A New Synthesis and Alkylations of Some Pyrimido[1,2-a]indoles

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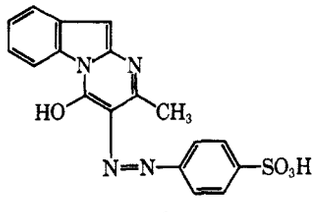
A new synthesis of pyrimido[1,2-a]indoles has been developed utilizing a base-catalyzed cyclization of a 2-(cyanomethyl)anilinomethylenemalonate. The mode of formation of this ring system and its structure proof are discussed. Base-catalyzed alkylations of pyrimido[1,2-a]indoles give mixtures of 1- and 10-substituted products **6** and **7a**, respectively. Hydrogenation or metal hydrides cause the reduction of the double bond. Decomposition occurs during attempted acid or base hydrolyses of these molecules.

In connection with studies in these laboratories on the reactions of derivatives of arylaminomethylenemalonates,[1] compound **1** was treated with 1 equiv of sodium ethoxide in refluxing ethanol. The product obtained, a stable orange solid, was shown to be the salt **2** which on acidification, gave the pyrimido[1,2-a]-indole derivative **3** in 84% over-all yield. This product was probably formed by the mechanism in Scheme I.

The structure of **3** was established by microanalyses and infrared and nmr spectra (see Experimental Section). The lactam rather than the tautomeric hydroxy imine structure was deduced from the infrared spectrum which showed a strong band at 1660 cm^{-1}, whereas the alternative structure should not exhibit a band above 1600 cm^{-1}.[2]

Only two examples of syntheses of pyrimido[1,2-a]indoles could be found in the literature. One[3] involves the reaction of ethyl 4-sulfobenzeneazoacetoacetate with 2-aminoindole to give **4** in 75% yield,



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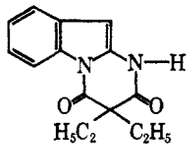

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while the other[4] describes the isolation of the dilactam **5** in 20% yield, as a by-product, from the reaction of 2-aminoindole and diethylmalonyl dichloride.

Since a facile synthesis of pyrimido[1,2-a]indoles was now available to us, a number of reactions, particularly alkylations, of these systems were investigated.

Hydrogenation of **3** over platinum (see Scheme II) gave the corresponding dihydro compound **10**. This transformation was also achieved with sodium borohydride. Lithium aluminum hydride failed to reduce **3** in ether, although the same reagent in refluxing tetrahydrofuran gave a complex mixture which was not studied.

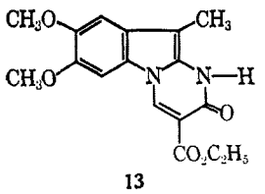
Alkylation of the salt **2** with methyl iodide or ethyl bromoacetate in a variety of solvents (ethanol, water, dimethylformamide, benzene) led in all cases to mixtures. The isomeric products arising from the ethyl bromoacetate reaction in ethanol were shown to be **6** and **7a** (Scheme II). The position of alkylation in **6** was established by examination of the nmr spectrum of its hydrogenation product (**8**) (**6** was not sufficiently soluble in suitable solvents) which did not show a peak between 5.5 and 6.0 ppm characteristic of the hydrogen in the 10 position in **3** and other compounds in this series. Compound **7a** exhibited a singlet for one proton at 5.64 ppm, indicating that alkylation had occurred on either the nitrogen or the oxygen of the lactam. The "C" ring in both **7a** and its hydrogenation product **9** were stable to dilute, refluxing hydrochloric acid.

The ultraviolet spectra of **7a** in neutral and acidic media were identical. The same holds true for **9**. The infrared spectrum of **7a** exhibited a strong band at 1664 cm^{-1}, while **9** had a band at 1680 cm^{-1}. On the basis of this evidence, structure **7a** rather than its O-alkylated analog, is proposed.

Whereas cyanoethylation of **2** or **3** failed to give a product (starting material was recovered in both cases), compound **10** was dicyanoethylated with acrylonitrile and triethylamine. The presence of the C–H in the 10 position in the nmr spectrum indicated that cyanoethylation had not taken place on this carbon; instead, cyanoethylation had occurred to the carbethoxy group and either on nitrogen or oxygen. A band at 1680 cm^{-1} in the ir spectrum suggested that the lactam carbonyl was unchanged; hence structure **11a** is indicated for the cyanoethylation product.

