is described in the literature,[9] we chose another route since we had available supplies of tryptamine and diethyl *trans*-2-carboxycyclohexaneacetate.[10] Condensation of the amine and diester gave hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione which was converted to **1** by lithium aluminum hydride reduction.

Treatment of **1** with mercuric acetate in aqueous acetic acid solution led to a good recovery of crude bases from which (±)-pseudoyohimbane was isolated in 31% yield by recrystallization. Attempts to obtain any other products by fractional recrystallization or chromatography were fruitless. However, thin layer chromatography of the total reaction product indicated the presence of minor amount of (±) yohimbane (**5**) and the four inside yohimbanes (**7**–**10**) in addition to (±)-pseudoyohimbane.

Experimental Section

The melting points were determined using a Thomas-Hoover apparatus which had been calibrated against known standards. Thin layer chromatography was carried out on silica gel G (Stahl) using a 0.2:1:0.5 or 1:1:0.5 mixture of acetone, benzene, and *n*-heptane as the eluent in an ammonia atmosphere, the chromatograms being developed by spraying with a solution of potassium iodoplatinate.

Hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione.—A mixture of 62 g of tryptamine and 91 g of dimethyl *trans*-2-carboxycyclohexaneacetate was heated at 175° for 20 hr. The reaction mixture was digested with 700 ml of methanol on the steam bath for 20 min. After cooling to room temperature filtration gave 83 g (70%) of a crystalline solid, mp 251–252°. Recrystallization from methanol gave an analytical sample, mp 252–253°.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.35; H, 7.31; N, 9.07.

Decahydro-2-(2-indol-3-ylethyl)-*trans*-isoquinoline (1).—To a solution of 12 g of lithium aluminum hydride in 500 ml of tetrahydrofuran was added over a 1-hr interval a hot solution of 10.5 g of hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione in 900 ml of tetrahydrofuran. After the addition had been completed, refluxing was continued for an additional 6 hr. The reaction mixture was decomposed by the addition of water. The tetrahydrofuran solution was decanted from the precipitate and the solvent was removed. Recrystallization of the residue from acetonitrile gave 7.6 g (80%) of a crystalline solid, mp 151–152° (lit.[9] 150–151°).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.64; H, 9.39; N, 9.70.

(±)-Pseudoyohimbane (6). Oxidation Method.—A solution of 14.1 g of decahydro-2-(2-indol-3-ylethyl(-*trans*-isoquinoline and 190 g of mercuric acetate in 1250 ml of 5% acetic acid was heated at 70–75° for 12 hr. The reaction mixture was saturated with hydrogen sulfide and was filtered while hot. The precipitate was washed with an additional 1500 ml of 5% acetic acid. The filtrates were combined, concentrated to 200 ml *in vacuo*, and 500 ml of methanol was added. The pH of the solution was adjusted to 5 with 10% sodium hydroxide solution and 25 g of sodium borohydride added at 10–20°. After standing at 25° for 20 hr the methanol was removed *in vacuo* and the solution was extracted with three 100-ml portions of chloroform. The chloroform layers were combined, washed with water, and dried over sodium sulfate, and the solvent was removed. The residue (12.9 g) after recrystallization from acetonitrile gave 4.4 g (31%) of a crystalline solid, mp 217–220°. Recrystallization from ethanol gave an analytical sample, mp 220–221°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.83; H, 8.63; N, 9.99. Found: C, 81.08; H, 8.67; N, 9.75.

From (±)-3-Dehydroyohimbane Chloride.—To a solution of 20 g of (±)-3-dehydroyohimbane chloride, 50 ml of perchloric acid, 250 ml of water, and 400 ml of tetrahydrofuran in 1.2 l. of methanol was added 50 g of zinc dust portionwise over a 30-min interval. After the addition had been completed the mixture was refluxed for an additional 3 hr. The reaction mixture was filtered and the solvent was removed. The residue was treated with 270 ml of 20% sodium hydroxide solution and 1.7 l. of chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from 400 ml of acetonitrile gave 8.9 g (50%) of a solid, mp 221–222°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.08; H, 8.53; N, 10.24.

