Studies in Biomimetic Alkaloid Syntheses. 1. Alkylations of 3-Chloroindolenines

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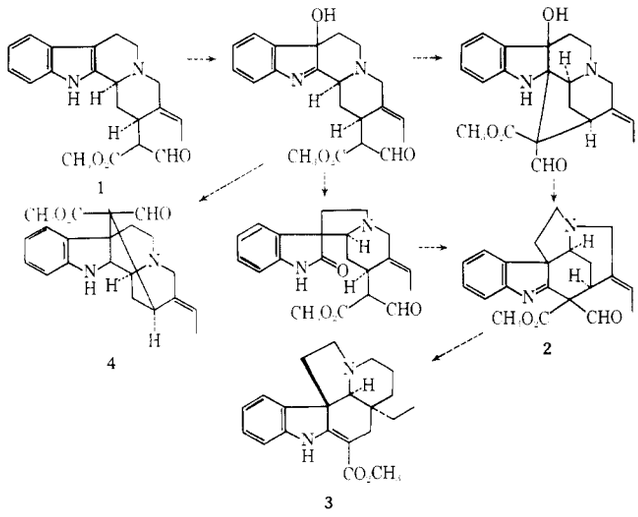
The chloroindolenine derivative (**6**) of tetrahydrocarbazole (**5**) reacted with thallium diethyl malonate by addition to the imine function and rearrangement to give the 3-spiro-2-alkylideneindoline (**9**). An analogous reaction was found with thallium ethoxide, leading to the imino ether **12**. However, with thallium ethyl acetoacetate the 2-spiro-3-alkylideneindoline (**15**) and the unrearranged O- and C-alkylation products **14** and **16** were formed. Substituting sodium diethyl malonate or sodium ethyl acetoacetate or the corresponding iodoindolenine in these reactions gave only tetrahydrocarbazole. The reactions are intermolecular parallels for key alkylation reactions proposed in the biosynthetic conversion of secoyohimbine to strychnos and picraline alkaloids.

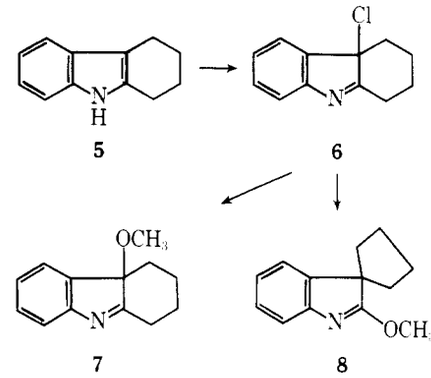
The chlorination of 2,3-disubstituted indoles readily provides 3-chloroindolenines. While reactions of the latter with hydroxide and alkoxide have been studied in the tetrahydrocarbazole[1] and in some indole alkloid[2] series and were found to lead to corresponding oxindoles, there have been no reports of the use of haloindolenines for C-alkylation reactions. Such alkylations would provide a new entry into syntheses of a variety of dihydroindole alkaloid structures and mimic key steps in the natural biosynthesis of these compounds.

Thus oxidation and intramolecular imine alkylation of secoyohimbine alkaloids (i.e., geissoschizine, **1**), followed by rearrangement, can be proposed as the natural pathway to a strychnos alkaloid skeleton (i.e., preakuammicinal, **2**) and ultimately to the aspidosperma alkaloids (i.e., vincadifformine, **3**), in accord with the result of biosynthetic plant feeding experiments with labeled precursors.[3] The proposed cyclization of an oxindole intermediate to the strychnos skeleton[3b] **2** (see Scheme I) would seem less favorable from a chemical point of view. Alternatively, direct intramolecular displacement of the (derivatized) hydroxyl group of the hydroxyindolenine leads to the picraline type alkaloids **4**. Details of the overall biosynthetic conversions of **1** to **2**, **3**, and **4** remain to be established and synthetic emulation of the biosynthetic steps leading to the strychnos skeleton has been posed as the "missing link" challenge in the formation of this major alkaloid class.[3b] The present studies provide a synthetic parallel to these hypothetical conversions. They could be extended to a total synthesis of the alkaloid vincadifformine (**3**), described in the following report.