The unsubstituted lactams **3** and **10** were unstable to both aqueous acid and base,[5] whereas their N-substituted derivatives **7a** and **11a** were stable to these reagents. In fact, **7a** was hydrolyzed smoothly to **7b** in dilute hydrochloric acid and treatment of **11a** with aqueous sodium hydroxide gave the decarbethoxylated dinitrile **12**.[6]

The sequence of reactions (**1** to **3**) was carried out with the α-methylacetonitrile analog of **1**, to give **13** as the final product. Therefore, it appears that 10-substituted pyrimido[1,2-a]indoles of the type **13** may also be prepared by this method.



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(1) W. F. Gannon and E. A. Steck, *J. Org. Chem.*, **27**, 4137 (1962).

(2) 4-Pyrimidone shows bands in the region 1600–1700 cm^{-1}, while 4-methoxypyrimidine does not [see D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953)].

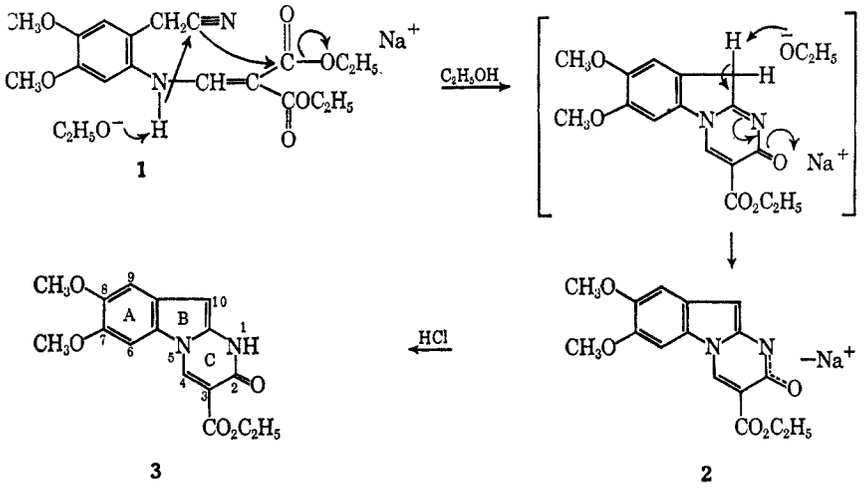
(3) U. S. Patent 2,432,419 (Dec 9, 1947); *Chem. Abstr.*, **42**, 2194a (1948).

(4) A. Ebnöther, *et al.*, *Helv. Chim. Acta*, **42**, 918 (1959).

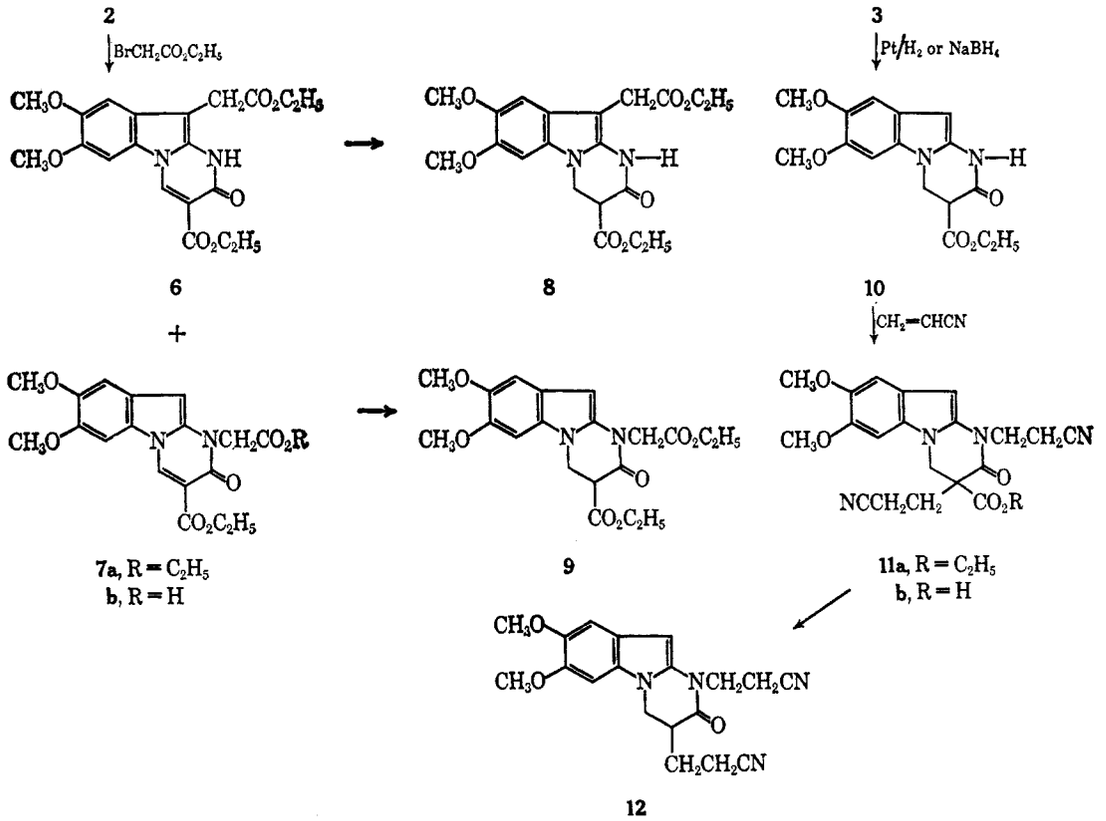
(5) Solutions of these lactams in aqueous ethanolic acid or base darken rapidly and only small amounts of water-insoluble, tarry materials are recovered. The lactam function presumably is hydrolyzed, leading to an amino indan which is quite susceptible to air oxidation.

