Some Reactions of 1-Carboethoxytetrahydrocarbazole Chloroindolenine

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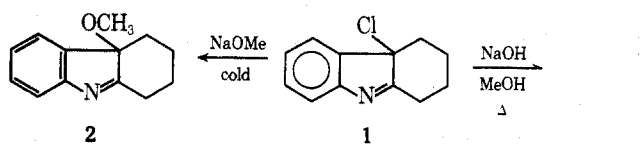
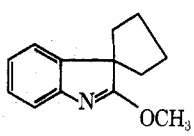
The chloroindolenine of 1-carboethoxytetrahydrocarbazole, when treated with excess methanolic base and worked up with mild acid, gave the 1-methoxy derivative **5**, while work-up with strong acid gave the 1-hydroxy product **6**. Treatment of **5** with dilute acid yielded **6**, which gave back **5** when treated with absolute methanol–acetic acid. Reaction of 1-carboethoxytetrahydrocarbazole with NBS–pyridine gave 1-carboethoxycarbazole.

Recently we reported that the chloroindolenine of tetrahydrocarbazole (**1**), when treated with cold NaOMe, gave 4a-methoxytetrahydrocarbazole (**2**), while 2-methoxy-3-(1′-spirocyclopentane)(3*H*)-indole (**3**) was formed in the presence of refluxing MeOH–NaOH.[1] Treatment of **1** with HCl–MeOH gave the bis-1,9-tetrahydrocarbazole dimer.



2 **1**



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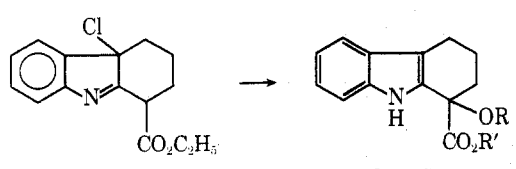
Though the expected 1-methoxytetrahydrocarbazole was not found in any of these reactions, it was readily prepared by the reaction of NaOMe with the 1-pyridinium bromide salt of tetrahydrocarbazole. This behavior of the chloroindolenine was unexpected in light of the work of Gassman et al.,[2] where, under appropriate conditions, the chloroindolenine of 2,3-dimethylindole thermally rearranged and gave 2-methoxymethyl-3-methylindole on treatment with NaOMe. While investigating the chemistry of the closely related 1-carboethoxytetrahydrocarbazole chloroindolenine (**4**), we discovered that it behaved anomalously when compared to **1**.

Reaction of 1-carboethoxytetrahydrocarbazole[3] with *tert*-butyl hypochlorite and triethylamine in methylene chloride gave a solution whose uv and NMR were compatible with **4**. Reaction of **4** with NaOMe at room temperature, followed by work-up with acetic acid and treatment with diazomethane, gave **5** in 83% yield.



4

5, R = R = CH_3

6, R = H; R′ = CH_3

7, R = CH_3; R′ = C_2H_5

In contrast, reaction of **4** with refluxing NaOH–MeOH, followed by addition of HCl, and reesterification gave a different product. The mass spectrum of this material gave a molecular ion at *m/e* 245, and peaks at M − 18 (minus OH) and M − 59 (minus CO_2CH_3). The uv spectrum was that of an indole, and the ir spectrum had a new band, compatible with an alcohol group, in addition to those found for **5**. The NMR differed from that of **5** only in the disappearance of a methoxyl signal, suggesting structure **6** for this product.