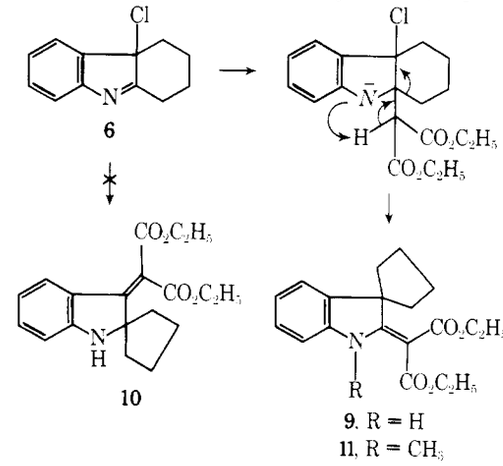
Scheme I. Biosynthetic Pathways for Generation of Strychnos, Picraline, and Aspidosperma-Type Alkaloids



The chloroindolenine **6**, prepared by chlorination of tetrahydrocarbazole **5** with *tert*-butyl hypochlorite, led on reaction with sodium methoxide in methanol at −20 °C predominantly to the methoxyindolenine **7** and to some of the rearrangement product **8**, while in methanolic sodium hydroxide the latter became the major product.[1,4]



Attempts to effect analogous halogen displacement or imine addition reactions with sodium diethyl malonate in ether, dimethylformamide, dimethyl sulfoxide, or methanol, under a variety of conditions, gave mainly recovered chloride **6** or tetrahydrocarbazole **5**. However, on refluxing thallium diethyl malonate and the chloroindolenine **6** in benzene, the unsaturated malonate **9** was formed in 47% yield, together with 10% of tetrahydrocarbazole **5**. Structure assignment as **9** for the product and exclusion of the alternative structure **10** were based on the compound's insolubility in acid, expected of a



vinylogous urethane, on a display of extended conjugation in UV (λ_{max} 299, 329 nm; ϵ 9400, 19 750) and IR (ν_{max} 1575 cm^{-1}, strong) spectra and particularly on a large difference in IR carbonyl stretching frequencies for the two ester groups. While one appears at 1710 cm^{-1}, the other is shifted to 1660 cm^{-1}

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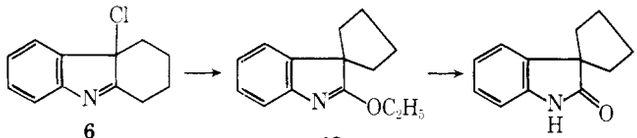
by internal hydrogen bonding. *N*-Methylation of the diester **9** gave a product **11** with a single ester carbonyl absorption band at 1695 cm^{-1}, showing about twice the extinction coefficient of those found for the two ester absorption bands in **9**.

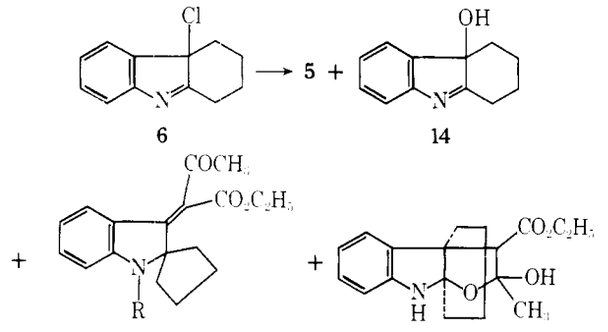
In analogy to the addition of thallium diethyl malonate to the imine function of the chloroindolenine **6** and rearrangement to the 3-spiroindoline **9**, a corresponding reaction of **6** with thallium ethoxide in benzene resulted in the formation of the imino ether **12**, which could be hydrolyzed to the oxindole **13**. No unrearranged ethoxyindolenine was formed in this reaction, in contrast to the predominant formation of the methoxyindolenine **7** obtained on reaction of the chloroindolenine **6** with sodium methoxide.



