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Methoxylation of Bromo-1,2,3,4-tetrahydrocarbazoles. Oxidation and Subsequent Rearrangement of 1,2,3,4-Tetrahydrocarbazoles to Spiro-(cyclopentane-1,2′-indolin)-3′-ones

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5-Bromo- and 7-bromo-1,2,3,4-tetrahydrocarbazoles (**2** and **4**) were converted to 4′-methoxy- and 6′-methoxy-spiro(cyclopentane-1,2′-indolin)-3′-ones (**14** and **16**) by treatment with excess sodium methoxide in methanol/DMF in the presence of cuprous iodide in 10.3% and 53.7% yields, respectively. On the other hand, N-substituted bromocarbazoles were converted to the corresponding methoxycarbazoles in good yields under the same reaction conditions.

Keywords——oxidation; rearrangement; 1,2,3,4-tetrahydrocarbazole; methoxylation; spiro compound; cuprous iodide; sodium methoxide; dimethylformamide

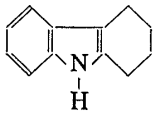
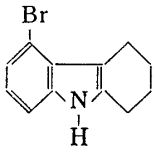
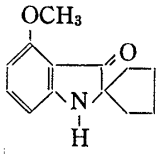
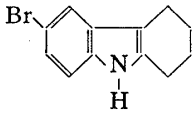
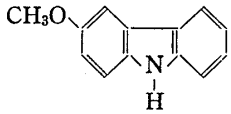
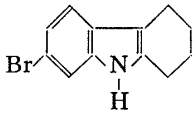
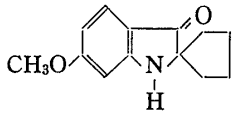
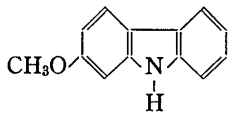
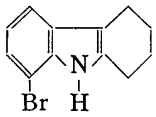
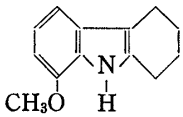
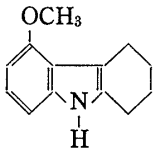
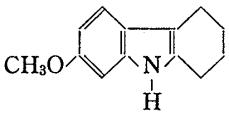
There are many indole alkaloids bearing hydroxyl or methoxyl groups on the benzene ring of the indole moiety. In the previous report[1] we described the introduction of a methoxyl group into indoles and indolines. As an extension of these investigations, we describe in this paper the scope and limitations of this methoxylation reaction and also the unexpected rearrangement of 1,2,3,4-tetrahydrocarbazoles to cyclopentane-spiro-2-pseudoindoxyls under the same reaction conditions.

Oxidation and Subsequent Rearrangement of 1,2,3,4-Tetrahydrocarbazoles

Treatment of 7-bromo-1,2,3,4-tetrahydrocarbazole (**4**) with an excess of sodium methoxide in methanol/dimethylformamide (DMF) in the presence of cuprous iodide resulted in the formation of a small amount of 2-methoxycarbazole (**17**) (yield, 3.5%) and 6′-methoxy-spiro-(cyclopentane-1,2′-indolin)-3′-one (**16**) (yield, 53.7%). The structure of the latter product was elucidated by elemental analysis and consideration of the spectral data. Methoxylation and oxidation followed by rearrangement of **4** took place to give **16**. As 7-methoxy-1,2,3,4-tetrahydrocarbazole (**7**) was rearranged to the spiro compound (**16**) (yield, 50.8%) under the same reaction conditions, it is assumed that the rearrangement occurred after the bromo group had been displaced by the methoxyl group. 5-Bromo-1,2,3,4-tetrahydrocarbazole (**2**) was subjected to the same reaction to give a 10.3% yield of the corresponding spiro compound (**14**). 6-Bromo-1,2,3,4-tetrahydrocarbazole (**3**) was not converted to a spiro compound, and instead only 3-methoxycarbazole (**15**) (yield, 4.4%), the aromatized product, was isolated from the tarry residue that was formed. 8-Bromo-1,2,3,4-tetrahydrocarbazole (**5**) underwent a normal substitution reaction to give the 8-methoxy compound (**18**) in good yield (80.5%) without formation of the spiro compound. The results are summarized in Table I. The reason why only the 8-bromo group was displaced by a methoxyl group in good yield without giving any tarry materials is not clear.