(6) This product might arise from saponification of the ester followed by decarboxylation of the resulting α-amido acid (**11b**) or alternatively from hydrolysis of the lactam followed by decarboxylation of the resulting α-carbethoxy acid and cyclization back to the lactam.

SCHEME I



SCHEME II



In general, the comparable order of reactivity of the many functional groups present in these systems and the hydrolytic instability of the unsubstituted lactam group limited the synthetic versatility of these molecules.

Experimental Section

All melting points are corrected and were taken in a stirred, oil bath. Infrared spectra were obtained on Perkin-Elmer Model 21 spectrometer and ultraviolet spectra on a Cary Model 14 spectrometer. The nmr spectra were determined on a Varian A-60 spectrometer at room temperature. The solutions were approximately 20% (w/v). Tetramethylsilane was used as an internal standard.

Diethyl [(2-Cyanomethyl-4,5-dimethoxy)anilino]methylenemalonate (1).—(2-Amino-4,5-dimethoxyphenyl)acetonitrile[7] (13.1 g, 0.068 mol) was refluxed with diethyl ethoxymethylenemalonate (14.8 g, 0.068 mol) in 170 ml of benzene for 2 hr. Concentration of the solvent to one-third its original volume separated a solid which was collected by filtration and recrystallized from benzene to give 20.0 g (80%) of diethyl [(2-cyanomethyl-4,5-dimethoxy)anilino]methylenemalonate as off-white crystals: mp 152–153°; $\nu_{max}^{CHCl_3}$ 2250 (C≡N), 1692 (C=O vinylogous carbamate), and 1610 cm^{-1} (C=C); $\lambda_{max}^{CH_3OH}$ sh 221 mμ (ε 17,900) and 320 mμ (ε 18,600).

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.28; H, 6.10; N, 7.79.

3-Carbethoxy-7,8-dimethoxypyrimido[1,2-*a*]indol-2(1H)-one (3).—To a solution of sodium ethoxide, prepared from 3.2 g

(7) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).

(0.14 g-atom) of sodium and 300 ml of ethanol was added 50 g (0.14 mol) of diethyl [(2-cyanomethyl-4,5-dimethoxy)anilino]-methylenemalonate as a slurry in 500 ml of ethanol, and the resulting mixture was refluxed for 3 hr. The separated orange solid (the sodium salt 2) was collected by filtration, washed with ethanol, and dried. It was then dissolved in water and the solution was made acidic (pH 5) with 10% hydrochloric acid. Upon standing at 4° for 18 hr the solution deposited a yellow solid and was filtered to give 36.5 g (84%) of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one, mp 239–241°. Two recrystallizations from dimethylformamide afforded yellow flakes: mp 240–241°; ν_{max}^{Nujol} 1695 (C=O conjugated ester) and 1660 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 278 mμ (ε 29,400), 299 (32,700), and 337 (10,400). The nmr spectrum (DMF-d_7) exhibited a triplet (three protons) at δ 1.32 (–C–CH_3 of ester), singlets (three protons each) at 3.87 and 3.93 (methoxy), a quartet (two protons) at 4.30 (O–CH_2– of ester), a singlet (1 proton) at 5.98 (C–H of indole ring), singlets (one proton each) at 7.09 and 7.92 (aromatic C–H), and a singlet (one proton) at 9.10 (vinyl, adjacent to nitrogen).

Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.96; H, 5.16; N, 8.81.

Ethyl 3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-10-acetate (6) and Ethyl 3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate (7a).—The sodium salt of 3-carbethoxy-7,8-dimethoxypyrimido-[1,2-a]indol-2(1H)-one (13 g, 0.038 mol) was suspended in 400 ml of absolute ethanol. Ethyl bromoacetate (38 g, 0.23 mol) was added and the mixture was refluxed for 1.5 hr. After cooling, the separated solid was collected and recrystallized three times from ethanol to give 2.0 g (13%) of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indol-10-acetate as yellow crystals: mp 256–260°; ν_{max}^{KBr} 1720 (C=O of ester), 1692 (C=O conjugated ester), and 1653 cm^{-1} (C=O of amide); $\lambda_{max}^{CH_3CN}$ 281 mμ (ε 26,300) 303 (31,600), and 338 (10,800).

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.95; H, 5.48; N, 6.83.

The filtrate of the above reaction mixture was allowed to stand at room temperature for 18 hr. The separated solid was isolated by filtration and recrystallized twice from ethanol to give 5.7 g (37%) of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate as a fluffy yellow solid: mp 208.5–209°; ν_{max}^{KBr} 1730 (C=O ester), 1695 (C=O conjugated ester), and 1664 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3CN}$ 277 mμ (ε 25,900), 300 (29,800), and 335 (10,400). The nmr spectrum ($CDCl_3$) exhibited appropriate peaks for 2 ethyl, 2 methoxy, and aromatic C–H groups and in addition a singlet (two protons) at δ 4.80 (–CH_2– adjacent to ester and nitrogen), a singlet (one proton) at 5.64 (CH of indole), and a singlet (one proton) at 8.50 (vinyl adjacent to nitrogen).

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.30; H, 5.51; N, 6.75.

3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetic Acid (7b).—A 21.5-g (0.054 mol) sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetate was stirred and refluxed for 1.5 hr in a mixture of 400 ml of 1,2-dimethoxyethane and 400 ml of 10% hydrochloric acid. After cooling, the separated solid was collected and recrystallized from dimethylformamide–water to give 6.6 g (33%) of 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetic acid as yellow crystals: mp 268–269°; ν_{max}^{KBr} 1735 (broad, C=O for conjugated ester and nonconjugated acid) and 1630 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 274 mμ (ε 31,200), 296 (27,100), and 332 (9800).

Anal. Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.66. H, 4.77; N, 7.51.

Ethyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-3-carboxylate (10). A.—A suspension of 9.5 g (0.03 mol) of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one in 250 ml of ethanol containing 0.9 g of platinum oxide was hydrogenated at room temperature at an initial pressure of 45 psi. The hydrogen uptake stopped after 4 hr, the separated white solid was dissolved by heating and the solution was filtered, the filtrate was diluted to 500 ml with water and cooled. The separated white solid amounted to 6.5 g (68%) of ethyl 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate: mp 166–166.5°; ν_{max}^{Nujol} 1730 (C=O ester) and 1680 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 283 mμ (ε 10,000), 294 (11,800), and 317 (17,800).

Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.56; H, 5.94; N, 8.74.

B.—A 3.16-g (0.01 mol) sample of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one was treated with 1.5 g (0.04 mol) of sodium borohydride in 100 ml of isopropyl alcohol for 5 hr at room temperature. The reaction mixture was poured onto ice containing dilute hydrochloric acid and extracted with chloroform. Removal of the organic solvent left an oil which was crystallized and then recrystallized from aqueous methanol to give a white solid, mp 165–166°, which was in all respects (infrared spectrum, melting points, and a mixture melting point determination) identical with the product obtained in part A above.

