PREPARATION OF 5-ETHOXYCARBONYL- AND 5-CYANO-5,6-DIHYDRO-3,7-DIPHENYL-4H-DIAZEPINES AND THEIR HALOGENATIONS

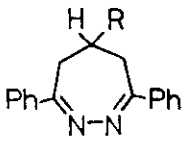
Kichinosuke Kamata[+] and Otohiko Tsuge*

[+]Department of Industrial Chemistry, Kurume College of Technology, Kurume 830, Japan

Research Institute of Industrial Science, Kyushu University, Kasugakoen, Kasuga 816, Japan

Abstract ——— 5-Ethoxycarbonyl- and 5-cyano-5,6-dihydro-3,7-diphenyl-4H-1,2-diazepines were prepared and their halogenations were investigated under various conditions. The halogenation products were found to be strongly dependent upon the nature of 5-substituents as well as the reaction conditions.

It has been found that the products in halogenations of 5,6-dihydro-3,7-diphenyl-4H-1,2-diazepines were greatly affected by the nature of substituents at the 5-position as well as by the reaction conditions. Namely, in contrast with easy contraction to pyridazines via 3,4-diazanorcaradienes in halogenations of the dihydrodiazepines (1: R=H, Me, Ph) having no electron-withdrawing groups[1-3], the dihydrodiazepines (**2a**)[4] and (**2b**)[5] bearing two electron-withdrawing groups at the 5-position afforded the corresponding 3,4-diazanorcaradienes or halogenated dihydrodiazepines in the halogenations under controlled conditions. In the halogenations of the dihydrodiazepine (**2c**) having two strong electron-withdrawing cyano groups, a diazanorcaradine was not obtained, but instead ring-contracted pyridazines or halogenated dihydrodiazepine were formed[5].



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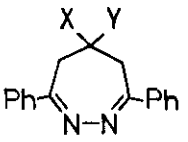

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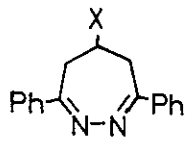
a : X=Y=COOEt
b : X=CN, Y=COOEt
c : X=Y=CN

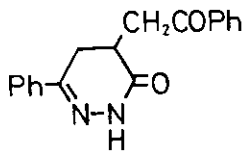
However, the halogenations of dihydrodiazepines having one electron-withdrawing group at the 5-position have not been reported up to date. Thus, our attention was directed to the halogenation of such a dihydrodiazepine system in order to obtain further information concerning the effect of nature of the 5-substituent on the mode of halogenation. In this paper we wish to report the preparation of 5-ethoxycarbonyl- (**3a**) and 5-cyano-5,6-dihydro-3,7-diphenyl-4H-1,2-diazepine (**3b**), and their halogenations.

Preparation. After hydrolysis of **2a** and **2b** in a 1.5% ethanolic potassium hydroxide solution at room temperature, the resultant mixture was refluxed to give **3a** and **3b** in 75 and 94% yields, respectively. The structural elucidation of **3a,b** was accomplished on the basis of spectral data[6]. Treatment of **3a** with hydrochloric acid in



3a : X= COOEt

3b: X=CN



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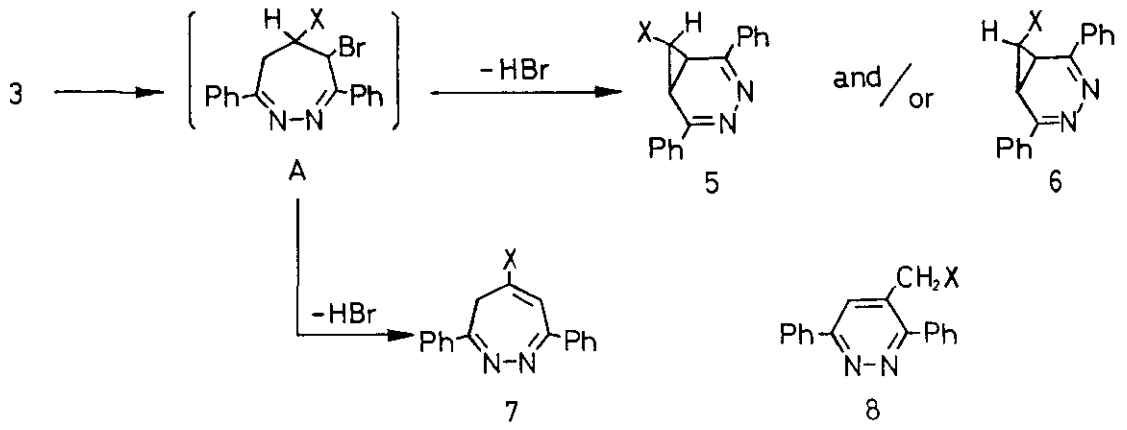
ethanol afforded 4,5-dihydro-4-phenacyl-6-phenyl-3(2H)-pyridazinone (**4**)[7] in 94% yield. The formation of **4** is closely similar to that of 4-cyanopyridazinone from **2b** in the same treatment[5].