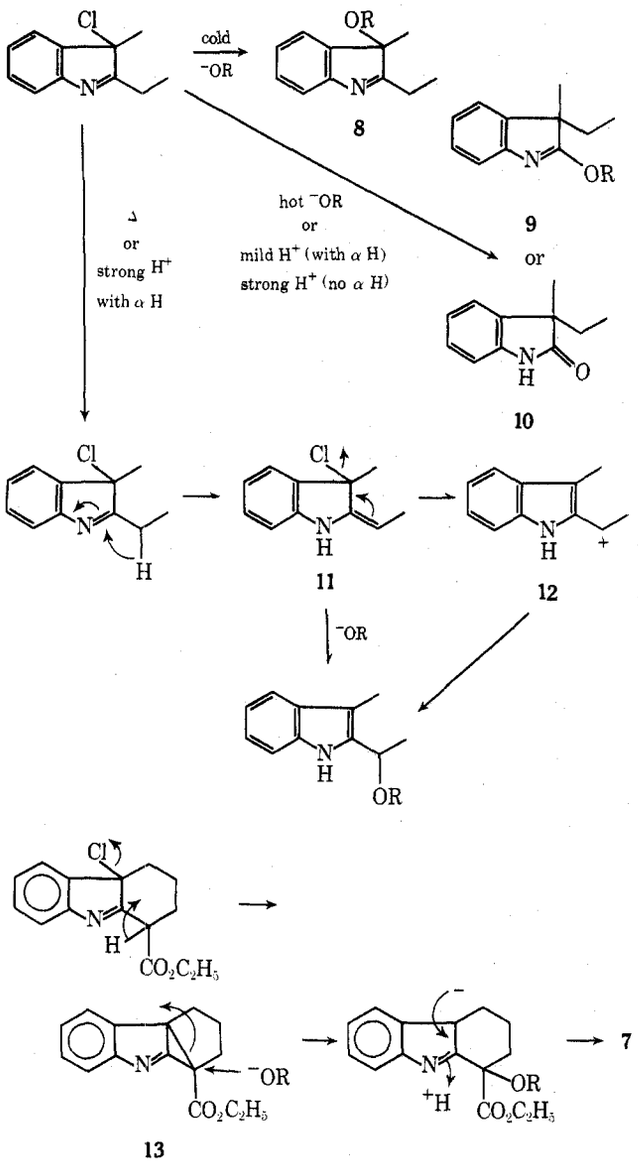
Further experiments showed that regardless of whether NaOMe at 0° or NaOH at reflux was employed, product **5** predominated when the reaction mixture was brought to pH 4 prior to extraction and diazomethane treatment, while **6** predominated when the pH was <1 (NMR). When a large volume of CH_2Cl_2 was used and treatment with either refluxing NaOH or cold NaOMe was performed with minimal MeOH present, the sole product was the ethyl ester **7**.

When **5** was treated with dilute HCl in THF at room temperature, it was readily hydrolyzed to **6** (NMR data). When 1-methoxytetrahydrocarbazole was treated with dilute aqueous HCl, or hot dilute aqueous HOAc, the only identifiable product was the bis-1,9-tetrahydrocarbazole dimer, not unexpected from prior reports[4,5] if the 1-hydroxy compound is initially formed. On the other hand, when 1-hydroxytetrahydrocarbazole was treated with 5% HOAc in absolute MeOH, 1-methoxytetrahydrocarbazole was readily formed at room temperature, in a manner similar to the methylation of the hydroxylactam of dihydrocorynantheine.[6] When **6** was treated in this latter manner, the major product was **5**, as well as a small amount of 1-carbomethoxycarbazole.

When 1-carboethoxytetrahydrocarbazole was treated with NBS and pyridine, in an attempt to prepare **5** via the expected 1-pyridinium bromide salt, the product was instead 1-carboethoxycarbazole, in contrast to the behavior of tetrahydrocarbazole in the same reaction sequence.[7]

We reviewed our past experience and that of others with chloroindolenines regarding the structural features and reaction conditions leading to each of the varied products obtained. When simple unsubstituted chloroindolenines are treated with cold base, the product is the 3-alkoxy indolenine **8**.[1,2] With base at elevated temperature,[1,8,9] mild acid,[10,11] or with strong acid where there is no α-methylene proton,[11] the product is the 2-alkoxyindolenine **9**, or its corresponding oxindole **10**, a result of the well-known Wagner–Meerwein rearrangement. When an α proton is present, either thermal rearrangement of the chloroindolenine[2] or the action of strong acid[1,10b,11,12] promotes formation of the tautomeric intermediate **11**. This intermediate may then readily either yield the carbonium ion **12** (or one of its many resonance forms), or react directly with base to give the α-substituted products observed.