6 **12** **13**

When the chloroindolenine **6** was heated with thallium ethyl acetoacetate, tetrahydrocarbazole **5** was produced as the major product, together with the known hydroxyindolenine **14** (14%) and the ethyl acetoacetate carbon alkylation products **15** (10%) and **16** (4%). The structural assignment of **15** was based on its acid solubility and indoline UV spectrum, which excluded a structure analogous to that of the malonate product **9**. In its NMR spectrum **15** showed an NH proton singlet at δ 4.75, which could be slowly removed by hydrogen–deuterium exchange in D_2O and NaOD, or shifted to δ 9.5 in trifluoroacetic acid (broad two-proton signal for the ammonium salt). On methylation the *N*-methyl derivative **17** was obtained. These observations are not compatible with an acetoacetate adduct having a methine proton. No carbon–nitrogen double bond stretch was seen in the IR spectrum. Since only one double bond isomer was isolated, the *E,Z* orientation of ester and acyl groups in **15** relative to the aromatic ring could not be defined in the absence of the alternative isomer.[5]

Assignment of the hemiketal structure **16** to the minor alkylation product is based on its indoline UV spectrum, on a molecular ion *m/e* 317 showing incorporation of one water equivalent, on saturated ester and OH absorptions but no acyl absorption in the IR spectrum, and on an NMR methyl singlet at δ 1.7, more consistent with **16** than with a structure with an acyl group.



6 **14**

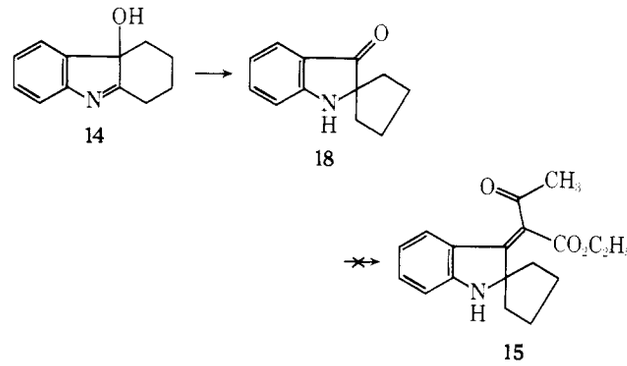
15, R = H
17, R = CH_3

16

In a search for alternatives to the thallium ethyl acetoacetate reagent it was found that detectable amounts (<3% yield) of the major alkylation product **15** were formed on reaction of the chloroindolenine **6** with ethyl acetoacetate and silver perchlorate in nitromethane[6] or with Triton B as base in a two-phase dichloromethane/water system. From a homogeneous solution of the latter reagents in an ethanol, methanol, and benzene mixture the hydroxyindolenine **14** was obtained as major acid soluble product, but no alkylation product **15** could be found.

Formation of the hydroxyindolenine **14** arises from initial O-alkylation of ethyl acetoacetate with direct displacement of chlorine in the chloroindolenine **6**. The resultant enol ether is subject to hydrolysis during acid extraction of the reaction mixture. While products **15** and **16** may be formed by an analogous direct displacement of chlorine in **6** with C-alkylation of ethyl acetoacetate, they could alternatively also be derived from O-alkylating addition of ethyl acetoacetate to the imine function of **6** and bridging of an initial enol ether product with displacement of chlorine, resulting in overall C-alkylation of ethyl acetoacetate. Preferential O- rather than C-alkylation in the ethyl acetoacetate reaction would then rationalize the lack of products analogous to **9**, derived from diethyl malonate.

In view of the facile rearrangement of the hydroxyindolenine **14** to the spiroindoxyl compound **18**,[7] these compounds were considered as possible precursors for the major alkylation product **15**. However, attempts to condense ethyl acetoacetate or its thallium salt with the ketone **18** in refluxing ethanol or benzene did not yield the keto ester **15**.



14 **18**

15

Preliminary efforts to extend this reaction to the thallium salts of acetylacetone, dimedone, ethyl benzoylacetate, ethyl cyanoacetate, malononitrile, and nitromethane, followed by an acid workup, showed that some hydroxyindolenine **14** was formed in the first three cases which can give rise to enol ethers, but not in the latter three. Tetrahydrocarbazole **5** was formed in all instances in addition to uncharacterized tarry material.

The ubiquitous formation of tetrahydrocarbazole **5** is assumed to originate from nucleophilic abstraction of halogen from the chloroindolenine **6**. Accordingly, the corresponding iodoindolenine and thallium diethyl malonate gave only tetrahydrocarbazole **5** ("$I^+ > Cl^+$").

