Alkylation of 2, 3-Dimethylindole in Liquid Ammonia

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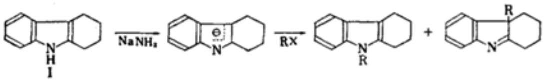
In the previous paper[1], formation of both 9-alkyltetrahydrocarbazoles (IIa, b, c) and 11-alkyltetrahydrocarbazolenines (IIIa, b, c) by the alkylation of tetrahydrocarbazole(I) in liquid ammonia with sodium amide and alkyl halides was reported. But, when isopropyl iodide was employed as alkylation reagent, 11-isopropyltetrahydrocarbazolenine (IIId) was a sole product isolated. These 11-alkyltetrahydrocarbazolenines could be also prepared by the Grignard synthesis, contrary to the negative result of Witkop[2].



II a, R=CH_3
b, R=CH_2-CH=CH_2
c, R=$CH_2C_6H_5$

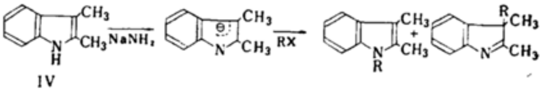
III a, R=CH_3
b, R=CH_2-CH=CH_2
c, R=$CH_2C_6H_5$
d, R=$CH(CH_3)_2$

When these experiments had been completed, Patts and Saxton[3] published a paper in which they reported formation of *N*-methyl derivatives in excellent yield from various indole derivatives by the alkylation with sodium amide and methyl iodide in liquid ammonia.

Beside indole itself, all compounds they tried were 2- or 3-monosubstituted indole, and no 2, 3-disubstituted indole was subjected to their alkylation method.

Since tetrahydrocarbazole is a 2, 3-disubstituted indole, and affords both 9- and 11-alkyl derivatives by the alkylation in liquid ammonia, 2, 3-dimethylindole can be expected to give indolenine derivatives by this method.

When the same procedure used in the alkylation of tetrahydrocarbazole was employed, 2, 3-dimethylindole gave *N*-methyl derivative (Va) accompanied by a small amount of 2, 3, 3-trimethylindolenine (VIa), but using allyl bromide and benzyl chloride there were found *N*-alkyl (Vb, c) and indolenine derivatives (VIb, c) in about the same amount.



V a, R=CH_3
b, R=$CH_2C_6H_5$
c, R=CH_2−CH=CH_2

Vl a, R=CH_3
b, R=$CH_2C_6H_5$
c, R=CH_2−CH=CH_2
d, R=$CH(CH_3)_2$

Isopropyl bromide failed to afford *N*-isopropyl derivative and a small amount of 2, 3-dimethyl-3-isopropylindolenine (VId) was the only prduct isolated. These results are exactly parallel to the one observed in the case of the alkylation of tetrahydrocarbazole in liquid ammonia.

The structures of all indolenine compounds provided by the alkylation in liquid

TABLE I

	Methyl iodide		Benzyl chloride		Allyl bromide		Isopropyl bromide	
Product	Va	VIa	Vb	VIb	Vc	VIc	*	VId
M. p.			59∼ 60	48∼ 49				
B. p. (mmHg)	117∼120 (6)	113 (21)	110∼115 (1.5)		159∼161 (16)	128∼132 (12)		100∼110 (11)
M. p.** of picrate	148∼149 B	158∼160 Y	98∼ 99 B	138∼141 Y	86 B	156∼157 Y		173∼174 Y

* Could not be obtained by the alkylation in liquid ammonia or by the Grignard synthesis.

** Picrates of *N*-alkyl derivatives are brown black needles (B), and picrates of indolenines are yellow (Y).

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[1] M. Nakazaki and S. Isoe, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 1159 (1955).

[2] B. Witkop, *J. Am. Chem. Soc.*, **72**, 614 (1950).

[3] K. T. Patts and J. E. Saxton, *J. Chem. Soc.*, **1954**, 2641. In our independent work, indole was found to give *N*-benzyl and *N*-allylindole in liquid ammonia with sodium amide and benzyl chloride and allyl bromide, respectively.

ammonia, were confirmed by the comparison with the specimens prepared by the Grignard synthesis, and their properties were shown in Table I, together with the one of *N*-alkyl-2,3-dimethylindoles.

Since 2,3-disubstituted indoles, as this experiment clearly shows, must be expected to give a considerable amount of indolenine derivatives even when methyl iodide is employed in the alkylation in liquid ammonia, adequate caution should be paid at the application of this alkylation method to the structure determination or the synthesis of indole alkaloids and the related compounds[4].

Experimental

N-Methyl-2,3-dimethylindole (Va) and 2,3,3-Trimethylindolenine (VIa). — *Alkylation in liquid ammonia.*—To 150 cc. of liquid ammonia collected in a three-necked flask chilled in a dry ice-acetone bath, 0.05 g. of ferric nitrate was added followed by the addition of 0.8 g. of sodium. After the blue color disappeared, a solution of 5 g. of 2,3-dimethylindole in 20 cc. of ether was added dropwise with stirring. After a mixture of 5 g. of methyl iodide and 5 cc. of ether was added over 20 min., the cooling bath was removed and the flask was allowed to stand overnight at room temperature to evaporate the ammonia off. Water was added to the residue left in the flask, and the oil separated was extracted with ether.