In the present set of reactions of the chloroindolenine of 1-carboethoxytetrahydrocarbazole, we have prepared the 1-alkoxy derivatives directly for the first time under cold basic conditions. We rationalized this on the basis that the electron-withdrawing 1-carboxyl group makes the α proton more acidic than normal, and promotes a facile tautomerization to structure **11**. This tautomeric enamine intermediate then reacts with RO^-, or eliminates Cl^-, to yield the 1-substituted products. An alternate route might involve the formation of a Favorskii-type intermediate, such as **13**, but we consider this very unlikely, as it would involve consider-



able strain in forming the three-membered ring, grossly distorting the planarity of the five-membered nitrogen-containing ring. For this reason, we consider **11** the most probable route of reaction.

Experimental Section[13]

1-Methoxy-1-carbomethoxytetrahydrocarbazole (5). A solution of 0.90 g (8.3 mmol) of *tert*-butyl hypochlorite in 5 ml of CH_2Cl_2 was run, over 15 min, into a mixture of 1.00 g (4.1 mmol) of 1-carboethoxytetrahydrocarbazole and 0.84 g (8.3 mmol) of triethylamine in 25 ml of CH_2Cl_2 precooled to 0°, and the reaction mixture was stirred for 30 min. The uv spectrum of this solution had maxima at 235 nm (ε 11080) and 275 (3330), and the NMR (of the reaction run in $CDCl_3$ followed by several washes with water) had signals at δ 1.0–2.3 (multiplet, 7 H), 2.4–3.1 (3 H), 3.8–4.5 (quartet, 2 H), and 7.0–7.7 (4 H). The above mixture was then run into a solution of 2.5 g of sodium in 50 ml of methanol at room temperature, and stirred for 2 hr. After evaporation of the solution, addition of water, and extraction with CH_2Cl_2, the aqueous solution was acidified and extracted with ether and the extract was treated with CH_2N_2 to give 0.89 g of **5** (83% yield). Crystallization twice from Et_2O gave colorless prisms melting at 111–112°: ir 3400, 1735 cm^{-1}; uv 227 nm (ε 16800), 278 (sh, 6370), 284 (6615), 292 (5365); NMR δ 1.75–2.50 (4 H), 2.59–2.92 (2 H), 3.28 (singlet, 3 H), 3.67 (singlet, 3 H), 7.01–7.67 (4 H), 8.55 (singlet, 1 H); mass spectrum *m/e* 259, 228, 200, 185, 167–168. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.52; H, 6.56, N, 5.40. Found: C, 70.12; H, 6.02; N, 5.34.

1-Hydroxy-1-carbomethoxytetrahydrocarbazole (6). A solution of the chloroindolenine **4** was prepared from 1.0 g of 1-carboethoxytetrahydrocarbazole, as in the case of **5** above, then run rapidly into a refluxing solution of 2.5 g of NaOH in 50 ml of methanol, and the reflux was continued for 30 min. Work-up identical with that for **5** above gave 0.68 g of **6** (67% yield). Crystallization and recrystallization from benzene gave a product melting at 138–139°; ir 3540, 3330, 1720 cm^{-1}; uv 230 nm (ε 16800), 276 (sh, 7600), 283 (8000), 292 (6500); NMR δ 1.78–2.50 (4 H), 2.60–2.90 (2 H), 3.71 (singlet, 3 H), 4.08 (singlet, 1 H), 6.94–7.65 (4 H), and 8.50 (singlet 2 H); mass spectrum *m/e* 245, 228, 186, 167–168. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.79; H, 6.22; N, 5.71.

1-Methoxy-1-carboethoxytetrahydrocarbazole (7). A solution of 4.0 g of 1-carboethoxytetrahydrocarbazole and 3.6 ml of triethylamine in 170 ml of CH_2Cl_2 was stirred under nitrogen in an ice bath. To this was added 3.6 ml of *tert*-butyl hypochlorite in 10 ml of CH_2Cl_2. The mixture was stirred for an additional 30 min, then one-half was run into 0.50 g of NaOH in 10 ml of MeOH and refluxed for 30 min, while the other one-half was run into 0.25 g of Na dissolved in 10 ml of MeOH at 0° and stirred for 30 min. Each reaction mixture was poured over NH_4OH–ice and extracted into CH_2Cl_2, which after drying over Na_2SO_4 was evaporated to give a quantitative yield of 1-methoxy-1-carboethoxytetrahydrocarbazole in both cases, as an oily, crystalline mass. Recrystallization from EtOH–H_2O gave white needles, melting at 98–100°: ir 3340 and 1730 cm^{-1}; uv 227, 285, and 294 nm; NMR δ 1.22 (triplet, 3 H), 1.90–2.50 (4 H), 2.73 (triplet, 2 H), 3.25 (singlet, 3 H), 4.23 (quartet, 2 H), 7.00–7.72 (4 H), 8.61 (singlet, 1 H); mass spectrum *m/e* 273, 259, 242, 200, 168–167.