The foregoing conversions of tetrahydrocarbazole to the alkylation and rearrangement product **9** and the alkylation product **16** provide intermolecular reaction parallels to biosynthetic conversions of the secoyohimbine (**1**) to strychnos (**2**) and pikraline (**4**) type alkaloids. In order to bring these reactions to closer analogy and to apply them to syntheses of naturally occurring alkaloids, they were extended to tetrahydrocarbolines, as described in the following report of a synthesis of vincadifformine (**3**).

Experimental Section

4a-Chloro-2,3,4,4a-tetrahydro-1*H*-carbazole (6). Tetrahydrocarbazole (1.71 g, 10 mmol) was dissolved in benzene (30 mL) containing triethylamine (1.1 mL). The mixture was cooled in ice, then *tert*-butyl hypochlorite (1.1 mL) was added slowly through a syringe needle dipping below the surface of the stirred solution. After addition was complete, stirring was maintained for 30 min, then the reaction mixture was washed three times with ice water. The benzene solution was dried by passing it through phase separating paper (Whatman No. 1 PS) and then distilling a small portion of the solvent. This solution was used directly for the subsequent reactions: IR (CCl_4) ν_{max} 3050, 2950, 2860, 1590, 1355 cm^{-1}; NMR (CCl_4) τ 2.32–2.80 (complex

m, 4 H), 7.04–7.20, 7.24, 7.41, 7.70–7.97, 8.04–8.80, 9.05 (complex m, 8 H).

2′-Ethoxyspiro(cyclopentane-1,3′-3′*H*-indole) (12). Thallium(I) ethoxide (2.5 g) was added to the above solution of **6.** The reaction mixture was stirred and refluxed for 6 h, then cooled and filtered through a short column of Florisil. Removal of the solvent furnished an oil which was absorbed on alumina (Woelm, Grade I) from light petroleum. Elution with ether–light petroleum (1:3) gave 2′-ethoxyspiro(cyclopentane-1,3′-3′*H*-indole) (**12**) (1.45 g, 67%), as a colorless oil: IR (film) ν_{max} 3010, 2960, 2880, 1580, 1460, 1400, 1380, 1340, 1270, 1025, 730 cm^{-1}; NMR (CCl_4) τ 2.6–3.1 (4 H), 5.54 (q, 2 H), 8.01 (br m, 8 H), 8.61 (t, 3 H). The structure was confirmed by acid hydrolysis[1] to spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-one (**13**), identical with an authentic sample.

Diethyl Spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-ylidenemalonate (9). Thallium(I) diethyl malonate (3.64 g, 10 mmol) was added to the above solution of **6.** The mixture was stirred and refluxed for 18 h and then the cooled reaction mixture was passed through a short column of Florisil. The filtrate was extracted twice with ice cold 2 N hydrochloric acid, then washed with water and dried over sodium sulfate. Removal of the solvent furnished a dark oil which partially crystallized on standing. After cooling to 0 °C, the crystals were filtered, and after recrystallization from *n*-heptane furnished diethyl spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-ylidenemalonate (**9**): mp 102–103 °C (1.54 g, 47%); IR (CCl_4) ν_{max} 3290, 3050, 2980, 2950, 2875, 1710, 1660, 1605, 1575, 1475, 1395, 1365, 1278, 1225, 1102, 1070 cm^{-1}; NMR (CCl_4) τ 2.76–3.12 (5 H), 5.77 (quartet, 4 H), 7.4–7.6, 8.04 (complex m, 8 H), 8.68 (t, 6 H); UV (EtOH) λ_{max} (ϵ) 204 (9000), 232 (12 000), 299 (9400), 329 nm (19 750); MS *m/e* (%) 329 (M^+, 45), 288 (100), 256 (57), 170 (56), 168 (37), 182 (22). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.37; H, 7.06; N, 4.16.