The ether extract was washed with water to neutral, and dried over anhydrous magnesium sulfate. After removal of the solvent, yellow residue was distilled under reduced pressure.

A forerun (1 g.) which boiled below 117°C at 6 mmHg and had a smell reminiscent of jasmine was dissolved in ether.

The basic fraction extracted with 4 N hydrochloric acid was liberated by the addition of 2 N sodium hydroxide solution and taken up in ether. An pale yellow oil (0.5 g.) obtained after removal of the ether, was converted into picrate which melted at 158°C after recrystallization from ethanol. The mixed melting point with the picrate of 2,3,3,-trimethylindolenine (m. p. 158∼160°C) prepared by the Grignard synthesis was 158∼161°C.

The main fraction boiling at 117∼120°C/6 mmHg, weighed 3.2 g. (58% yield).

Anal. Found: C, 82.80; H, 8.29; N, 8.80. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.24; N, 8.80%.

The picrate was recrystallized from benzene to yield brown-black needles, m. p. 148∼149°C. (literature[5]: m. p. 150°C). The mixed m. p. with the picrate of 2,3-dimethylindole (m. p. 152∼153°C) was 140∼143°C.

Grignard synthesis.—2,3,3-Trimethylindolenine was prepared following Hoshino's procedure[6], b. p. 113°C/21 mmHg. The picrate was recrystallized to give yellow needles melting at 158∼160°C (literature[6]: m. p. 160∼161°C).

N-Benzyl-2,3-dimethylindole (Vb) and 2,3-Dimethyl-3-benzylindolenine (VIb).—*Alkylation in liquid ammonia.*—Into a solution of sodium amide prepared from 200 cc. of liquid ammonia, 0.05 g. of ferric nitrate and 0.78 g. of sodium, a mixture of 5 g. of dimethylindole in 10 cc. of ether was added followed by the addition of 4 g. of benzyl chloride in 10 cc. of ether with stirring. After being kept overnight at room temperature in order to evaporate the ammonia, the residue was extracted with ether, and a basic fraction was extracted with 2 N hydrochloric acid. The basic fraction was liberated by the addition of 4 N sodium hydroxide solution to the hydrochloric acid solution, and extracted with ether. The ether layer, after being washed with water and dried, was evaporated to afford a viscous liquid which solidified gradually (1.80 g.). A small amount was sublimed to give crystals, m. p. 48∼49°C. This was found identical with 2,3-dimethyl-3-benzylindolenine prepared by the Grignard synthesis[7] by mixed m. p. determination.

The picrate was recrystallized from ethanol to yield yellow needles, m. p. 138∼140°C. The mixed melting point with the picrate prepared from the indolenine synthesized by the Grignard synthesis[7] was 138∼141°C.

The natural fraction. — The ether layer freed of the indolenine was washed with water and dried. The solvent was removed to give 5.74 g. of a brown viscous liquid which solidified when allowed to stand at room temperature overnight. After 1.4 g. of dimethylindole (m. p. 94∼97°C. picrate: m. p. 153∼154°C, identified by mixed m. p. determinations) was recovered by sublimation at 3 mmHg, the residue was distilled in vacuo. A pale yellow fraction boiling at 110∼115°C/1.5 mmHg was collected (1.7 g.) and recrystallized from methanol to give large needles, m. p. 59∼60°C.

Anal. Found: C, 86.74; H, 7.32. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28%.

The picrate was recrystallized to give brown black needles, m. p. 98∼99°C.

Anal. Found: C, 59.79; H. 4.60; N, 12.20. Calcd. for $C_{23}H_{20}O_7N_4$: C, 59.88; H, 4.34; N, 12.06%.

N-Allyl-2,3-dimethylindole (Vc) and 2,3-Dimethyl-3-allylindolenine (VIc).—*Alkylation in liquid ammonia.* — To a solution of sodium amide prepared from 200 cc. of liquid ammonia, 0.05 g. of ferric nitrate and 1.2 g. of sodium, 7.0 g. of dimethylindole was added with 20 cc. of ether followed by the addition of a mixture of 7.7 g. of allyl bromide and 10 cc. of ether. The basic and neutral fractions were separated by the procedure described above.

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[4] M. F. Bartlett, D. F. Dickel and W. I. Taylor., *J. Am. Chem. Soc.*, **80**, 126 (1958), in which is obtained the only *N*-methylibogaine from iboganine (a 2,3-disubstituted indole) following the procedure of Patts and Saxton.

[5] J. Degen, *Ann.*, **236**, 162 (1886).

[6] T. Hoshino, ibid., **500**, 35 (1932).

