936).

(8) J. J. Fox, L. F. Cavalieri, and N. Chang [*ibid.*, **75**, 4315 (1953)] obtained the nucleoside **8** in unspecified yield by coupling syrupy 3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexosyl chloride with 2,4-diethoxypyrimidine, followed by hydrolysis of the protecting groups.

(9) In a private communication, Dr. T. V. L. Ulbricht, who carried out the O.R.D. studies, stated that the nucleosides were *probably* β anomers, because they were virtually the only pyranosides of a large number of nucleosides studied by him. However, his interpretation of the reason for the sign of the Cotton effect being positive or negative predicts that pyranosides would obey the rule.

(10) M. Zimmerman, Merck Sharp and Dohme Research Laboratories, Rahway, N. J., unpublished results.

(11) M. Zimmerman, *Biochem. Biophys. Res. Commun.*, **16**, 600 (1964).

(12) Fisher Scientific Co.

(13) Repeated attempts at purification failed to give material whose values for carbon and hydrogen were within the allowable limits of error. The ultraviolet and infrared spectra were concordant with the structure assigned to **10**; moreover, the nucleoside was homogeneous as disclosed by paper chromatograms, and traveled as a single spot when chromatographed by an ascending technique, employing saturated aqueous ammonium sulfate–2-propanol–water (2:28:70).

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

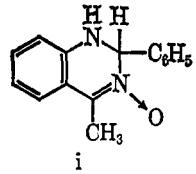
(1) Paper XXV: L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, **8**, 815 (1965).

(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.