Diethyl 1′-Methylspiro(cyclopentane-1,3′-3′*H*-indole)-2′-ylidenemalonate (11). A mixture of 1 g (3.3 mmol) of the malonyl adduct **9** and lithium amide (280 mg, 13.2 mmol) was refluxed in anhydrous tetrahydrofuran (20 mL) for 4 h under an atmosphere of dry nitrogen. The reaction was then cooled and a solution of methyl iodide (1.5 mL, 26.4 mmol) in dimethylformamide (5 mL) was added; the resulting mixture was stirred at 20 °C for 60 h, then poured into water and extracted three times with ether. The organic extracts were washed with water and dried over sodium sulfate and the solvent was evaporated to leave an oil which slowly crystallized. Recrystallization from *n*-heptane gave diethyl 1′-methylspiro(cyclopentane-1,3′,3′-*H*-indole)-2′-ylidenemalonate: mp 100–102 °C (600 mg, 58%); IR (CCl_4) ν_{max} 3050, 2980, 2870, 1695, 1545, 1485, 1450, 1365, 1275, 1200, 1095, 1050, 960 cm^{-1}; NMR (CCl_4) τ 3.00 (W = 46 Hz, 4 H), 5.80 (q, 4 H), 6.85 (s, 3 H), 7.3, 8.0 (br m, 8 H), 8.71 (t, 6 H); UV (EtOH) λ_{max} (ϵ) 207 (6200), 237 (8200), 302 (3700), 342 nm (10 500); MS *m/e* (%) 343 (M^+, 20), 303 (91), 184 (100), 168 (34), 167 (27), 157 (26). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.89; H, 7.44; N, 3.86.

Reaction of 4a-Chloro-2,3,4,4a-tetrahydro-1*H*-carbazole (6) with Thallium(I) Ethyl Acetoacetate Enolate. To the above solution of **6** was added thallium(I) ethyl acetoacetate enolate (3.24 g, 10 mmol). The two substances were allowed to react and the reaction mixtures worked up as in the preparation of the malonyl adduct **9.** The nonbasic product was a dark oil (1.1 g, 64%) and at least 60% of this oil was tetrahydrocarbazole (650 mg, 38%). It contained no tetrahydrocarbazole–ethyl acetoacetate adducts. The acid extracts were neutralized with ice cold potassium carbonate solution and then made strongly basic with potassium hydroxide and extracted three times with dichloromethane. The organic extracts were combined, washed with water, and dried, and the solvent was removed to give a partially crystalline material. This product was adsorbed onto a column of dry alumina, which was developed with light petroleum–ether (75:25). After development, the column was sliced into three separate bands (determined by examination under UV light) and the products were eluted from the adsorbent with dichloromethane. The most polar compound was identified as 4a-hydroxy-2,3,4,4a-tetrahydro-1*H*-carbazole (**14**) (254 mg, 14%), identical with an authentic sample.[7] The compound of middle polarity was assigned as ethyl 2-hydroxy-2-methyl-2,3,3a,8a-tetrahydro-3a,8a-butanofuro[2,3-*b*]indole-3-carboxylate (**16**) (125 mg, 4%): IR (CCl_4) ν_{max} 3385, 3000, 2945, 2860, 1730, 1615, 1480, 1465, 1450, 1423, 1375, 1347, 1315, 1305, 1280, 1250, 1185, 1128, 1047, 1005, 962, 956, 946, 905, 880 cm^{-1}; NMR ($CDCl_3$) τ 2.95 (m, 5 H), 4.3 (s, 1 H, exchanged rapidly with D_2O), 5.27 (s, 1 H, exchanged slowly with D_2O), 5.74 (q, 2 H), 6.70 (s, 1 H), 8.30 (s, 3 H), 8.65 (t, 3 H), 7.25–9.30 (complex absorption, 9 H); UV (EtOH) λ_{max} (ϵ) 212 (10 000), 240 (8700), 294 nm (2300); MS *m/e* (%) 317 (M^+, 20), 299 (41), 216 (44), 184 (100), 170 (88), 169 (79). The least polar compound was assigned as ethyl spiro(cyclopentane-1,2′-3′*H*-indole)-3′(1′*H*)-ylideneacetoacetate (**15**): mp 118–118.5 °C (300 mg, 10%); IR (CCl_4) ν_{max} 3395, 3050, 2960, 2880, 1700, 1680, 1632, 1605, 1480, 1460, 1395, 1370, 1330, 1310, 1265, 1105, 1090, 970 cm^{-1}; NMR ($CDCl_3$) τ 2.65–3.34 (7 lines, 4 H), 5.28 (s, 1 H), 5.75 (q, 2 H), 7.80 (s, 3 H), 8.68 (t, 3 H), 7.6–8.0, 8.3–8.7 (br m, 8 H); NMR (CF_3CO_2H) τ 0.5 (br s, 2 H), 2.2 (4 H), 5.61 (q, 2 H), 7.60 (s, 3 H), 8.55 (t, 3 H), 7.0–8.5 (br m, 8 H); UV (EtOH) λ_{max} (ϵ) 208 (26 000), 242 (27 500), 293 nm (5300); addition of acid gave no shifts in band positions, but all bands were weaker; addition of base increased the intensity of the 208-nm band approximately 30-fold; MS *m/e* (%) 299 (M^+, 24), 256 (100), 228 (40), 182 (48), 170 (60). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.13; H, 7.23; N, 4.45.

