Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.63; H, 7.16; N, 12.35.

1-(*p*-Chlorobenzyl)-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]-indole (8).—To a stirred solution of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (3.0 g, 17.4 mmoles) in dry dimethylformamide (90 ml), under nitrogen, was added a 53.4% suspension of sodium hydride in mineral oil (1.02 g, 22.6 mmoles). The resulting mixture was stirred at room temperature for 1 hr, cooled in an ice bath, and treated during 10 min with 3.63 g (22.6 mmoles) of *p*-chlorobenzyl chloride. It was then allowed to warm up to room temperature and stand for 20 hr. The reaction mixture was poured into ice water (500 ml) and extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was decolorized with Darco G 60 and recrystallized several times from ethyl acetate–Skellysolve B to yield 2.0 g (39%) of 1-(*p*-chlorobenzyl)-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 116–117.5°. The ultraviolet spectrum had λ_{max} 226 and 313 mμ (ε 32,050 and 9900, respectively) with inflections at 269, 278, and 290 mμ (ε 4200, 5700, and 7300, respectively).

Anal. Calcd for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; Cl, 11.95; N, 9.44. Found: C, 73.11; H, 5.80; Cl, 12.13; N, 9.74.

1-[3-(Dimethylamino)propyl]3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole Dihydrochloride (9).—To a stirred solution of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (3.0 g, 17.4 mmoles) in dry dimethylformamide (90 ml), under nitrogen, was added a 53.4% suspension of sodium hydride in mineral oil (1.02 g, 22.6 mmoles). The resulting mixture was stirred at room temperature for 1 hr, cooled in an ice bath, and treated, during 10 min, with 4.86 ml (22.6 mmoles) of a 50% solution of 3-(dimethylamino)propyl chloride in toluene. It was then allowed to warm up to room temperature and stand for 20 hr. The reaction mixture was poured into ice water (600 ml) and extracted with ether. The ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in ether was acidified with ethereal hydrogen chloride. The resulting hydrochloride was recrystallized from methanol–Skellysolve B to yield 2.14 g (38.9%) of 1-[3-(dimethylamino)-propyl]-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole dihydrochloride, mp 268–269° dec. The analytical sample, mp 276° dec, was prepared by recrystallizing some of this material from methanol–Skellysolve B. The ultraviolet spectrum had λ_{max} 233, 291, and 313 mμ (ε 29,400, 7200, and 8800, respectively) with an inflection at 214 mμ (ε 16,900).

Anal. Calcd for $C_{16}H_{23}N_3 \cdot 2HCl$: C, 58.18; H, 7.63; N, 12.72; Cl, 21.47. Found: C, 57.81; H, 7.33; N, 12.30; Cl, 20.26.

6-Acetyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (11).—A mixture of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole (1.19 g, 6.88 mmoles) and acetic anhydride (15 ml) was allowed to stand under nitrogen, for 18 hr. It was then poured into water. The solid product was collected by filtration, washed with water, and dried under reduced pressure at 35°. A solution of this material in ethyl acetate was decolorized with Darco G-60 and crystallized to yield 1.06 g (72%) of 6-acetyl-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole, mp 196–197.5°. The analytical sample, mp 197–199°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had λ_{max} 228 and 294 mμ (ε 38,700 and 8450, respectively) with an inflection at 285 mμ (ε 7750).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.73; H, 6.33; N, 13.14.

6-Acetyl-1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydra-1H-azepino[4,3,2-*cd*]indole Hydrochloride (12).—A suspension of 1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydro-1H-azepino-[4,3,2-*cd*]indole dihydrochloride (1.50 g, 4.74 mmoles) in dilute sodium hydroxide was stirred with ether. The resulting ether solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in acetic anhydride (20 ml) was allowed stand at room temperature for 18 hr. It was then poured into water. The aqueous solution was made alkaline with sodium hydroxide and the product was extracted with ether. The ether solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A solution of the residue in ether was acidified with ethereal hydrogen chloride; the resulting hydrochloride was crystallized from ethanol–ether to yield 1.49 g of 6-acetyl-1-[3-(dimethylamino)propyl]-3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indole hydrochloride, mp 250–251°. The ultraviolet spectrum had λ_{max} 231 and 301 mμ (ε 38,550 and 9150, respectively) with an inflection at 283 mμ (ε 6600).