The mother liquor was concentrated to 100 ml. On standing there was deposited 4.3 g (24%) of (±)-yohimbane, mp 179–181°.

Registry No.—**1**, 14325-28-1; **6**, 14210-12-9; hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione, 14210-22-1; mercuric acetate, 1600-27-7.

(9) E. E. van Tamelen, M. Shamma, and P Aldrich, *J. Am. Chem. Soc.*, **78**, 4628 (1956).

(10) J. Rubinfeld, Ph.D. Thesis, Columbia University, 1961.

Quinazolines. V. Synthesis and Proof of Structure of 1,3-Diamino-5,6-dihydrobenzo[*f*]quinazoline[1]

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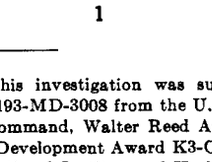
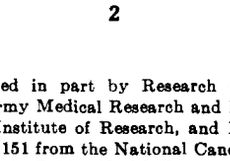
The direct synthesis of various monocyclic and condensed pyrimidines by condensation of acyclic and alicyclic ketones with dicyandiamide under fusion conditions has been reported previously from these laboratories.[2] Among the ketones investigated was 2-tetralone, which could be expected to yield either 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**) or 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline (**2**), depending upon the direction of cyclization. Earlier experiments in these laboratories suggested that cyclization had occurred at the 3 position, giving **2**.[3] In the present



1



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(1) This investigation was supported in part by Research Contract DA-49-193-MD-3008 from the U. S. Army Medical Research and Development Command, Walter Reed Army Institute of Research, and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication No. 230 from the Army Research Program on Malaria.

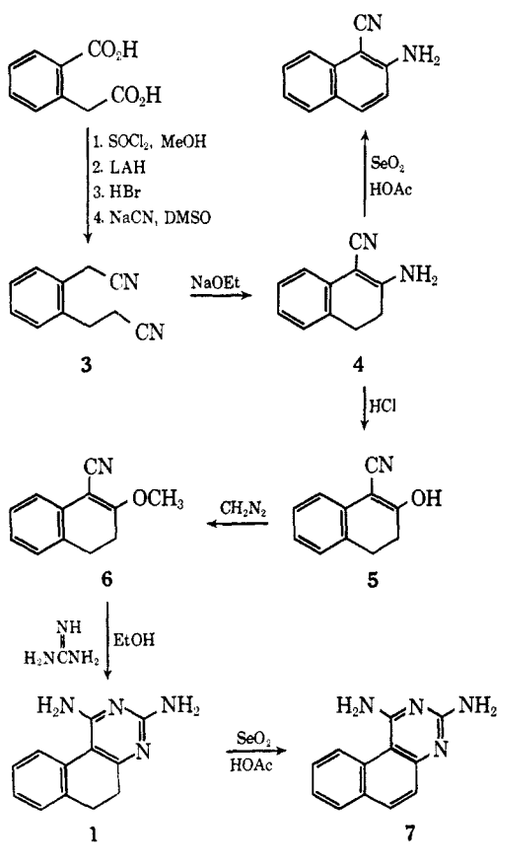
(2) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(3) S. K. Sengupta, S. Chatterjee, H. Kangur, and E. J. Modest, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 3, 1963, p 37-L. The tentative structural assignment was based on the isolation of 2,4-diaminobenzo[*g*]quinazoline as the major product (13% yield) of dehydrogenation of the dicyandiamide–2-tetralone fusion product with palladium–charcoal in tetralin and 2-[(2′-ethoxy)-ethoxy]ethanol. Apparently the benzo[*g*]quinazoline resulted from a skeletal rearrangement under disproportionation conditions (to be submitted for publication).