Ethyl 1′-Methylspiro(cyclopentane-1,2′-3′*H*-indole)-3′(1′-*H*)-ylideneacetoacetate (17). The acetoacetate adduct **15** (75 mg) was methylated with lithium amide (30 mg) in tetrahydrofuran and methyl iodide (250 μL) in DMF, as described for the malonate adduct **9**, yielding a brown oil which was taken up in light petroleum–ether (72:25) and passed through a short column of alumina to furnish ethyl 1′-methylspiro(cyclopentane-1,2′-3′*H*-indole)-3′-(1′*H*)-ylideneacetoacetate (**17**) (45 mg, 57%): IR (CCl_4) ν_{max} 3050, 2935, 2853, 1687, 1615, 1480, 1377, 1330, 1310, 1095, 977 cm^{-1}; NMR (CCl_4) τ 2.8 (2 H), 3.2–3.7 (2 H), 5.75 (q, 2 H), 7.08 (s, 3 H), 7.8 (s, 3 H), 8.66 (t, 3 H), 7.0–9.2 (complex absorption, 8 H); UV (EtOH) λ_{max} (ϵ) 211 (30 400), 247 (32 150), 317 nm (3240); MS *m/e* (%) 313 (M^+, 27), 271 (22), 270 (100), 256 (22), 242 (35), 184 (20).

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Registry No.—**5,** 942-01-8; **6,** 42540-51-2; **9,** 66842-54-4; **11,** 66842-55-5; **12,** 66842-56-6; **13,** 41058-67-7; **14,** 42738-99-8; **15,** 66842-57-7; **16,** 66842-58-8; **17,** 66842-59-9; thallium(I) ethoxide, 20398-06-5; thallium(I) diethyl malonate, 66859-38-9; thallium(I) ethyl acetoacetate enolate, 42283-28-3.

References and Notes

(1) R. J. Owellen, *J. Org. Chem.*, **39,** 69 (1974).
(2) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84,** 3871 (1962).
(3) (a) A. I. Scott, *Acc. Chem. Res.*, **3,** 151 (1970); (b) *Bioorg. Chem.*, **3,** 398 (1974).
(4) This difference has been ascribed to alternative reactions of a rearranging carbonium ion,[1] but we prefer to consider these products to be derived from respective S_N2 displacement of chloride by methoxide vs. methanol addition to the imine function and rearrangement.
(5) From other studies it is known that in 3-alkylideneoxindoles proximity of the aromatic peri proton to a *Z* (but not an *E*) oriented carbonyl group results in a downfield shift of this proton [R. I. Autrey and F. C. Tahk, *Tetrahedron*, **23,** 901 (1967)]. Comparison of NMR spectra of 3-alkylidineoxindoles bearing the required ester and acyl *Z* substituents showed the peri protons respectively shifted downfield to δ 8.45 and 8.68. (The model compounds were prepared in our group by Mr. Marvin DeTar for another synthetic project which will be described later.) However, with introduction of a tetrahedral carbon in **15** in place of the oxindole carbonyl group the aromatic proton region extends only to δ 7.4 and prevents correlation of the oxindole and indoline series and *E* vs. *Z* assignment in **15.**
(6) P. Boldt, H. Militzer, W. Thielecke, and L. Schultz, *Justus Liebigs Ann. Chem.*, **718,** 101 (1968).
(7) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73,** 2188 (1951).