Anal. Calcd for $C_{18}H_{25}N_3O \cdot HCl$: C, 64.36; H, 7.80; N, 12.51; Cl, 10.56. Found: C, 64.84; H, 8.12; N, 12.62; Cl, 10.24.

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4-Indol-3-yl-1-methylhexahydroazepines

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Our interest in the chemistry of 3-(1-methyl-2-pyrrolidinyl)indole[1] (1) led us to investigate the susceptibility of this graminelike compound to nucleophilic ring opening reactions. After several abortive attempts to condense 1 with potassium cyanide, we studied its sodium hydroxide catalyzed reaction with diethyl malonate, a reaction which proceeds well with gramine to give ethyl 2-carboethoxy-3-(indol-3-yl)propionate.[2] In theory, diethyl malonate could in this case serve both as a nucleophile and as an anion acceptor. Thus, displacement of the amine from C-2 of the pyrrolidine ring would yield a highly reactive anion which could be accepted by one of the ester groups to form a cyclic amide, driving the reaction to completion. In practice, reaction of 1 with diethyl malonate and powdered sodium hydroxide under forcing conditions (refluxing xylene for 2 days) yielded *trans*-3-carboethoxy-4-(indol-3-yl)-1-methylhexahydroazepin-2-one (2) which was isolated by chromatography in about 13% yield (Scheme I). Structure 2 was supported by its infrared (ν_{max} 3290, 1740, and 1627 cm^{-1}) and ultraviolet (λ_{max} 220, 281.5, and 290 mμ) spectra which provide evidence for an NH, ester, and amide carbonyls, and the indole chromophore. The nmr spectrum[3a] had a singlet at 647 cps for the indole NH, a complex multiplet at 460–410 cps for the five additional indole protons, a doublet centered at 258 cps[4] (J = 9.5 cps) assigned to the C-3 proton of the azepine ring, a quartet centered at 234 cps and a triplet centered at 56.5 cps (apparent J = 7 cps) for the ethyl group of the ester, a sharp singlet at 175.5 cps for the N-methyl protons, and a broad absorption centered at about 104 cps for the C-5 and C-6 protons. The C-4 proton of the azepine ring (centered at 211 cps[4]) was partially obscured by the C-7 proton absorption at about 236–214 cps.

The stereochemical assignment for the indole and ester groups of 2 was obtained by a consideration of the

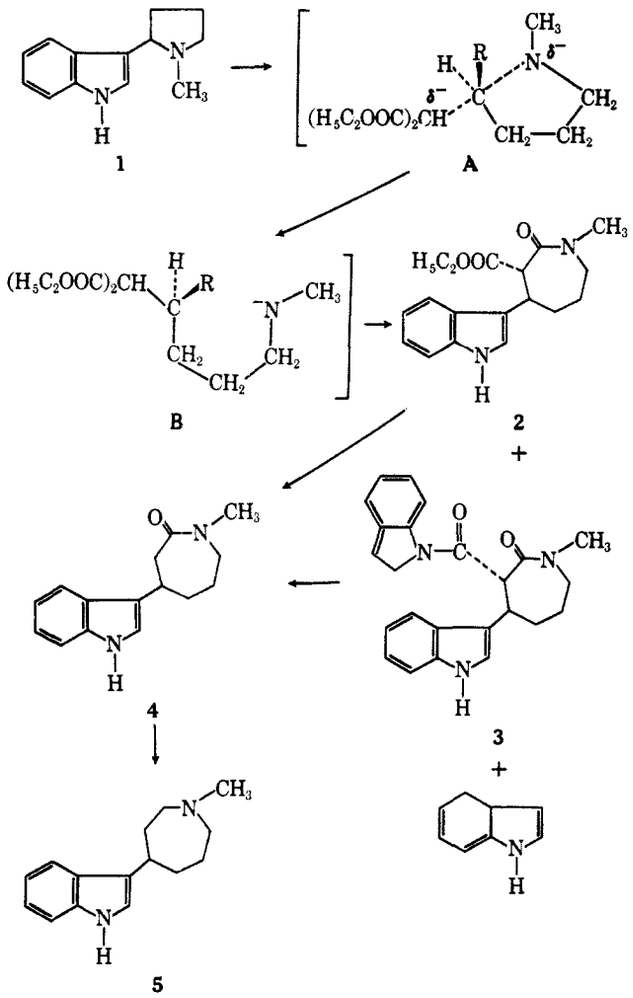
(1) G. A. Youngdale, *et al.*, *J. Med. Chem.*, **7**, 415 (1964).