Ethyl 1,3-Bis(2-cyanoethyl)-1,2,3,4-tetrahydo-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate (11a).—A 20-g (0.063 mol) sample of ethyl 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate was caused to react with excess (75 ml) acrylonitrile by 24-hr reflux in 300 ml of ethanol containing 10 ml of triethylamine. After concentration of the solvent, the residual oil was chromatographed on neutral alumina (200 g). Fractions eluted with 50% ether–chloroform were combined and concentrated to give a solid which on recrystallization from ethyl acetate–cyclohexane gave 11 g (45%) of ethyl 1,3-bis(2-cyanoethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate as white crystals: mp 117–118°; $\nu_{max}^{CHCl_3}$ 2255 (C≡N), 1732 (C=O ester), and 1678 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 214 mμ (ε 24,400) and 315 mμ (ε 15,400). The nmr spectrum ($CDCl_3$) showed a singlet (one proton) at δ 5.89 (CH of indole) and appropriate peaks for the protons in the rest of the molecule.

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.48; H, 5.93; N, 13.45.

1,2,3,4-Tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-1,3-dipropionitrile (12).—A 1.15-g (0.0028 mol) sample of ethyl 1,3-bis(2-cyanoethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate was saponified by refluxing with 0.12 g of sodium hydroxide in 30 ml of aqueous ethanol for 5 hr. Cooling deposited 1.06 g of a white solid which was suspended in water and acidified with dilute hydrochloric acid. After the gas evolution had stopped, the separated solid was collected and recrystallized from ethanol–dimethylformamide to give 0.67 g (70%) of 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido-[1,2-a]indole-1,3-dipropionitrile as white crystals: mp 158–159°: ν_{max}^{KBr} 2242 (C≡N) and 1670 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ sh 282 mμ (ε 9500), 291 (11,000), and 315 (17,400).

Anal. Calcd for $C_{19}H_{20}N_4O_3$: N, 15.90. Found: N, 15.87.

3-Carbethoxy-7,8-dimethoxy-10-methylpyrimido[1,2-a]indol-2(1H)-one, (13).—A 77-g (0.35 mol) sample of (2-nitro-4,5-dimethoxyphenyl)acetonitrile[4] was alkylated with 70 g (0.5 mol) of methyl iodide in the presence of 17.5 g (0.35 mol) of sodium hydride, in standard fashion, to give α-(2-nitro-4,5-dimethoxyphenyl)propionitrile (26 g), mp 135–137°. This material, without further characterization, was reduced with palladium on carbon in ethyl acetate[4] to the corresponding amino derivative. The latter was treated with diethyl ethoxymethylenemalonate, as described in the preparation of **5b**. The resulting product, mp 100–105° (3.6 g), was treated with 1 equiv of sodium ethoxide in 150 ml of ethanol as described above (see preparation of **8**). The product, after recrystallization from dimethylformamide, had mp 281–282°; ν_{max}^{KBr} 1730 (C=O ester) and 1685 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 284 mμ (ε 18,700), 304 (20,600), and 335 (10,000).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: N, 8.48. Found: N, 8.78.

Ethyl 3-Carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-10-acetate (8).—A 2-g sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-10-acetate was hydrogenated at 50 psi in 120 ml of ethanol in the presence of platinum oxide. After 6 hr the catalyst was filtered and ether was added to the filtrate. The separated solid was recrystallized from dimethylformamide–water to give 1.2 g (60%) of ethyl 3-carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-10-acetate: mp 210.5–211.5°; ν_{max}^{KBr} 1738 (C=O ester) and 1660 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3CN}$ 223 mμ (ε 21,400), sh 282 (10,000), sh 294 (12,400), and 316 (16,300). The nmr spectrum (DMF-d_7) exhibited the usual triplets and quartets for the O–CH_2CH_3 groups, singlets for the O–CH_3 groups, multiplets between 4 and 5 ppm for the protons of the 3 and 4 positions, and two singlets for the aromatic protons.

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.23; H, 5.83; N, 7.15.

Ethyl 3-Carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate (9).—A 10-g sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-

indole-1-acetate was hydrogenated at an initial pressure of 50 psi in 200 ml of ethanol in the presence of 1 g of platinum oxide. After 4 hr the catalyst was filtered, the filtrate was concentrated, and the residual oil was chromatographed on neutral alumina. Fractions eluted with ether were combined and concentrated, and the residual solid was recrystallized from ethyl acetate–hexane to give 3.0 g (30%) of ethyl 3-carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-*a*]indole-1-acetate: mp 96–98°; $\nu_{max}^{CHCl_3}$ 1736 (C=O ester) and 1682 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ sh 281 mμ (ε 8000), sh 289 (9700), and 314 (15,500).

Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.51; H, 5.98; N, 6.84.