Bromination. When **3a** was treated with an equivalent of bromine in methanol at room temperature, 7-exo-ethoxycarbonyl-2,5-diphenyl-3,4-diazanorcaradiene (**5a**); yellow needles, mp 233-234 °C (lit.[4] mp 233-234 °C), was obtained in 96% yield. On the other hand, the bromination of **3b** under similar conditions gave the 7-exo-cyano- (**5b**) and 7-endo-cyano-2,5-diphenyl-3,4-diazanorcaradiene (**6b**) in 49 and 34% yields, respectively. The structures of **5b** and **6b** were confirmed on the basis of spectral data[8]. In addition, **6b** was identical with an authentic sample prepared from the hydrolysis of the 7-endo-cyano-7-exo-ethoxycarbonyldiazanorcaradiene[5].

In the reaction with an equivalent of N-bromosuccinimide in carbon tetrachloride under reflux, however, **3a** and **3b** afforded the 4H-diazepines (**7a**; 24%) and (**7b**; 3%), and pyridazines (**8a**; 32%) and (**8b**; 73%), respectively[9]. Although it has been reported that the photolysis of 7,7-dimethyl-2,5-diphenyl-3,4-diazanorcaradiene gave the corresponding 4H-diazepine[10], the formation of **7a,b** is the first example for that from halogenation-dehydrohalogenation process of dihydroazepines.

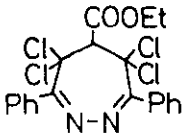
The pathways for the formation of **5** - **8** can be readily understood. Although the



a : X=COOEt , b : X=CN

monobromide A could not be isolated, it is clear that the diazanorcaradienes, 5 and 6, are formed via A by internal nucleophilic displacement. In the reaction with N-bromosuccinimide in carbon tetrachloride under reflux, A undergoes the competitive internal nucleophilic displacement and 1,2-dehydrobromination to yield 5 and 6, and 7, respectively. However, the formed 5 and 6 are transformed, by the ring opening catalyzed by the generated hydrogen bromide under the conditions, into the stable pyridazines 8.

Chlorination. When an equivalent of sulfuryl chloride was slowly added to a solution of 3a or 3b in dichloromethane at room temperature, 5a (54%) or 5b (47%) and 6b (3%) were obtained together with tarry materials, respectively. The tetrachlorodihydrodiazepine (9) or trichloro-4H-diazepine (10b) was formed in 87 or 77% yield, respectively, however, when 3a or 3b was allowed to react rapidly with six equivalents of sulfuryl chloride in dichloromethane at room temperature. Treatment of 9 with triethylamine in benzene at room temperature afforded the trichloro-4H-diazepine (10a) in quantitative yield. Thermolysis of 10a and 10b in benzene under reflux for 5 h afforded the ring-contracted cyclopentadienes 11a and 11b in 43 and 29% yields, respectively, with the elimination of nitrogen. The dechlorination of 9 with sodium iodide in boiling acetone for 2 h gave 4-chloro-5-ethoxycarbonyl-3,6-diphenylpyridazine (12) in 82% yield, whereas 8a was obtained in 21% yield together with tarry materials in dechlorination with zinc dust in ethanol under reflux for



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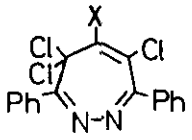

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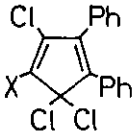
a : X= COOEt , b : X= CN



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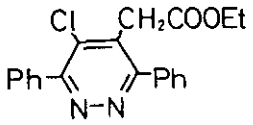
a : X= COOEt , b : X= CN



12

2 h. Structural elucidation of 9 — 12 was accomplished on the basis of spectral data[11].