1-Carboethoxycarbazole. To a solution of 3.00 g of 1-carboethoxytetrahydrocarbazole and 3.60 ml of pyridine in 60 ml of benzene was added at once 3.40 g of *N*-bromosuccinimide, and following an exothermal reaction, the mixture was stirred at room temperature for 2 hr. The benzene phase was separated from a crystalline mass, washed four times with water, and dried over Na_2SO_4, and after evaporation of the solvent in vacuo, the residue was crystallized from ethanol to yield 2.45 g (83%) of 1-carboethoxycarbazole, which after recrystallization from ethanol melted at 104–106° (lit. 106–107°[14]): uv 358, 305, 279, 249, 240, 227 nm; NMR δ 1.46 (triplet, 3 H), 4.52 (quartet, 2 H), 7.15–7.62 (4 H), 8.05–8.42 (3 H), 10.05 (singlet, 1 H). Treatment of 1-carboethoxycarbazole with NaOMe, followed by acid (HCl) and ether extraction, gave the free acid, mp 260–264° (lit. 268–269°[15]), while treatment of the acid with diazomethane in ether gave 1-carbomethoxycarbazole, which when recrystallized from 2-propanol gave fine tan needles melting at 140–141.5°: ir 3440, 1675, 1600 cm^{-1}; uv 359 nm (ε 6000), 303 (6700), 279 (15700), 250 (11800), 243 (11600), 225 (23000); NMR δ 3.92 (singlet, 3 H), 6.98–7.50 (4 H), 7.88–8.27 (3 H), 9.91 (singlet, 1 H); mass spectrum *m/e* 225, 193, 165, 139.

1-Hydroxytetrahydrocarbazole. To a solution of 440 mg of 1-ketotetrahydrocarbazole[16] in 15 ml of absolute methanol was added 180 mg of $NaBH_4$, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated, water was added, and the mixture was extracted into $CHCl_3$; the $CHCl_3$ was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 318 mg (72%) of crystalline product, melting at 115.5–117.5° (lit. 115–116°[4,17]); ir (Nujol) 3430, 3270 cm^{-1}; uv 293 nm (ε 4200), 284 (5000), 229 (16500); NMR δ 1.55–2.20 (4 H), 2.48–3.10 (2 H), 4.64–4.94 (1 H), 7.00–7.63 (4 H), 8.22–8.49 (1 H).

1-Methoxytetrahydrocarbazole (from 1-Hydroxytetrahydrocarbazole). A solution of 100 mg of 1-hydroxytetrahydrocarbazole in 10 ml of 5% HOAc in absolute MeOH was stirred overnight at room temperature, then evaporated to dryness. The ir, uv, and NMR of the resulting oil were identical with those of 1-methoxytetrahydrocarbazole, and crystallization from hexane gave 60 mg of material melting at 75–76°[1]; a mixture melting point with authentic 1-methoxytetrahydrocarbazole was undepressed.

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Registry No.—**4**, 56995-01-8; **5**, 56995-02-9; **6**, 56995-03-0; **7**, 56995-04-1; *tert*-butyl hypochlorite, 507-40-4; 1-carboethoxytetrahydrocarbazole, 50845-41-5; 1-carboethoxycarbazole, 56995-05-2; *N*-bromosuccinimide, 128-08-5; NaOMe, 124-41-4; 1-carbomethoxycarbazole, 51035-15-5; 1-hydroxytetrahydrocarbazole, 1592-62-7; 1-ketotetrahydrocarbazole, 3456-99-3; 1-methoxytetrahydrocarbazole, 42540-57-8.

