Alkylation of Sodio-2, 3-dimethylindole and Sodio-tetrahydrocarbazole in Non-polar Solvent

By Masao NAKAZAKI

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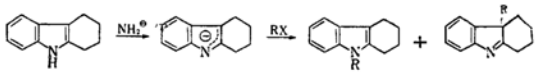
In the previous paper[1], the formation of 11-alkyltetrahydrocarbazolenines (IV) and 9-alkyltetrahydrocarbazoles (III) by the alkylation of tetrahydrocarbazole (I) with sodium amide and alkyl halides in liquid ammonia was reported.

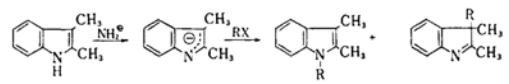


I II III IV

III a $R=CH_2C_6H_5$ IV a $R=CH_2C_6H_5$
b $R=CH_2-CH=CH_2$ b $R=CH_2-CH=CH_2$
c $R=CH_3$ c $R=CH_3$

The ratio of the yield of 11-alkyltetrahydrocarbazolenines (IV) to 9-alkyltetrahydrocarbazoles (III) was found to be affected by the halides employed: benzyl chloride gave the highest ratio and was followed by ally bromide, isopropyl iodide and methyl iodide.

The same sort of "ambident" alkylation[2,3] to give 1-alkyl-2, 3-dimethylindoles (VII) and 3-alkyl-2,3-dimethylindolenines (VIII) was observed in the alkylation of 2, 3-dimethylindole (V) in liquid ammonia with sodium amide and alkyl halides, and the ratio of *C*-alkyl/*N*-alkyl products were also found to depend on the nature of alkyl halides in the same sequence as that demonstrated in the alkylation of tetrahydrocarbazole. On the other hand, the alkylation of sodio-indole (IX) in non-polar solvent (benzene or without solvent) was studied by Funakubo[4], who reported the preparation of

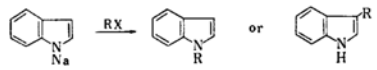


V VI VII VIII

VII a $R=CH_3$ VII a $R=CH_2C_6H_5$
b $R=CH_2-CH=CH_2$
c $R=CH_3$

1) M. Nakazaki and S. Isoe, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 1159 (1955).
2) M. Nakazaki, This Bulletin, **32**, 838 (1959).
3) The Grignard complex of I and V give 11-alkyltetrahydrocarbazolenines(IV) and 3-alkyl-2,3-dimethylindolenines (VIII) respectively, and there can be found no formation of *N*-substituted derivatives. T. Hoshino, *Ann.*, **500**, 35 (1932); B. Witkop, *J. Am. Chem. Soc.*, **72**, 614 (1950); Ref. 1.
4) E. Funakubo, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **48**, 652 (1927). Cf. R. Weisberger, *Ber.*, **42**, 3520 (1910).

N-alkyl indoles (X) (methyl, ethyl, *n*-propyl, isopropyl, allyl, *n*-butyl, isobutyl and isoamyl) by this method.



IX X XI

a $R=CH_2-CH=CH_2$
b $R=CH_2C_6H_5$
c $R=C(C_6H_5)_3$
d $R=CH_2COOC_2H_5$

But on our repetition of his experiment[1], his *N*-allylindole picrate (m. p. 169~170°C) turned out to be the picrate of recovered indole, and from the mother liquor was isolated another picrate (m. p. 105~106°C) which was established to be identical with the picrate of 3-allylindole (XIa)[5] prepared by the Grignard synthesis.

Kubota also found another example of β-alkylation of sodio-indole in non-polar solvent when he obtained 3-benzyl(XIb)[6], 3-triphenylmethyl-indole (XIc)[7] and ethyl β-indoleacetate (XId)[8] by heating a suspension of sodio-indole in dry benzene with benzyl chloride, triphenylmethyl chloride and ethyl chloroacetate respectively.

Unfortunately these authors did not dare to examine their alkylation method for 2, 3-disubstituted indoles, and this contribution is concerned with the alkylation of sodio-2, 3-disubstituted indoles in non-polar solvent as a natural extension of our alkylation studies in liquid ammonia.