paper, we wish to report an unambiguous synthesis of **1**, which establishes that the dicyandiamide fusion product is, in fact, the angular isomer. This compound is of interest as the parent member of a series of bridged pyrimethamine analogs in which free rotation of the phenyl and pyrimidine rings is restricted.[4,5]

The synthesis of **1** is outlined in Scheme I. Homophthalic acid was converted to 1-(2-cyanoethyl)-2-cyanomethylbenzene (**3**) *via* the dimethyl ester, diol, and dibromide. Thorpe cyclization of dinitrile **3** proceeded quantitatively, giving 2-amino-1-cyano-3,4-dihydronaphthalene (**4**). The structure of **4** was proved by spectroscopic means, as well as by dehydrogenation with selenium dioxide in refluxing acetic acid[6] to 1-cyano-2-naphthylamine. The exclusive formation of **4** in the Thorpe reaction was consistent with the expectation that cyclization would take place *via* the more stabilized carbanion. The complex highly symmetrical 12-line A_2B_2 nmr pattern shown by the methylene protons of **4** is reproduced in Figure 1a. A broad two-

SCHEME I



proton singlet at δ 5.0 was due to the amino group. The remainder of the spectrum showed only absorption by four aromatic protons from δ 6.9 to 7.3.

Prolonged treatment of **4** with concentrated hydrochloric acid at room temperature gave 1-cyano-3,4-dihydro-2-hydroxynaphthalene (**5**) in good yield. The infrared spectrum proved that the compound had the enolic structure **5** as a solid and the nmr and infrared spectra showed that the enol form also predominated to >95% in chloroform solution. The four methylene protons (Figure 1b) gave rise to a nearly symmetrical 10-line A_2B_2 pattern and the enol hydrogen appeared as a broad singlet at *ca.* δ 7.9, well downfield from the aromatic protons. Enol ether **6**, obtained by treatment of **5** with diazomethane, showed the expected three-proton singlet at δ 3.94 and a complex A_2B_2 pattern, similar to that of **5** but less highly symmetrical.

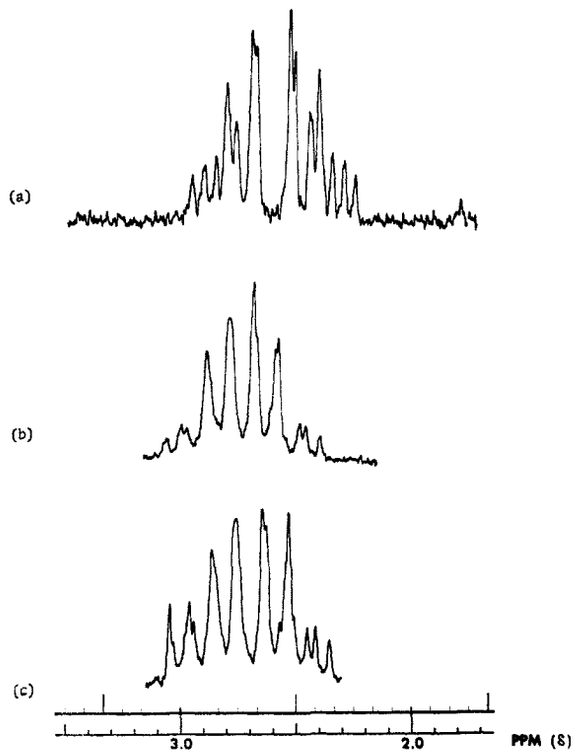


Figure 1.—Partial nmr spectra (in $CDCl_3$) of (a) 2-amino-1-cyano-3,4-dihydronaphthalene, (b) 1-cyano-3,4-dihydro-2-hydroxynaphthalene, and (c) 1-cyano-3,4-dihydro-2-methoxynaphthalene.

