Chem. Pharm. Bull.
16(9)1831—1834(1834)

UDC 547.759.1.07

1-Acylindoles. V.[1] Reaction of N^1-Acylphenylhydrazine Derivatives with 2-Methylcyclohexanone

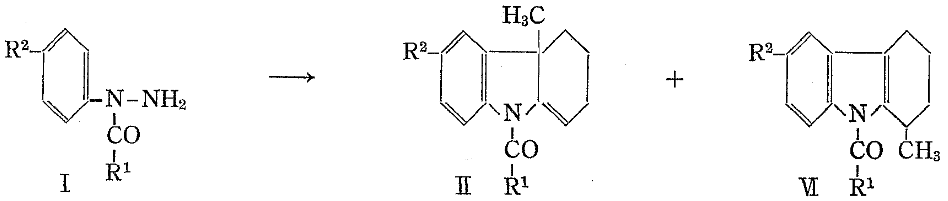
Hisao Yamamoto and Toshio Atsumi

Pharmaceuticals Division, Sumitomo Chemical Co., Ltd.[2]

(Received September 11, 1967)

It has been found that 9–acyl–1,2,3,4–tetrahydrocarbazole derivatives are obtained by the reaction of N^1–acylphenylhydrazine derivatives (I) with cyclohexanone.[3]

Similarly, the reaction of I with 2–methylcyclohexanone, instead of cyclohexanone, causes generally corresponding two isomers; 9–acyl–11–methyltetrahydrocarbazole (II) and 9–acyl–1–methyltetrahydrocarbazole (VI) (Chart 1). However, when N^1–acylated phenylhydrazine is treated with 2–methylcyclohexanone in acetic acid, a corresponding 11–methyl–2,3,4,11–tetrahydrocarbazole derivative (II) only is given, but another isomer, 1–methyl–1,2,3,4–tetrahydrocarbazole derivative (VI) is entirely not obtained.



a: $R^1=CH_3$, $R^2=H$ b: $R^1=C_6H_5$, $R^2=H$ c: $R^1=p\text{-}Cl\text{-}C_6H_4$, $R^2=OCH_3$

Chart 1

A N^1–substituted acetyl group is so easily cleaved even in acetic acid, that a considerable quantity of a deacylated compound (11–methyl–1,2,3,4–tetrahydrocarbazolenine, III) is obtained as a by–product besides 9–acetyl–2,3,4,11–tetrahydrocarbazole (IIa). While, the acid–amide linkage of N^1–benzoylated compound is not cleaved in acetic acid, so 9–benzoyl–11–methyl–2,3,4,11–tetrahydrocarbazole (IIb) only is given in a good yield.

When N^1–*p*–chlorobenzoyl–*p*–methoxyphenylhydrazine was heated with 2–methylcyclohexanone under the same condition, a significant quantity of a compound (V) is obtained as a reaction product besides 11–methyl–2,3,4,11–tetrahydrocarbazole derivative (IIc). The infrared spectrum showed bands at 3270, 1712 and 1647 cm^{-1}, suggesting the presence of CONH group and CO group. The NMR spectrum showed a singlet signal (1H) at 1.89τ and doublet signal (3H) at 8.94τ, which demonstrated each the presence of NH and $CH_3\left(>\overset{H}{C}\text{–}\underline{CH_3}\right)$ groups. Moreover, the found values of the elementary analysis were identical with the calculated values for a empirical formula, $C_{21}H_{22}O_3NCl$. V was identified as hitherto unknown N–(*p*–chlorobenzoyl)–2–(2′–oxo–3′–methylcyclohexyl)–4–methoxyaniline by these results. Robinson's mechanism of Fischer's indolization[4] is supported by formation of V, which is thought to proceed by a following process (Chart 2). This result shows that the ring formation of 9–(*p*–chlorobenzoyl)–1–methyl–6–methoxy–1,2,3,4–tetrahydrocarbazole (VIc) from V is more

---

[1] Part IV: H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 647 (1968).
[2] Location: *Kasugade–cho, Konohana–ku, Osaka.*
[3] H. Yamamoto, *J. Org. Chem.*, 32, 3693 (1967).
[4] R.B. Carlin and E.E. Fischer, *J. Am. Chem. Soc.*, **70**, 3421 (1948).

difficult than the formation of IIc from a corresponding intermediate, because V may be too inactive to occure the ring closure under such the reaction condition.