[7] M. Nakazaki, S. Isoe and K. Tanno, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 1262 (1955).

The basic fraction boiled at 128~132°C/12 mmHg and weighed 3.82 g. This 2, 3-dimethyl-3-allylindolenine (VIc) was very sensitive to air oxidation and rapidly turned brown at the surface, but was able to be kept a little while in a refrigerator in a sealed bottle.

Anal[8]. Found: C, 82.75; H, 8.32; N, 7.06. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56%.

The picrate was recrystallized from ethanol to give yellow needles, m. p. 156~157°C, and it was found identical with the picrate of 2, 3-dimethyl-3-allylindolenine prepared by the Grignard synthesis (vide infra).

The neutral fraction boiled at 159~160°C/16 mmHg and weighed 3.22 g.

Anal. Found: C, 84.11; H, 8.38; N, 7.35. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56%.

The picrate was recrystallized from ethanol to give brown black needles, m. p. 86°C.

Anal. Found: C, 54.85; H, 4.34; N, 13.37. Calcd. for $C_{19}H_{18}O_7N_4$: C, 55.07; H, 4.38; N, 13.52%.

Grignard synthesis.—To a Grignard compound prepared from 11.1 g. of methyl iodide and 1.9 g. of magnesium in 20 cc. of ether, a solution of 7.0 g. of dimethylindole in 20 cc. of ether was added dropwise over a period of 25 min. After generation of methane subsided, 7.7 g. of allyl bromide was added slowly over 20 min., and stirred for one additional hour. The ether layer was separated, after the Grignard complex was decomposed by the addition of 4 cc. of acetic acid with 15 cc. of water, and the aqueous layer was extracted thoroughly with ether. The combined ether extracts were shaken with 2 N hydrochloric acid to extract the basic fraction.

The oil which separated from the hydrochloric acid solution by being made alkaline was extracted with ether. After removal of the solvent, the residual liquid was distilled in vacuo to give a liquid which had a camphor-like smell, b. p. 80~90°C/2 mmHg, weighed 4.05 g.

2, 3-Dimethyl-3-allylindolenine was found quickly to turn brown in color by air oxidation.

Anal[8]. Found: C, 82.86; H, 8.41; N, 6.95. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56%.

The picrate was recrystallized from ethanol to give yellow crystals, m. p. 157~158°C.

Anal. Found: C, 55.22; H, 4.60; N, 13.54. Calcd. for $C_{19}H_{18}O_7N_4$: C, 55.07, H, 4.38; N, 13.52%.

2, 3-Dimethyl-3-isopropylindolenine (VId). —*Alkylation in liquid ammonia.*—To a solution of sodium amide prepared from 250 cc. of liquid ammonia, 0.1 g. of ferric nitrate and 1.5 g. of sodium in a 3-necked flask chilled in a dry ice-acetone bath, 7.0 g. of dimethylindole was added with 20 cc. of ether, followed by the addition of 7.5 g. of isopropyl bromide over 20 min. with stirring. The cooling bath was removed and the reaction mixture was allowed to stand at room temperature overnight to evaporate the ammonia. Following the same procedure described above, the basic and neutral fractions were separated. The basic fraction boiled at 100~110°C/11 mmHg, weighed 0.2 g. This compound was noticed to have a characteristic indolenine smell.

Anal. Found: C, 82.62; H, 9.59; N, 7.92. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

The picrate was recrystallized to give yellow crystals, m. p. 173~174.5°C.

Anal. Found: C, 55.00; H, 5.08; N, 13.92. Calcd. for $C_{19}H_{20}O_7N_4$: C, 54.80; H, 4.84; N, 13.46%.

The neutral fraction weighed 7.9 g., and from it 4.6 g. of dimethylindole was recovered by sublimation. But attempts to isolate *N*-isopropyl derivative from the viscous residue in the form of picrate failed, and the picrate of dimethylindole was the only material traceable.

Grignard synthesis.—To a Grignard solution prepared from 1.9 g. of magnesium and 11.1 g of methyl iodide in 20 cc. of ether, a mixture of 7.0 g. of dimethylindole in 10 cc. of ether was added dropwise.

After the evolution of methane subsided, 7.9 g. of isopropyl bromide was added over a period of 30 min. with stirring and cooling in an ice bath. After being kept at room temperature for 2 hr., the Grignard complex was decomposed by the addition of 4 cc. of acetic acid and 15 g. of ice. The basic and neutral fractions were separated by the same procedure described above.

The basic fraction was distilled in vacuo to give a liquid which boiled at 75~90°C/10 mmHg. Yield, 0.7 g.

The picrate was recrystallized to afford yellow crystals, m. p. 173~175°C which melted at 172~173°C when admixed with the picrate of 2, 3-dimethyl-3-isopropylindolenine prepared by the alkylation of dimethylindole in liquid ammonia. From the neutral fraction, only dimethylindole was recovered.

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[8] This rather poor result may be due to the sensitivity of the indolenine to air oxidation.