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1. R. G. Amiet, R. B. John, and K. R. Markham, J. C. S. Chem. Commun., 1965, 128.
2. R. G. Amiet and R. B. John, Aust. J. Chem., 1968, 21, 1279.
3. O. Tsuge and K. Kamata, Heterocycles, 1975, 3, 15.
4. O. Tsuge, K. Kamata, and S. Yogi, Bull. Chem. Soc. Jpn., 1977, 50, 2153.
5. K. Kamata and O. Tsuge, J. Heterocyclic Chem., 1986, 23, 557.
6. All the new compounds in this paper gave satisfactory elemental analyses.
   3a: Mp 101-102 °C; colorless needles; IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, t), 2.98 (4H, m), 3.58 (1H, m, ≥C<u>H</u>), 4.15 (2H, q), 7.3-7.6 (6H, m), 7.8-8.1 (4H, m); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 28.2 (t, 4- and 6-<u>C</u>), 49.8 (d, 5-<u>C</u>), 61.5 (t), 127.1, 128.8, 130.4 (each d), 136.5 (s), 157.5 (s, 3- and 7-<u>C</u>), 172.8 (s, <u>C</u>=O); MS m/z 320 (M^+).
   3b: Mp 187-188 °C; colorless needles; IR (KBr) 2240 cm^{-1}; ^1H NMR (DMSO-d_6) δ= 2.94 (4H, m), 4.12 (1H, m, ≥C<u>H</u>), 7.4-7.65 (6H, m), 7.85-8.15 (4H, m); ^{13}C NMR (DMSO-d_6) δ=28.3 (t, 4- and 6-<u>C</u>), 34.4 (d, 5-<u>C</u>), 121.2 (s, <u>C</u>≡N), 126.8, 128.6, 130.3 (each d), 135.6 (s), 155.4 (s, 3- and 7-<u>C</u>); MS m/z 273 (M^+).
7. **4**: Mp 190-191 °C; colorless needles; IR (KBr) 3230 (NH), 1690, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.5-3.9 (5H, m), 7.3-8.2 (10H, m), 11.13 (1H, s, N<u>H</u>); ^{13}C NMR (DMSO-d_6) δ=125.7, 128.1, 128.7, 128.8, 129.4, 133.4 (each d), 136.1, 136.8 (each s), 150.0 (s, 6-<u>C</u>), 169.1 (s, 3-<u>C</u>), 197.9 (s, Ph<u>C</u>O); MS m/z 292 (M^+).
8. **5b**: Mp 183-185 °C (dec); yellow needles; IR (KBr) 2240 cm^{-1}; ^1H NMR (CF_3COOD)

δ=2.46 (1H, t, ≥CH, J=4.9 Hz), 4.15 (2H, d, ≥CH, J=4.9 Hz), 7.6-8.1 (6H, m), 8.1-8.4 (4H, m); ^{13}C NMR (CF_3COOD) δ=13.0 (d, 7-C), 28.8 (d, 1- and 6-C), 116.2 (s, C≡N), 130.7 (s), 131.4, 132.1, 139.2 (each d), 165.9 (s, 2- and 5-C); MS m/z 271 (M^+).

6b : Mp 260-262 °C (dec); yellow needles; IR (KBr) 2240 cm^{-1}; ^{1}H NMR (CF_3COOD) δ=4.18 (3H, s, ≥CH), 7.6-8.1 (6H, m), 8.1-8.4 (4H, m); ^{13}C NMR (CF_3COOD) δ=8.3 (d, 7-C), 29.4 (d, 1- and 6-C), 112.9 (s, C≡N), 131.0 (s), 131.4, 132.2, 139.2 (each d), 165.3 (s, 2- and 5-C); MS m/z 271 (M^+).

9. **7a** : Mp 130-131 °C; yellow prisms; IR (KBr) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.36 (3H, t), 2.19 (1H, dd, 4-H, J=12.9, 1.8 Hz), 4.36 (2H, q), 4.57 (1H, dd, 4-H, J=12.9, 2.2 Hz), 7.3-7.7 (7H, m), 7.8-8.4 (4H, m); ^{13}C NMR ($CDCl_3$) δ=14.2 (q), 29.6 (t, 4-C), 61.9 (t), 126.6, 127.5, 128.2, 128.6, 130.2, 130.3 (each d), 134.6, 134.9 (each s), 137.1 (s, 5-C), 149.9, 155.5 (each s, 3- and 7-C), 164.1 (s, C=O); MS m/z 318 (M^+).