(2) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(3) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) deuteriodimethyl sulfoxide or (b) deuteriodimethylformamide. The peaks are reported in cycles per second downfield from tetramethylsilane.

(4) Calculated, *cf.* R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 165, p 84.

SCHEME I



reaction mechanism and the nmr absorption of the C-3 proton. We suggest that the reaction has two separate steps. The first includes the displacement of the amino group from C-2 of the pyrrolidine ring to give the adduct B. In the second step, the amide ion of B condenses with one of the ester groups to form the final product. Although both ester groups of B are chemically equivalent, it was noted from the Newman projections that the intermediates formed by condensation of the esters with the amide ion are different in that the steric interactions ultimately to be found in the azepine ring are already becoming apparent. In particular the intermediate which would ultimately lead to the *trans* product has fewer unfavorable skew interactions between bulky groups than does the intermediate which would give the *cis* stereochemistry. From this analysis, we would predict that the indole and ester groups of **2** would have the *trans* configuration about the seven-membered ring. A similar conclusion would also be reached by assuming a base-catalyzed equilibration of the ester group after cyclization. Examination of Dreiding models shows that the chair conformation of *trans* **2** is more stable than the corresponding boat conformation since in the latter either the ester or the indole group becomes axial and in so doing undergoes serious transannular interactions with either the C-7 or the C-6 axial hydrogen, respectively. In the chair conformation, the axial C-3 and C-4 protons display a dihedral angle of about 150°. The observed coupling constant (J = 9.5 cps) for these protons is compatible with the predicted value[5] and thus supports the assigned configuration.

In addition to **2**, a second product was obtained from this reaction in low yield (1.4%). Structure **3** for this compound was suggested by its nmr spectrum[3b] which was similar to that of **2** but had an additional six aromatic hydrogens and no peaks assignable to an ethyl group. The mass spectrum had a molecular ion at m/e 385 with major fragmentation peaks at m/e 269 and 241, suggesting the successive loss of indole and carbon monoxide from a structure such as **3**. The infrared spectrum had a carbonyl band at 1720 cm^{-1} in addition to the amide carbonyl absorption which suggested that the additional indole moiety was attached to the carboxyl carbon *via* nitrogen rather than, for example, the β-carbon which ketone would be expected to absorb at a lower frequency.[6] This conclusion was supported by two experiments. Alkaline hydrolysis of **3** gave indole and a carboxylic acid which was converted by pyrolysis to **4** (*vide infra*). Base-catalyzed ethanolysis of **3** gave the ester (**2**) in good yield. By analogy to structure **2** the assigned stereochemistry of **3** is based on the nmr absorption, centered at 325 cps (J = 9.5 cps), assigned to the C-3 hydrogen of the azepine ring.

Indole, a by-product of this reaction, was probably the result of a base-catalyzed cleavage of **2** perhaps *via* a reverse Michael reaction. This type of cleavage has been observed during attempted alkaline hydrolysis of 3-skatyl-3-carboethoxyheptan-2-one[7] and ethyl 2-acetamido-2-carboethoxy-3-(indol-3-yl)butyrate.[8]

Conversion of **2** to the amine **5** was uneventful. Thus, alkaline hydrolysis of **2** followed by pyrolytic decarboxylation of the resulting acid gave lactam **4** which was converted to **5** by lithium aluminum hydride reduction.

Experimental Section[9]

***trans*-3-Carboethoxy-4-indol-3-yl-1-methylhexahydroazepin-2-one (2); *trans*-1-[(Hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole (3).**—A stirred mixture of 3-(1-methyl-2-pyrrolidinyl)indole (100 g, 0.500 mole), diethyl malonate (78 ml, 0.513 mole), powdered sodium hydroxide (2.0 g), and xylene (1200 ml) was refluxed under nitrogen for 48 hr. During this period ethanol, formed in the reaction, was removed by distillation. Additional 1.0-g portions of powdered sodium hydroxide were added to the reaction mixture after the reaction had proceeded for 18.3 and 25 hr. The cooled reaction mixture was poured into dilute acetic acid and the product was extracted with chloroform. The extract was washed successively with water, dilute ammonium hydroxide, and saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product from two identical reactions (1.00 mole) was chromatographed on silica gel (9 kg) with 60% ethyl acetate–cyclohexane. Indole was eluted first, mp and mmp with an authentic sample 52–54°. It was identified by infrared (chloroform) comparison with an authentic sample. The second compound eluted from the column was crystallized from methanol–ethyl acetate to give 5.4 g (1.4%) of *trans*-1-

(5) See ref 4, p 36.