Condensation of **6** with guanidine by the usual procedure for the formation of pyrimidines from β-alkoxy-α-arylacrylonitriles[7] gave 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**). This product was identical with the compound obtained earlier from the dicyandiamide fusion reaction[2,3] and its structure was established conclusively by dehydrogenation with selenium dioxide in refluxing acetic acid[6] to 1,3-diaminobenzo[*f*]quinazoline (**7**).[5,8] An attempt to prepare **1** directly from **4** by reaction with cyanamide in the presence of pyridine hydrochloride[5] was not successful, unchanged **4** being recovered.

The present finding that condensation of 2-tetralone with dicyandiamide occurs at the 1 position provides a convenient method for the synthesis of substituted 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines of potential chemotherapeutic interest.[4] Furthermore, the facile dehydrogenation of **1** with selenium dioxide suggests a

(4) Our rationale for the design of bridged pyrimethamine analogs, of which **1** is only one example, was first presented in connection with the synthesis of fully aromatic 1,3-diaminobenzo[*f*]quinazolines;[5] *cf.* E. J. Modest, A. Rosowsky, S. Farber, and G. E. Foley, Abstracts of Papers, Ninth International Cancer Congress, Tokyo, Japan, October 24, 1966, p 325. The same concept has been invoked recently by Taylor and co-workers in their work on benzo[*f*]quinazolines: E. C. Taylor, A. McKillop, Y. Shvo, and G. H. Hawks, *Tetrahedron*, **23**, 2081 (1967).

(5) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966).

(6) S. W. Pelletier, R. L. Chappell, P. C. Parthasarathy, and N. Lewin, *ibid.*, **31**, 1747 (1966).

(7) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951); B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951); B. H. Chase and J. Walker, *ibid.*, 3518 (1953).

(8) A. Rosowsky and E. J. Modest, *J. Heterocyclic Chem.*, **3**, 387 (1966).

different route to the fully aromatic 1,3-diaminobenzo[*f*]quinazolines which may be superior, in some instances, to the methods previously described.

Experimental Section[9]

1-(2-Cyanoethyl)-2-cyanomethylbenzene (3).—Dimethyl homophthalate, bp 102–105° (0.1 mm), was prepared from homophthalic acid (Aldrich Chemical Co.) in 80% yield by the published procedure[10] and the diester was reduced with excess lithium aluminum hydride in ether. The undistilled diol[11] (114 g, 81%) ws heated at 120° for 40 min while dry hydrogen bromide was bubbled through. The product was taken up in ether, washed three times with sodium chloride, dried, and distilled. The fractions containing 90% 1-(2-bromoethyl)-2-bromomethylbenzene[12] by glpc analysis (107 g, 51%; bp 122–123° (0.5 mm))[13] were used for the preparation of dinitrile **3**.

To a stirred suspension of sodium cyanide (44.0 g, 0.90 mole) in dimethyl sulfoxide (500 ml, dried over Linde Molecular Sieves 4A) under nitrogen was slowly added a solution of the dibromide (101.6 g, 0.365 mole) in dimethyl sulfoxide (300 ml). The temperature was kept at 40–45° first by gentle external heating and then, as addition was continued, by a mildly exothermic reaction. The nitrogen was removed and the closed flask was stirred for 64 hr. Water (2 l.) and ether (1 l.) were added, the mixture was shaken, and the aqueous layer was extracted twice with ether.[14] The combined ether solutions were washed three times with dilute sodium chloride solution and dried. Dinitrile **3** crystallized on concentration of the ether and was obtained pure by washing with ether: 42.3 g, 68%; mp 55–57°; $\nu_{max}^{CHCl_3}$ 2250 cm^{-1}. The analytical sample, mp 57–57.5°, was recrystallized from ethanol.[15]

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.55; H, 5.98; H, 16.55.