It is well known that the reaction of 1,2,3,4-tetrahydrocarbazoles with *tert*-butyl hypochlorite yields chloroindolenines,[2] highly reactive intermediates, which can be transformed to the spiro derivatives by treatment with alkali. 7-Bromo-1,2,3,4-tetrahydrocarbazole (**4**) was subjected to the same transformation procedure to give the spiro compound (**13**), which was methoxylated by our method. The structure of this spiro compound (**23**) apparently differed from that of the spiro compound (**16**) which was obtained in a single step from 7-bromo-

Table I. Oxidation and Subsequent Rearrangement of 1,2,3,4-Tetrahydrocarbazoles

Starting compound	Reaction time (hr)	Product (yield, %)	
 **1**	20	**1** (54.0)	
 **2**	10	 **14** (10.3)	
 **3**	13	 **15** (4.4)	
 **4**	6	 **16** (53.7)	 **17** (3.5)
 **5**	4	 **18** (84.5)	
 **6**	9	**14** (17.6) + **6**(18.5)	
 **7**	7	**16** (50.8) + **17** (4.7)	

1,2,3,4-tetrahydrocarbazole (**4**) as shown in Chart 1. Lithium aluminum hydride reduction of the carbonyl group of **16** gave the methylene compound (**24**) due to the electron releasing effect of the methoxyl group.[3] The result obtained is in good accordance with the concomitant formation of the corresponding methylene and hydroxy compounds by the same reduction of spiro(cyclopentane-1,2′-indolin)-3′-one, reported by Witkop.[4]

Effect of Catalysts and Reaction Mechanism

Table II shows the effects of some variations in the experimental conditions for converting 7-methoxy-1,2,3,4-tetrahydrocarbazole (**7**) into 6′-methoxy-spiro(cyclopentane-1,2′-indolin)-3′-one (**16**). The results suggested that cuprous iodide was the most effective catalyst for the rearrangement, and that the use of an excess of alkoxide was beneficial. The starting methoxy compound (**7**) is unstable to prolonged heating and yielded trace amounts of the spiro compound

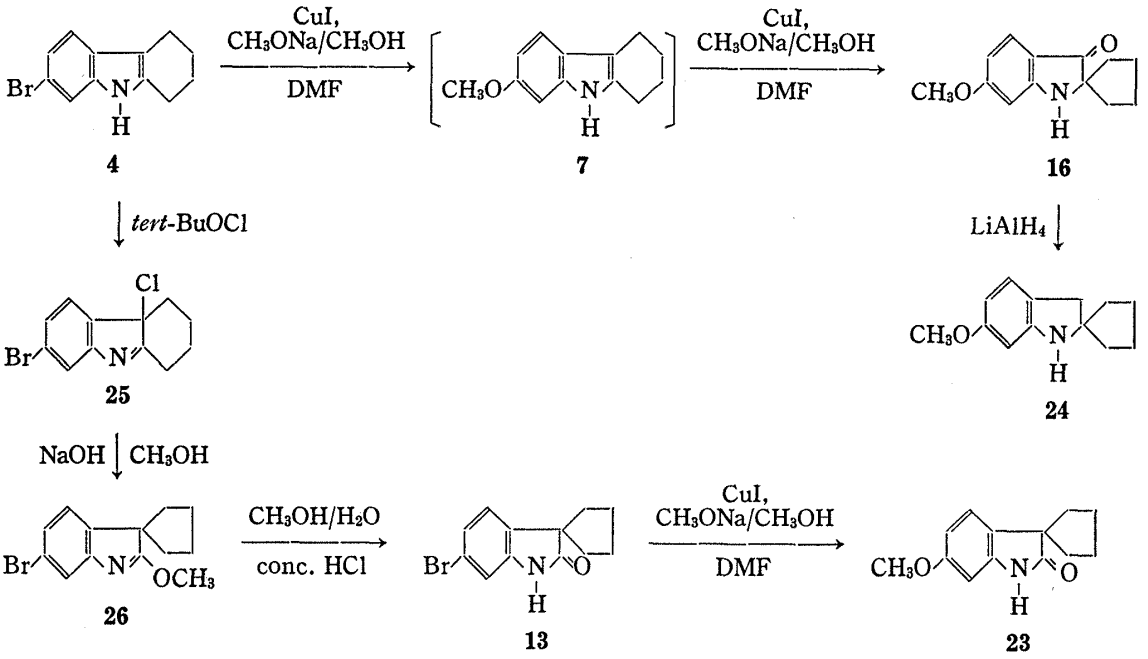
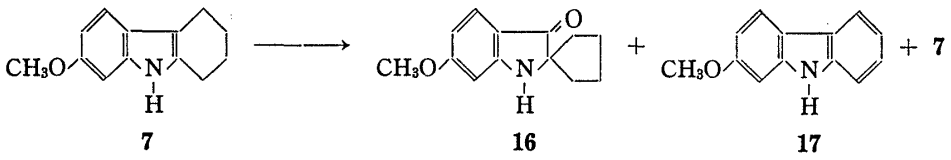


Chart 1

TABLE II.