7b : Mp 182-183 °C (dec); pale yellow needles; IR (KBr) 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.53 (1H, dd, 4-H, J=13.5, 1.5 Hz), 4.01 (1H, dd, 4-H, J=13.5, 1.8 Hz), 6.98 (1H, distorted t, =CH), 7.3-7.6 (6H, m), 7.7-8.1 (4H, m); ^{13}C NMR ($CDCl_3$) δ=33.0 (t, 4-C), 115.5, 116.5 (each s), 127.4, 128.0, 128.9, 129.0, 130.7, 130.8, 132.2 (each d), 133.8, 136.1 (each s), 148.4, 154.1 (each s, 3- and 7-C); MS m/z 271 (M^+).

8a : Mp 139-140 °C (lit.[4] mp 139-140 °C). **8b** : *Mp 156-157 °C; colorless prims;* IR (KBr) 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.82 (2H, s, CH_2), 7.4-7.6 (8H, m), 8.0 (1H, s, 5-H), 8.0-8.2 (2H, m); ^{13}C NMR ($CDCl_3$) δ=21.7 (t), 116.0 (s, C≡N), 123.7 (d, 5-C), 127.1, 129.0, 129.1, 129.5, 129.7, 130.5, 135.4 (s), 158.3, 159.1 (each s, 3- and 6-C); MS m/z 271 (M^+).

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11. **9** : *Mp 100-101 °C; colorless prims;* IR (KBr) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30 (t), 4.33 (2H, q), 5.10 (1H, s, ≥CH), 7.4-7.6 (6H, m), 7.6-7.9 (4H, m); ^{13}C NMR ($CDCl_3$) δ=14.0 (q), 62.6 (t), 78.6 (s, 4- and 6-C), 85.6 (d, 5-C), 127.8, 129.2, 129.9 (each d), 135.2 (s), 151.8 (s, 3- and 7-C), 163.3 (s, C=O); MS m/z 456, 458, 460, 462, 464 (M^+).

10a : Mp 114-115 °C (dec); pale yellow prisms; IR (KBr) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.38 (3H, t), 4.45 (2H, q), 7.3-8.0 (10H, m); ^{13}C NMR ($CDCl_3$) δ=14.0 (q), 61.8 (s, 4-C), 63.2 (t), 127.8, 128.5, 128.6, 129.0, 129.8, 131.0 (each d), 133.8, 134.9 (each s), 136.8, 142.5 (each s, 5- and 6-C), 151.2, 153.5 (each s, 3- and

7-C), 161.3 (s, C=O); MS m/z 420, 422, 424, 426 (M^+).

10b : Mp 123-124 °C (dec); yellow prisms; IR (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 7.4-7.7 (8H, m), 7.7-7.9 (2H, m); ^{13}C NMR ($CDCl_3$) δ=73.6 (s, 4-C), 111.5 (s, C≡N), 123.3 (s, 5-C), 128.2, 128.8, 129.7, 130.4, 131.5 (each d), 132.7, 134.3, 136.3 (each s), 150.0, 152.3 (each s, 3- and 7-C); MS m/z 373, 375, 377, 379 (M^+).

11a : Mp 100-101 °C; colorless prisms; IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20 (3H, t), 4.18 (2H, q), 7.2-7.6 (10H, m); ^{13}C NMR ($CDCl_3$) δ=14.3 (q), 61.8 (t), 104.2 (s, 5-C), 111.8, 123.1 (each s), 127.6, 128.0, 128.2, 128.7, 129.0, 129.5, 130.0, 131.2 (s), 133.6 (s), 136.7 (s), 170.4 (s, C=O); MS m/z 392, 394, 396, 398 (M^+).

11b : Mp 136-137 °C; yellow prisms; IR (KBr) 2210 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.2-7.6 (m); ^{13}C NMR ($CDCl_3$) δ=111.2 (s, C≡N), 119.5 (s), 126.2 (d), 128.3, 128.5, 128.7, 129.5, 129.6, 129.9, 131.7 (s), 133.4 (s), 147.5 (s), 149.1 (s); MS m/z 345, 347, 349, 351 (M^+).

12 : Mp 99-100 °C; colorless needles; IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (3H, t), 3.86 (2H, s), 4.20 (2H, q), 7.4-7.7 (8H, m), 7.7-8.0 (2H, m); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 36.8 (t, CH_2COOEt), 61.8 (t), 128.4, 128.9, 129.3, 129.7, 129.8, 130.0 (each d), 132.1, 135.5, 136.4, 138.8 (each s), 158.7, 161.7 (each s, 3- and 6-C), 169.0 (s, C=O); MS m/z 352, 354 (M^+).

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