2-Amino-1-cyano-3,4-dihydronaphthalene (4).—To a stirred solution of dinitrile **3** (17.0 g, 0.1 mole) in absolute ethanol (100 ml) at 90° under nitrogen was added a solution of sodium (2.4 g, 0.104 mole) in absolute ethanol (50 ml). The mixture was stirred 2 hr at 90°, cooled, diluted with water, and extracted twice with methylene chloride. The methylene chloride solution was washed with dilute sodium chloride solution, dried, and evaporated, and the crystalline residue was dissolved in a minimum of boiling carbon tetrachloride. From this solution on cooling was deposited 16.0 g (94%) of aminonitrile **4**: mp 83–84°; $\nu_{max}^{CHCl_3}$ 3550 (s), 3450 (s), 3230 (w), 2220 (s), 1620 cm^{-1} (s); λ_{max}^{EtOH} mμ (ε), 227 (15,800), 252 (7970), 295 (14,000), 315 (10,800, infl); nmr, 12 lines centered at δ 2.60 (4 H), 5.0 (br singlet, 2 H), 6.9–7.3 (multiplet, 4 H). The analytical sample, mp 84–85°, was recrystallized from carbon tetrachloride.

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.93; H, 6.01; N, 16.55.

1-Cyano-2-naphthylamine from 4.—A mixture of **4** (510 mg, 3 mmoles), selenium dioxide (350 mg, 3.2 mmoles), and glacial acetic acid (20 ml) was stirred at 105–110° for 1 hr, then cooled and filtered through Celite. The filtrate was evaporated to near dryness and the residue was dissolved in benzene. The benzene solution was washed with dilute sodium bicarbonate, dried, concentrated to 10 ml, and filtered through a column of Florisil (9 g) topped with powdered silver oxide (6 g). The crude 1-cyano-2-naphthylamine so obtained (206 mg, 41%) had an infrared spectrum identical with that of authentic material[16] and the mixture melting point of a sample recrystallized from carbon tetrachloride–benzene was not depressed (129–130°).

1-Cyano-3,4-dihydro-2-hydroxynaphthalene (5).[17]—Aminonitrile **4** (4.60 g) was dissolved in 55 ml of concentrated hydrochloric acid and was allowed to stand at room temperature for 2.5 days. The hydrochloric acid was decanted from a gummy precipitate, which was taken up in ether and washed with sodium chloride solution until the washings were neutral. Removal of ether from the dried extracts left 4.38 g of syrup, which crystallized slowly on trituration with carbon tetrachloride. Essentially pure **5** (3.60 g, 79%; mp 112–113°) was obtained by washing with carbon tetrachloride: $\nu_{max}^{CHCl_3 \text{ or } KCl}$ 3200–3300 (br), 2250, 1650 cm^{-1}; λ_{max}^{EtOH} mμ (ε), 224 (16,750), 284 (9930); nmr, ten lines centered at δ 2.75 (4 H), 7.0–7.3 (multiplet, 4 H), 7.9 (br singlet, 1 H). The analytical sample, mp 117–118°, was recrystallized from ether–petroleum ether (bp 30–60°) and then from ether alone.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.12; H, 5.38; N, 8.07.

1-Cyano-3,4-dihydro-2-methoxynaphthalene (6).—Treatment of **5** with diazomethane in ether until rapid evolution of nitrogen ceased, followed by evaporation and recrystallization of the residue from ether–petroleum ether, gave enol ether **6**: mp 55–56°; $\nu_{max}^{CHCl_3}$ 2250, 1620 cm^{-1}; λ_{max}^{EtOH} mμ (ε), 227 (15,450), 287 (9400); nmr, nine lines centered at δ 2.70 (4 H), 3.94 (singlet, 3 H), 6.9–7.4 (multiplet, 4 H).

Anal. Calcd for $C_{12}H_{10}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.56; H, 6.16; N, 7.80.