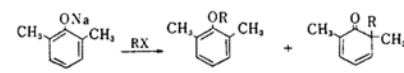
Tetrahydrocarbazole (I) and 2, 3-dimethylindole (V) were chosen as representatives of 2, 3-disubstituted indoles, because various 11-alkyltetrahydrocarbazlenines (IV), 3-alkyl-2, 3-dimethylindolenines (VIII) and *N*-alkyl derivatives III and VII have been prepared by our hands[1,2] and their structures were firmly established.

The general procedure carried out in our alkylation study was as follows: to a suspension of sodium amide in liquid ammonia (prepared in situ), a solution of indole derivatives (I or V) in toluene was added and the liquid ammonia was evaporated at room temperature. After residual ammonia was expelled by heating the solution up to the boiling point of toluene, a solution of halide in toluene was added under refluxing with stirring. The separation of indolenine derivatives and *N*-alkyl derivatives was worked out by the conventional method as in the case of alkylation in liquid ammonia.

The same directing effect of the alkylation reagents was confirmed in this alkylation in non-polar solvent; i. d. with benzyl chloride and allyl bromide, sodio-tetrahydrocarbazole afforded 11-alkyltetrahydrocarbazolenines (IV) predominantly, whereas with methyl iodide, *N*-methyl derivative was the sole product isolated; 2, 3-dimethyl-indole gave only indolenine derivatives VIII with benzyl chloride and allyl bromide, but with methyl iodide, *N*-methyl derivative VIIa accompanied with a small amount of indolenine derivative VIIIc.

It is noteworthy to compare these results with the directing effects of alkylation reagents in the alkylation of sodium salt of 2, 6-disubstituted phenols (XII) in non-polar solvent, which was studied strenuously by Curtin and his collaborators[9] recently.

To explain their observation that benzyl chloride and ally bromide give predominantly the *C*-alkyl derivative(6-alkyl-2, 6-dimethyl-2, 4-cyclohexadienone) XIII, whereas methyl iodide gives XIV with a trace of XIII, various factors which seem to control the direction of alkylation were considered, however, no decisive conclusion seems have to have been reached. We have proposed a reasonable mechanism to explain the marked directing effect of benzyl



XII XIV XIII

and ally halides in the alkylation of tetrahydrocarbazole in liquid ammonia, but this can not be advanced to rationalize the ambident alkylations in non-polar solvent without further experimental supports.

Studies of alkylation of 2, 6-dimethylphenol in liquid ammonia are now in progress in our laboratory, and should be the subject of a subsequent communication.

Experimental

Alkylation of Tetrahydrocarbazole (I).—*1) With Benzylchloride.*—A mixture of 5 g. of tetrahydrocarbazole and 100 cc. of toluene was added to a suspension of sodium amide in lipuid ammonia

5) Authentic *N*-allylindole (b. p. 114~116°C/6 mmHg., picrate: m. p. 79~79.5°C) was prepared by the alkylation of indole in liquid ammonia with sodium amide and allyl bromide. Ref. 1.

6) T. Kubota, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **59**, 407 (1938).

7) T. Kubota and I. Mita, ibid., **59**, 409 (1936). This 3-triphenylmethyl-indole was found to be identical with the compound which had been prepared by E. Funakubo and T. Hirotani (*Ber.*, **69**, 2123 (1936)) by the reaction of the Grignard complex of indole with triphenylmethyl chloride and had been assigned the structure of *N*-triphenylmethyl derivative by them.

8) T. Kubota, Japan Pat., 166925 (1934).

9) D. Y. Curtin et al., *J. Am. Chem. Soc.*, **79**, 3156 (1957); **80**, 1391, 4339, 6016 (1958); *J. Org. Chem.*, **23**, 9 (1958).

prepared from 0.5 g. of sodium and 200 cc. of liquid ammonia. The liquid ammonia was evaporated at room temperature and the resulting suspension of sodio-tetrahydrocarbazole in toluene was refluxed in order to expel the last trace of ammonia. A solution of 4 g. of benzyl chloride in 20 cc. of toluene was added dropwise. After the solution was stirred and refluxed for 1.5 hr., the toluene was distilled with steam, and the residue was extracted with ether. The ether solution was washed with 2 N hydrochloric acid to separate the basic and neutral fractions.