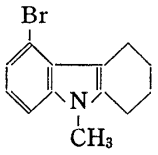
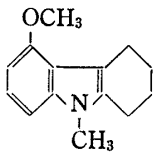
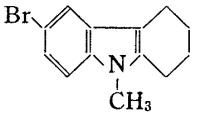
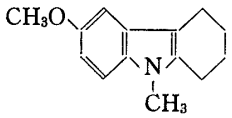
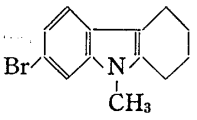
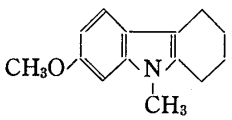
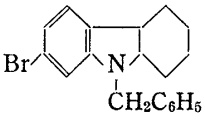
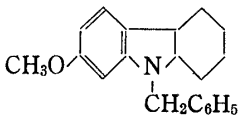
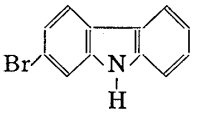
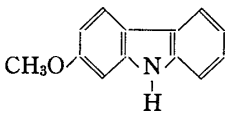
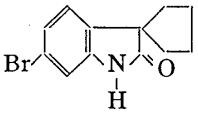
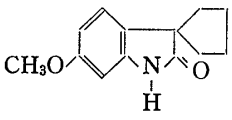
Catalyst Molar ratio, cat./7=2	Molar ratio $NaOCH_3$/7	Reaction time (hr)	Product (%) 16	17	7
CuI	10	7	50.8	4.7	—
CuCl	10	13.5	29.7	9.6	—
CuBr	10	14	28.4	12.9	—
CuI	—	15	6.2	—	—
—	10	6	8.7	—	36.0
—	10	14.5	13.8	1.7	—

(**16**) in the absence of a catalyst, together with a large quantity of intractable tarry materials. Both cuprous iodide and sodium methoxide are essential to obtain moderate yields of the spiro compound. The spiro compound (**16**) has been synthesized[5] through the reduction and subsequent alkali treatment of 9a-hydroperoxy-7-methoxycarbazolenine, which was obtained by air oxidation of 7-methoxy-1,2,3,4-tetrahydrocarbazole. In our case the yield of **16** was reduced to 25—30% under an oxygen atmosphere. In a control experiment which was carried out to examine the stability of **16** under an oxygen atmosphere by gas chromatographic analysis using carbazole as an internal standard, **16** was not extensively decomposed. Furthermore, in view of the result that a small amount of **16** was formed even without catalysts or sodium methoxide (Table II), the nature of the reaction mechanism remains ambiguous.

Methoxylation of N-Substituted Carbazoles

As mentioned above, methoxylation of a series of bromo-1,2,3,4-tetrahydrocarbazoles often resulted in the formation of spiro compounds and/or intractable tarry materials. On the

Table III. Methoxylation of Carbazoles

Starting compound	Reaction time (hr)	Product	Yield (%)
 **8**	5	 **19**	72.1
 **9**	5	 **20**	97.3
 **10**	6	 **21**	79.6
 **11**	13	 **22**	79.7
 **12**	7	 **17**	87.6
 **13**	4	 **23**	64.9

other hand, methoxylation of N-substituted 1,2,3,4-tetrahydrocarbazoles and 1,2,3,4,4a,9a-hexahydrocarbazole proceeded smoothly in good yield, as shown in Table III. As the benzyl group is easily removed, if desired, it is evident that this procedure offers a versatile route for the practical introduction of a methoxyl group into 2,3-disubstituted indole and indoline rings.

Experimental

All melting points are uncorrected. The following instruments were used to obtain physical data. Infrared (IR) spectra, Shimadzu IR-400; nuclear magnetic resonance (NMR) spectra (tetramethylsilane as an internal standard), JNM-C-60HL; gas chromatography, Shimadzu GC-4BM; mass spectra (MS), Shimadzu LKB-9000.