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Synthesis of Some 5-Trimethylsilylindoles

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5-Trimethylsilylindole has been synthesized starting from indole which was N-benzylated and brominated in the 5 position, metalated to 5-lithio-N-benzylindoline, and treated with trimethylchlorosilane to yield 5-trimethylsilyl-N-benzylindoline. Catalytic hydrogenolysis in the presence of acetic anhydride gave 5-trimethylsilyl-N-acetylindoline, which was hydrolyzed by KOH in diethylene glycol to 5-trimethylsilylindoline, which in turn was converted into 5-trimethylsilylindole by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. 5-Trimethylsilylgramines were synthesized. 5-Trimethylsilylgramine methiodide was converted into the nitrile by reaction with sodium cyanide and the latter was hydrolyzed to 5-trimethylsilylindole-3-acetic acid, or reduced to 5-trimethylsilyltryptamine.

Various indole derivatives substituted in the 5 position have been synthesized, such as 5-acetyl-,[1] 5-amino-,[2] 5-chloro-,[3] and 5-fluorotryptamines[4] and 5-nitro- and 5-aminogramines.[5] These are interesting in that they are related to the physiologically active 5-hydroxytryptamine.

We report here the synthesis of 5-trimethylsilylindole and some of its derivatives.

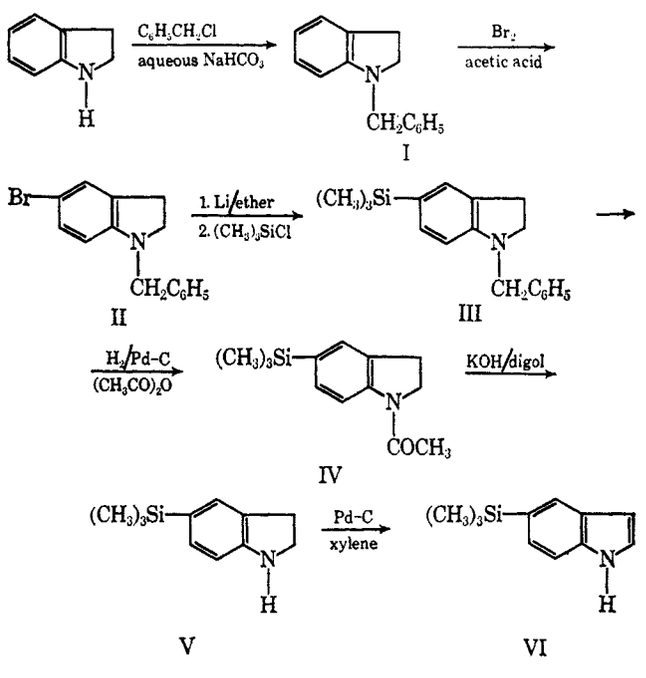
The preparation of compounds having a silicon–aryl bond involves difficulties because of the sensitivity of the silicon–aryl bond, to cleavage by acids and halogens. For this reason, although there are many methods for the preparation of indole derivatives, most of them are unsuitable for the preparation of silicon-containing indole derivatives since they require acid conditions in some step of the synthesis.

5-Trimethylsilylindole was synthesized starting from indoline[6,7] according to Scheme I.

N-Benzylindoline (I) was brominated with 1 equiv of bromine in acetic acid solution giving 5-bromo-N-benzylindoline (II), which was identical (melting point, mixture melting point, and ir spectrum) with the compound resulting from the N-benzylation of 5-bromoindoline.[8]

Catalytic hydrogenolysis of the N-benzyl group from 5-trimethylsilyl-N-benzylindoline (III) was easy, but in methanol, 2-propanol, or acetic acid solution it was accompanied by cleavage of the trimethylsilyl group. This was attributed to activation by the electron-releasing amino group in the *para* position. Consequently,

SCHEME I



hydrogenolysis was done in acetic anhydride, so that after the N-benzyl was split off the amino group was acetylated. The silicon–aryl bond was then stable and the resultant 5-trimethylsilyl-N-acetylindoline (IV) partially precipitated out of solution. The reaction was stopped immediately after the required amount of hydrogen was absorbed.

5-Trimethylsilylindole (VI) was obtained from V by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. The reaction at lower temperature (boiling toluene) was not satisfactory.

5-Trimethylsilylgramine (VII) was obtained from VI by the Mannich reaction using formaldehyde and dimethylamine. It was converted into 5-trimethylsilyl-3-piperidinomethylindole (VIII) by reaction with piperidine (Scheme II).

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