1,3-Diamino-5,6-dihydrobenzo[*f*]quinazoline (1).—To a solution of **6** (892 mg, 4.83 mmoles) in absolute ethanol (5 ml) was added a guanidine solution prepared by treatment of guanidine hydrochloride (550 mg, 5.75 mmoles) with excess sodium (290 mg, 12.6 mmoles) in ethanol (35 ml) followed by filtration. The mixture was stirred under reflux 4 hr and then cooled. The resulting solid, after being filtered, washed with water and ethanol, and dried *in vacuo*, afforded 309 mg of **1**, mp 263°. An additional 42 mg was obtained from the filtrate, increasing the yield to 34%:[18] ν_{max}^{KCl} 3450, 3230, 1650, 1640 cm^{-1}; λ_{max}^{EtOH} mμ (ε), 277 (18,700), 295 (16,900); $\lambda_{max}^{EtOH\ pH\ 1}$ mμ (ε), 271 (17,100), 283 (13,100, infl), 290 (12,000, infl); nmr (in trifluoroacetic acid), δ 2.75 (singlet, 4 H), 6.9–7.5 (multiplet, 4 H). The analytical sample, crystallized from dimethylformamide, melted at 263–264° and was identical (melting point, mixture melting point, infrared and ultraviolet spectra) with the compound previously obtained in these laboratories[2] by reaction of dicyandiamide with 2-tetralone.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.70; H, 5.70; N, 26.10.

1,3-Diaminobenzo[*f*]quinazoline (7) from 1.—A mixture of **1** (513 mg, 2.42 mmoles), selenium dioxide (285 mg, 2.55 mmoles), and glacial acetic acid (20 ml) was stirred at 115–120° for 18 hr and then cooled and centrifuged. The dark red supernatant was evaporated to dryness and the residue was treated with 75 ml of 0.1 *N* hydrochloric acid on a steam bath. The mixture was filtered hot, cooled, and neutralized with sodium hydroxide solution. The heavier selenium, which precipitated with the benzoquinazoline, was allowed to settle while the latter remained suspended in the water, which was then decanted. Extraction of the aqueous suspension with an equal volume of chloroform and evaporation of the chloroform suspension gave 280 mg (55%) of 1,3-diaminobenzo[*f*]quinazoline (**7**), melting point and mixture melting point with authentic material,[5] 204–205°. Infrared spectra of the two samples were identical. An additional 25 mg, mp 202–204°, was separated from the selenium in the precipitated mixture above by vacuum sublimation.

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(9) Nmr spectra were determined in deuteriochloroform on a Varian A-60 instrument. Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer and a Perkin-Elmer Model 137 B spectrophotometer was used for the infrared spectra. An F & M Model 720 gas chromatograph with 2 ft × 0.25 in. 10% silicone rubber (SE-30) columns was used for glpc analyses. Solvents were removed under reduced pressure with a rotary evaporator and magnesium sulfate was the drying agent throughout. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Werby Laboratories, Boston, Mass.

(10) J. C. Sheehan and R. C. O'Neill, *J. Am. Chem. Soc.*, **72**, 4614 (1950).

(11) E. L. Anderson and F. G. Holliman, *J. Chem. Soc.*, 1037 (1950).

(12) F. G. Holliman and F. G. Mann, *ibid.*, 737 (1942).

(13) Lower boiling fractions consisted largely of the ether, 5,6-dihydro-(2H)-3,4-benzopyran [J. Colonge and P. Boisde, *Bull. Soc. Chim. France*, 1337 (1956)].

(14) Extraction of the aqueous layer with methylene chloride after the ether extractions was later found to increase the yield of **3** by 5–10%.

(15) This compound was first prepared in small quantity by Dr. M. W. Fordice and analytical and spectral data were obtained by him at the Massachusetts Institute of Technology. We are grateful to Dr. Fordice for helpful discussions and for permission to reproduce the analytical data here.

(16) L. H. Krol, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **71**, 545 (1952).

(17) While this manuscript was in preparation, a report of the synthesis of **5** by a different route appeared: R. T. Parfitt, *J. Chem. Soc.*, 140 (1967).

(18) Subsequent use of this condensation with other cyano enol ethers [A. S. Dey, A. Rosowsky, and E. J. Modest, unpublished results] suggests that if excess sodium ethoxide is avoided, this yield may be substantially increased.