Starting Materials——Compounds **1**,[6] **4**,[6] **5**,[6] **7**,[6] and **13**[2] were prepared by the cited methods. Compound **2** was prepared by acid hydrolysis of the corresponding N-acetyl derivative[7] before use due to its instability. Compound **3**[8] and **12**[9] were prepared by the cited methods. Compound **8**, **9**, **10**, and **11** were prepared by the alkylation of the corresponding carbazoles with appropriate alkylating agents in the presence of alkali.[10] The physical constants of the new compounds are listed in Table IV.

Typical Procedure for the Reactions described in Table I

6′-Methoxy-spiro(cyclopentane-1,2′-indolin)-3′-one (16)——Dimethylformamide (DMF) (10 ml), cuprous iodide (1.52 g, 7.98 mmol), and 7-bromo-1,2,3,4-tetrahydrocarbazole (**4**) (1.00 g, 4.00 mmol) were added to a solution of metallic sodium (919 mg, 40.9 atom) in absolute MeOH (13 ml). The reaction mixture was

TABLE IV. Physical Constants of the Starting Compounds

Starting compound	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
5	59.5—61	Cyclohexane	$C_{12}H_{12}BrN$	57.60 (57.87	4.80 4.78	5.60 5.64)
8	100.5—101.5	Ether	$C_{13}H_{14}BrN$	59.11 (58.91	5.34 5.37	5.30 5.47)
9	73—74	Hexane	$C_{13}H_{14}BrN$	59.11 (59.12	5.34 5.37	5.30 5.24)
10	118—119	Hexane	$C_{13}H_{14}BrN$	59.11 (58.97	5.34 5.23	5.30 5.25)
11	126—127[a] (dec.)	Ethanol	$C_{25}H_{23}BrN_4O_7$	52.54 (52.51	4.03 4.02	9.81 9.75)

a) Picrate.

TABLE V. Physical Constants of the Products

Compd.	mp (°C) (recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Others
14	150—151 (ether)	$C_{13}H_{15}NO_2$	71.86 (71.98	6.96 6.91	6.45 6.51)	MS *m/e*: 217 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 1660 (C=O); NMR ($CDCl_3$) δ: 1.40—2.40 (8H, m, $CH_2\times4$), 3.90 (3H, s, OCH_3), 4.90 (1H, br s, NH, exchangeable with D_2O), 6.07—6.50 (2H, m, arom. 5′- and 7′-H), 7.20—7.50 (1H, m, arom. 6′-H).
15	149—151 (methanol) (lit.[a] 149—151)					
18	144—145[b] (ethanol) (lit.[c] 145—146)					
19	147—148 (methanol)	$C_{14}H_{17}NO$	78.10 (78.13	7.96 7.93	6.51 6.49)	MS *m/e*: 215 (M^+); NMR ($CDCl_3$) δ: 1.67—2.20 (4H, m, $CH_2\times2$), 2.50—2.83 (2H, m, CH_2), 2.83—3.20 (2H, m, CH_2), 3.58 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 6.50 (1H, dd, J=2, 7 Hz, arom. 6-H), 6.73—7.40 (2H, m, arom. 7- and 8-H).
20	88—89 (methanol) (lit.[d] 87—88)					
22	69 (cyclohexane)	$C_{20}H_{21}NO$	82.44 (82.27	7.26 7.30	4.81 4.96)	MS *m/e*: 293 (M^+); NMR ($CDCl_3$) δ: 1.17—2.00 (8H, m, $CH_2\times4$), 2.83—3.23 (1H, m, 4a-H), 3.33—3.70 (1H, m, 9a-H), 3.70 (3H, s, OCH_3), 4.10, 4.40 (2H, dd, J=16 Hz, $C\underline{H}_2Ph$), 6.07 (1H, d, J=2Hz, arom.8-H), 6.20 (1H, dd, J=2, 8Hz, arom. 6-H), 6.97 (1H, d, J=8 Hz, arom. 5-H), 7.20—7.53 (5H, m, $CH_2\underline{Ph}$).
23	149—150 (benzene)	$C_{13}H_{15}NO_2$	71.86 (71.90	6.96 7.05	6.45 6.46)	MS *m/e*: 217 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O); NMR ($CDCl_3$) δ: 1.63—2.50 (8H, m, $CH_2\times4$), 3.80 (3H, s, OCH_3), 6.23—6.73 (2H, m, arom.5′- and 7′-H), 7.10 (1H, d, J=9 Hz, arom. 4′-H), 9.27 (1H, br s, NH, exchangeable with D_2O).