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Intramolecular Diels–Alder Reactions. Synthesis of 3a-Phenylisoindolines as Analgetic Templates

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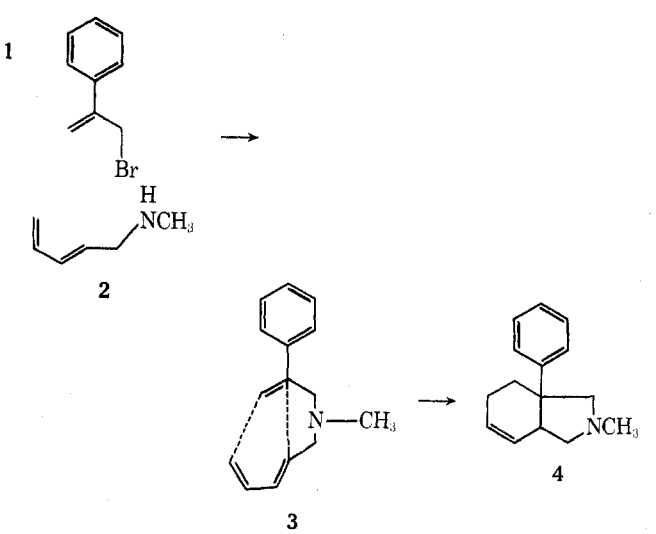
A preparatively efficient method for the synthesis of the substrate **10** is described. This undergoes an intramolecular [4 + 2] cycloaddition to give the lactam **11**. Reduction of the amide carbonyl gives **6**, the product of an extremely facile [4 + 2] cycloreversion, and no trace of the Diels–Alder adduct **7** was found. A number of transformations of **11**, including a skeletal rearrangement of **14** to **16**, are described, and the structure and relative stereochemistry of the products is elaborated largely on the basis of their NMR data. The cis stereochemistry of **20**, a product obtained from the cycloadduct **11** via hydrogenation, eliminative ether cleavage, and hydrogenation, is established by correlation with a relay compound **27**, independently synthesized via a bimolecular Diels–Alder reaction.

The application of intramolecular Diels–Alder reactions in the elaboration of substituted perhydroisoindolines, as well as kinetic aspects of these reactions, was the subject of earlier reports.[1-3] In this study we describe the use of these intramolecular cycloadditions in the synthesis of 3a-phenylisoindolines. Such compounds appeared particularly attractive to us, as this structural type incorporates some of the essential molecular features of such potent analgetics as Profadol[4] and related molecules.[5]

Our initial goal, in essence, was the preparation of a substrate **3** from α-bromomethylstyrene (**1**) and a pentadienyl amine **2**, followed by an intramolecular [4 + 2] cycloaddition to give the desired **4** (Scheme I). Our attempts to attain practical access to the amine **2** (or the corresponding halide) failed because of its inherent instability. We therefore turned our attention to alternate sources of suitable diene–methylamines, such as *N*-methylfurfurylamine (**5**). In fact we were rather encouraged by earlier reports[6,7] on the successful internal cycloaddition of the *N*-allyl derivative of **5**. The choice of **5** as the diene part added a considerable amount of flexibility, as the oxygenated character of the resulting cycloadduct provides numerous possibilities for further modifications.[8]

The desired substrate **6** was prepared readily and in high yield from **1** and **5**. Surprisingly, however, **6** resisted any attempt to effect the desired cycloaddition to produce **7**; in fact, compound **6**, when heated in a sealed NMR tube (C_6D_6), remained unchanged up to temperatures of 230°. Suspicions about an extremely facile retro-Diels–Alder reaction led us to lower the temperatures, but even at −60° the NMR spectrum of **6** did not reveal a trace of the elusive cycloadduct **7**. In view of the results reported with the de-

Scheme I



phenyl derivative of **6**,[6] we concluded that the phenyl substituent in **7** would sufficiently destabilize the σ bond to be formed to make **7** essentially nonexistent between −60 and 230°. That this was indeed the case will be corroborated below. Faced with these results we planned to neutralize the destabilizing effects of the phenyl group in **7** with the introduction of a carbonyl group as in **10**, i.e., to synthesize a molecule which would incorporate the "normal" electron-rich diene and an electron-deficient dienophile.[9] The synthesis outlined in Scheme II proved to be more efficient over some more obvious routes involving the highly unsta-