(6) D. R. Liljegren and K. T. Potts, *J. Org. Chem.*, **27**, 377 (1962).

(7) A. A. Semenov and I. V. Terenteva, *Chem. Heterocyclic Compds.*, **1**, 153 (1965).

(8) H. R. Snyder and D. S. Matteson, *J. Am. Chem. Soc.*, **79**, 2217 (1957).

(9) Melting points were taken in capillary tubes and are corrected. Unless otherwise indicated, ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer; infrared spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Mass spectra were obtained on an Atlas CH4 spectrometer. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Darco G-60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. The silica gel used for chromatography was obtained from E. Merck AG, Darmstadt, Germany.

[(hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole, mp 266–269°. The analytical sample, mp 269–270°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had end absorption, λ_{max} 221, 241, 283, and 291 mμ (ε 43,500, 25,750, 10,410, and 11,480, respectively) with inflections at 263, 269, and 299 mμ (ε 13,200, 12,300, and 8350, respectively). The infrared spectrum showed NH 3410 and C=O 1720, 1640, and 1630 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90. Found: C, 74.63; H, 5.85; N, 11.11.

The third compound eluted from the column was crystallized from methanol–ethyl acetate to give 41.8 g (13.3%) of *trans*-3-carboethoxy-4-indol-3-yl-1-methylhexahydroazepin-2-one, mp 198–202°. The analytical sample, mp 196.5–198°, was prepared by recrystallizing some of this material from methanol–ethyl acetate. The ultraviolet spectrum had λ_{max} 220, 281.5, and 290 mμ (ε 35,750, 5950, and 5150, respectively) with an inflection at 275 mμ (ε 5550). The infrared spectrum showed NH 3290 and C=O 1740 and 1627 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.36; H, 7.13; N, 8.98.

Hydrolysis of *trans*-1-[(Hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole (3).—A mixture of *trans*-1-[(hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole (1.00 g, 2.60 mmoles), 8% aqueous sodium hydroxide (15 ml), and ethanol (15 ml) was refluxed for 2 hr, cooled in an ice bath, diluted with water, and extracted with ether. The ether extract was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A benzene solution of the residue was filtered through a little alumina and the filtrate was crystallized from benzene–Skellysolve B to give 0.187 g of indole, mp 52–53°. The infrared spectrum (chloroform) of this material was identical with that of authentic indole.

The combined aqueous layers from the above extraction were cooled in an ice bath and acidified with hydrochloric acid. The resulting solid was collected by filtration, washed with water, and dried to give 0.474 g of crude acid. This was heated in an evacuated (18 mm) flask at 172–177° for 1 min. An ethyl acetate solution of the cooled product was decolorized with Darco G-60 and crystallized to give 0.330 g (52.4%) of 4-indol-3-yl-1-methylhexahydroazepin-2-one, mp and mmp 149–150.5°, with **4** prepared as below.

Ethanolysis of *trans*-1-[(Hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole (3).—*trans*-1-[(Hexahydro-4-indol-3-yl-1-methyl-2-oxo-3-azepinyl)carbonyl]indole (1.00 g, 2.60 mmoles) was added to a solution of sodium (64 mg) in dry ethanol (50 ml) and the resulting mixture was refluxed under nitrogen for 6 hr and allowed to stand at ambient temperature for 18 hr. It was then poured into ice water. The crystalline product was collected by filtration, washed with water, dried, and crystallized from methanol to give 0.511 g of **2**, mp and mmp 200–201.5°, and 0.047 g of **2**, mp 199.5–200.5°.