a) B. Åkermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.*, **40**, 1365 (1975).
b) Picrate.
c) J. R. Chalmers, H.T. Openshaw, and G.F. Smith, *J. Chem. Soc.*, **1957**, 1115.
d) A. Smith and J.H.P. Utley, *J. Chem. Soc. (C)*, **1970**, 1.

refluxed (oil bath temperature, 120°) for 6 hr under an argon atmosphere. After the reaction, the reaction mixture was cooled and the insoluble materials were filtered off. The filtrate was concentrated *in vacuo* and H_2O was added to the residue. The aqueous layer was extracted with CH_2Cl_2 and the extract was washed with sat. NaCl, then dried over anhyd. Na_2SO_4. After the removal of the solvent, the residue was purified by column chromatography (SiO_2, benzene for elution). **7** and **17** were detected in the first fraction by gas chromatographic analysis [the temperatures of the glass column (2.0 m×3 mm i.d.; packed with 10% SE-30 on Chromosorb W, 60—80 mesh), and the injection chamber were kept at 220° and 280°, respectively. **7**, t_R=4.8 min; **17**, t_R=5.4 min]. Both compounds were identified by comparison of the retention times with those of authentic samples. **17**, mp 237—238° (reported[11] mp 235—236°) after recrystallization from ethanol, could be actually isolated. The second fraction was concentrated and the residue was subjected to column chromatography (Al_2O_3, benzene for elution) to give **16** (466 mg, yield 53.7%), mp 135—136° after recrystallization from ether (reported[5] mp 137.5—139°); MS *m/e*: 217 (M^+); NMR ($CDCl_3$) δ: 1.20—2.33 (8H, m, $CH_2\times4$), 3.83 (3H, s, OCH_3), 4.90 (1H, br s, NH, exchangeable with D_2O), 6.23 (1H, d, J=2 Hz, arom. 7′-H), 6.40 (1H, dd, J=2, 8 Hz, arom. 5′-H), 7.55 (1H, d, J=8 Hz, arom. 4′-H); IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 1660 (CO). The physical constants of the other products are listed in Table V.

6′-Methoxy-spiro(cyclopentane-1,2′-indoline) (**24**)——A solution of **16** (212 mg, 0.98 mmol) in absolute ether (15 ml) was mixed with $LiAlH_4$ (75 mg) in absolute ether (15 ml). The reaction mixture was refluxed for 5 min and stirred for 3 hr at room temperature. After careful decomposition of excess $LiAlH_4$ with ice and water, the aqueous layer was extracted with ether. The extract was washed with sat. NaCl, and dried over anhyd. Na_2SO_4. After the removal of the solvent, the residue was purified by column chromatography [SiO_2, acetone–benzene (1: 20) for elution] to give **24** (102 mg, yield 51.5%); MS *m/e*: 203 (M^+); NMR ($CDCl_3$) δ: 1.76 (8H, s, $CH_2\times4$), 2.91 (2H, s, CH_2), 3.20 (1H, br s, NH, exchangeable with D_2O), 3.73 (3H, s, OCH_3), 6.13—6.37 (2H, m, arom. 5′- and 7′-H), 6.75—7.07 (1H, m, arom. 4′-H); IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH).

Typical Procedure for the Reactions described in Table III

7-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**21**)——DMF (4 ml), cuprous iodide (434 mg, 2.28 mmol), and 7-bromo-9-methyl-1,2,3,4-tetrahydrocarbazole (**10**) (300 mg, 1.14 mmol) were added to a solution of metallic sodium (216 mg, 11.4 atom) in absolute MeOH (3 ml). After additional DMF (4 ml) had been added to the reaction mixture, the whole was refluxed (oil bath temperature, 120°) for 6 hr under an argon atmosphere. After the reaction, the reaction mixture was cooled and the insoluble materials were filtered off. The filtrate was concentrated *in vacuo* and H_2O was added to the residue. The aqueous layer was extracted with CH_2Cl_2 and the extract was washed with sat. NaCl, then dried over anhyd. Na_2SO_4. Removal of the solvent by evaporation gave a colorless solid which was purified by column chromatography [SiO_2; benzene–hexane (1: 1) elution for **17**, **18**, **21**, and **22**; benzene–hexane (1: 2) elution for **19** and **20**; MeOH–CH_2Cl_2 (1: 50) elution for **23**] to give **21** (195 mg, yield 79.6%), mp 95—96° after recrystallization from MeOH (reported[12] mp 94°). The physical constants of the other products are listed in Table V.

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References and Notes

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