N-Benzyltetrahydrocarbazole (IIIa): — The ethereal extract was washed with water twice and dried over anhydrous sodium sulfate. Removal of the solvent gave a semisolid which was washed with petroleum ether-ether to give 0.5 g. of recovered tetrahydrocarbazole. The washing was concentrated to afford a pale yellow oil, which was distilled in vacuo, 0.4 g. b. p. 170~180°C/2 mmHg (literature[1]: b. p. 195°C/2 mmHg). The picrate was recrystallized from ethanol to give red needles which melted at 110~111°C, alone and admixed with an authentic sample of *N*-benzyltetrahydrocarbazole (m. p. 110~111°C).

Found: N, 11.49. Calcd. for $C_{19}H_9N \cdot C_6H_3O_7N_3$: N, 11.42%.

11-Benzyltetrahydrocarbazolenine (IVa):—After the acidic solution was washed with ether, 4 N sodium hydroxide solution was added to precipitate the basic material which was extracted with ether.

The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed to give a semisolid which was filtered free from viscous mother liquor. The crystals were recrystallized from ethanol-water to afford prisms melting at 84~85°C, which was found identical with 11-benzyltetrahydrocarbazolenine by the mixed melting point determination with an authentic specimen (literature: m. p. 85~86°C[1]). The picrate was recrystallized from ethanol to give yellow prisms, m. p. 176~177.5°C (literature: 176~177°C[1]). The mixed melting point with an authentic specimen was 176~177.5°C.

Found: N, 11.53. Calcd. for $C_{19}H_{19}N \cdot C_6H_3O_7N_3$: N, 11.42%.

2) With Allyl Bromide. — To a suspension of sodio-tetrahydrocarbazole in toluene prepared from 200 cc. of liquid ammonia, 0.7 g. of sodium, 5 mg. of ferric nitrate, 5 g. tetrahydrocarbazole (I) and 100 cc. of toluene, as described previously, a solution of 4 g. of ally bromide in 20 cc. of toluene was added dropwise with stirring and refluxing in a period of 2 hr. After the reaction mixture was refluxed for an additional 5 hr., the solvent was removed by steam distillation and the residue was extracted with ether. The neutral and basic fractions were separated as described above.

N-Allyltetrahydrocarbazole (IIIb):—From the neutral fraction, 0.5 g. of tetrahydrocarbazole was recovered (m. p. 110~116°C). The residue was distilled in vacuo to afford a viscous pale yellow liquid, b. p. 125~128°C/2 mmHg (literature[1]: b. p. 157°C/3 mmHg). The picrate was recrystallized to give red needles melting at 76~77°C, which were found to be identical with the picrate of *N*-allyltetrahydrocarbazole by the mixed melting point determination with an authentic sample, m. p. 76~77°C[1].

Found: N, 13.05. Calcd. for $C_{15}H_{17}N \cdot C_6H_3O_7N_3$: N, 12.73%.

11-Allyltetrahydrocarbazolenine (IVb): — The basic fraction gave 2.0 g. of crystals which were recrystallized from petroleum ether to afford 11-allyltetrahydrocarbazolenine, m. p. 54~56°C, identified by the mixed melting point determination with an authentic sample (literature[1]: m. p. 57~58°C). The picrate was recrystallized from ethanol to give yellow prisms, m. p. 139~142°C, the identity of which with the picrate of 11-allytetrahydrocarbazolenine was established by the mixed melting point determination with an authentic sample (literature[1]: m. p. 142~143°C).

Found: N, 12.94. Calcd. for $C_{15}H_{17}N \cdot C_6H_3O_7N_3$: N, 12.72%.

3) With Methyl Iodide. — The alkylation with methyl iodide was carried out following the general procedure described above. A solution of 8 g. of methyl iodide in 40 cc. of toluene was added dropwise during 6 hr. in a suspension of sodio-tetrahydrocarbazole (0.02 mol.) on toluene prepared from 200 cc. of liquid ammonia, 0.7 g. of sodium, 3.4 g. of sodium and 80 cc. of toluene. After the usual work up, the basic and neutral fractions were separated.

N-Methyltetrahydrocarbazole (IIIc): — The vacuum distillation of the neutral fraction gave 1.4 g. of viscous pale yellow oil, b. p. 124~126°C/2 mmHg. The picrate was recrystallized from ethanol to give brown-red needles melting at 109~112°C. The mixed melting point with an authentic specimen[1] (m. p. 113~114°C) was 109~112°C.