4-Indol-3-yl-1-methylhexahydroazepin-2-one (4). A.—A solution of 1.00 g (3.18 mmoles) of *trans*-3-carbethoxy-4-indol-3-yl-1-methylhexahydroazepin-2-one in 50 ml of warm, absolute ethanol was treated with 7.33 ml of 0.433 *N* aqueous potassium hydroxide and refluxed, under nitrogen, for 7 hr. The mixture was concentrated under reduced pressure and the residue was suspended in water and filtered. The solid obtained in this manner was washed with water and dried *in vacuo* to yield 64 mg of starting material, mp 187–189°. The aqueous filtrate was cooled in an ice bath and acidified with concentrated hydrochloric acid. The solid which precipitated was collected by filtration, washed with water, and dried *in vacuo* to yield 753 mg (82.9%) of the acid, mp 151.5–154° dec. This material was insoluble in most organic solvents and was therefore not characterized. The infrared spectrum showed NH 3346 and C=O 1714 and 1589 cm^{-1}.

B.—The acid (0.589 g, 2.05 mmoles) was heated in a small evacuated (14 mm) flask at 178° for 5 min. Decarboxylation occurred rapidly as the compound melted. The cooled, colorless glass that resulted was dissolved in ethyl acetate and crystallized to yield 443 mg (89.5%) of 4-indol-3-yl-1-methylhexahydroazepin-1-one, mp 147–149°. An analytical sample, mp 148–150°, was prepared by recrystallizing this material three times from ethyl acetate. The ultraviolet spectrum had λ_{max} 221.5, 281.5, and 290 mμ (ε 38,300, 6000, and 5250, respectively) with an inflection at 275 mμ (ε 5550). The infrared spectrum showed NH 3240 and C=O 1625 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.34; H, 7.37; N, 11.22.

4-Indol-3-yl-1-methylhexahydroazepine (5).—4-Indol-3-yl-1-methylhexahydroazepin-2-one (6.0 g, 24.7 mmoles) was added, under nitrogen, to an ice-cold stirred suspension of 6.0 g of lithium aluminum hydride in 600 ml of dry tetrahydrofuran and the resulting mixture was refluxed for 6.7 hr and allowed to stand at room temperature for 18 hr. It was then cooled in an ice bath and treated successively with 6 ml of water, 6 ml of 15% aqueous sodium hydroxide, and 18 ml of water. The inorganic salts were collected by vacuum filtration and washed with ether. Concentration of the combined filtrates yielded a colorless oil which was dissolved in ether, filtered, and crystallized from ether–Skellysolve B to yield 5.07 g, mp 81–85° (89.8%), of 4-indol-3-yl-1-methylhexahydroazepine. The analytical sample, mp 81–85°, was prepared by recrystallizing a portion of this material twice from ether–Skellysolve B. The ultraviolet spectrum had λ_{max} 222, 282, and 292 mμ (ε 35,200, 5850, and 5100, respectively) with an inflection at 275 mμ (ε 5400).

Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.78; H, 9.10; N, 11.91.

Registry No.—**2**, 14319-54-1; **3**, 14319-55-2; **4**, 14255-42-6; **5**, 14255-43-7.

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A Convenient Synthesis of 5-Iodoindole

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Our interest in 5-iodo-DL-tryptophan led us to investigate various routes to a key intermediate in its synthesis, 5-iodoindole (**1b**).

One method of preparation of **1b** began with the nitration[1,2] of *m*-toluidine to form 5-amino-2-nitrotoluene[3] by diazotization. Treatment of the iodo compound with ethyl oxalate by the Reissert method,[4] followed by reductive cyclization of the intermediate pyruvate with alkaline ferrous hydroxide, gave 5-iodoindole-2-carboxylic acid. Decarboxylation of the acid in quinoline with copper chromite catalyst then gave 5-iodoindole (**1b**).[5,6] Although the preparation of **1b** by this method was successful, the yield was low (4%) and the procedure was laborious.

Accordingly, we hoped to make use of a facile method of preparing 5- and 7-substituted indoles published recently by Thesing, Semler, and Mohr.[7] This method involved treatment of indole with sodium hydrogen sulfite to yield indoline-2-sulfonic acid sodium salt, which on acetylation gave N-acetylindoline-2-sulfonic acid sodium salt. Treatment of this compound with

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(7) D. Thesing, G. Semler, and G. Mohr, *Chem. Ber.*, **95**, 2205 (1962); British Patent 919,864 (1963); German Patent 1,123,668 (1962).