Found: N, 13.79. Calcd. for $C_{13}H_{15}N \cdot C_6H_3O_7N_3$: N, 13.52%.

The Basic Fraction: — Removal of the ether afforded an amber yellow solid which was sparingly soluble in dilute sodium hydroxide, dilute hydrochloric acid, ethanol and ether respectively add could not be converted into crystalline picrate. This substance was not studied further.

Alkylation of 2, 3-Dimethylindole (V).—*1) With Benzylchloride*:—A solution of 5 g. of 2, 3-dimethylindole (V) in 100 cc. of toluene was added dropwise into a suspension of sodium amide in liquid ammonia prepared from 200 cc. of liquid ammonia, 1 g. of sodium and 5 mg. of ferric nitrate. The liquid ammonia was evaporated and the remaining mixture was refluxed with stirring. To the reaction mixture, a solution of 5.3 g. of benzyl chloride in 20 cc. of toluene was added and refluxing with stirring was continued for 8 hr. After the reaction mixture was worked up as described in the alkylation of tetrahydrocarbazole, the basic and the neutral fractions were separated.

2, 3-Dimethyl-3-benzylindolenine (VIIIa):—Removal of the solvent afforded 4.6 g. of a solid, which was recrystallized from petroleum ether to give crystals melting at 48~49°C, alone and admixed with an authentic specimen (m. p. 48~49°C[10]).

The picrate was recrystallized from ethanol to give

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

yellow prisms, m. p. 137~139°C, the mixed melting point of which with an authentic sample[10] was found 137~140°C.

Found: N, 12.20. Calcd. for $C_{17}H_{17}N \cdot C_6H_3O_7N_3$: N, 12.06%.

The Neutral Fraction: — A small amount of 2,3-dimethylindole was recovered, but the search for *N*-benzyl derivative was fruitless.

2) With Allyl Bromide.—Using 5 g. of allyl bromide, the alkylation was carried out exactly as the procedure described above.

2,3-Dimethyl-3-allylindolenine (VIIIb): — The crude basic fraction (1 g.) was distilled in vacuo to give a yellow liquid, b. p. 125~128°C/12 mmHg. The picrate was recrystallized from ethanol to afford yellow needles m. p. 158~160°C, the mixed melting point with an authentic sample[2] (m. p. 156~157°C) showed 159~160°C.

Found: N, 13.65. Calcd. for $C_{13}H_{15}N \cdot C_6H_3O_7N_3$: N, 13.52%.

Neutral Fraction: — The crude neutral fraction (2 g.) was distilled in vacuo to give two fractions: 1. 1.4 g. b. p. 100~125°C/2 mmHg. which was proved as 2,3-dimethylindole recovered, 2. 0.5 g. b. p. 125~130°C/2 mmHg which did not give crystalline picrate and was not studied further.

3) With Methyl Iodide. — The alkylation was carried out using 12 g. of methyl iodide, and the basic and neutral fractions were separated as described above.

2,3,3-Trimethylindolenine (VIIIc):—The crude basic fraction (1.1 g.) was distilled in vacuo to give 0.4 g. of VIIIc, b. p. 80°C/1 mmHg, the characteristic odor of which resembles that of jasmin. The picrate was recrystallized from ethanol to afford yellow needles melting at 158°C, which was found identical with the picrate of 2,3,3-trimethylindolenine (literature[2]: m. p. 158°C) by the mixed melting point determination.

Found: N, 14.54. Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: 14.43%.

1,2,3-Trimethylindole (VIIa): — From the neutral fraction, a small amount of 2,3-dimethylindole was recovered by recrystallization from petroleum ether. The mother liquor, after removal of the solvent, was distilled in vacuo to give 1.1 g. of yellow liquid, b. p. 90~93°C/2 mmHg (literature[2]: b. p. 117~120°C/6 mmHg). The picrate was recrystallized from ethanol to afford brownish-black needles, m. p. 145~147°C which was not depressed on admixing with an authentic specimen[2] of the picrate of 1,2,3-trimethylindole (m. p. 148~149°C).

Found: N, 14.70. Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: N, 14.43%.

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Institute of Polytechnics
Osaka City University
Kita-ku, Osaka