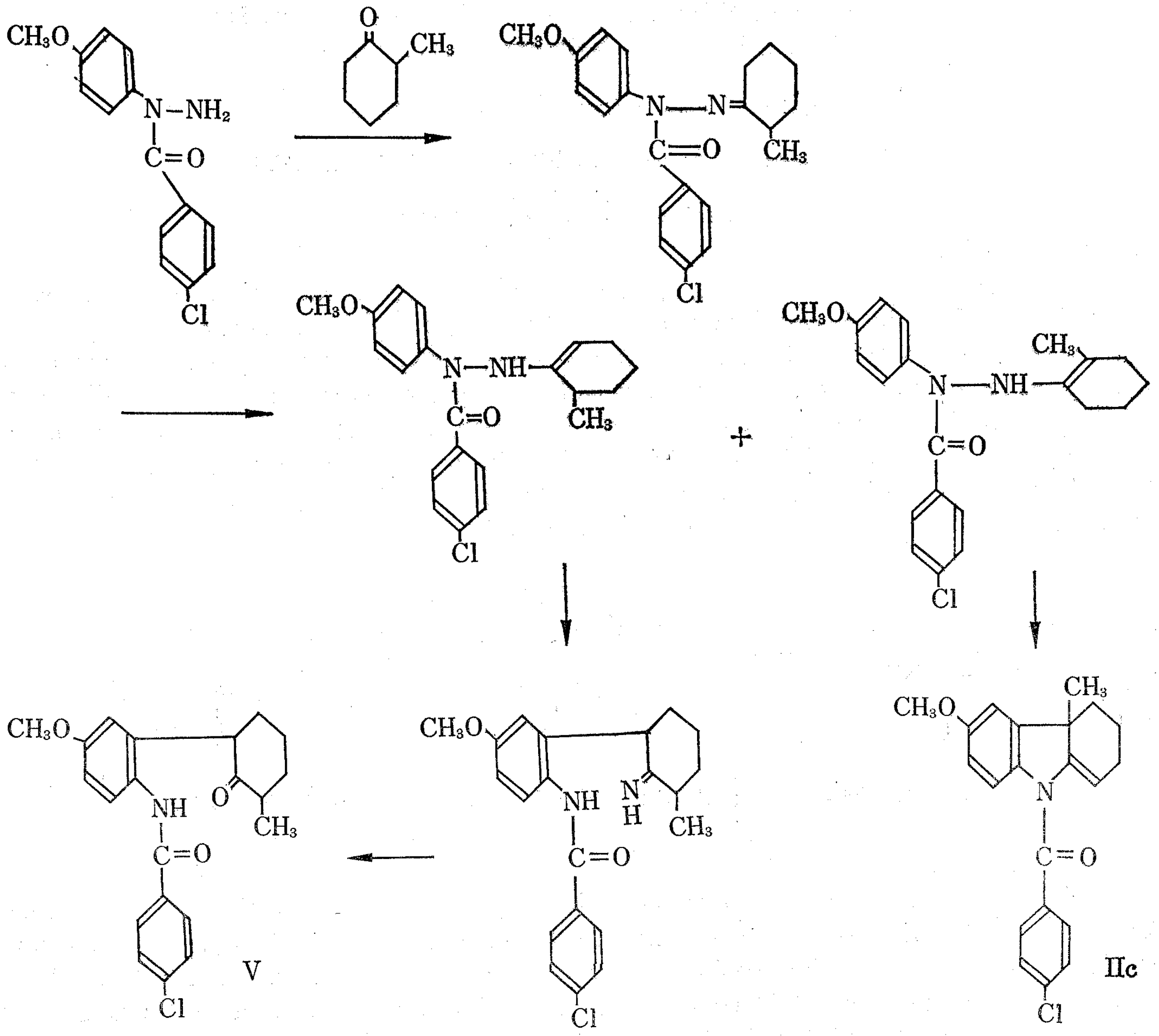
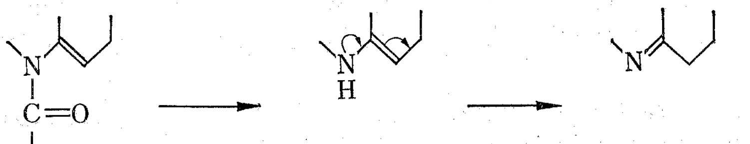


Chart 2

The tetrahydrocarbazole ring can undergo elimination of the double bond with cleavage of acid–amide linkage. When II is hydrolyzed, the double bond of $\Delta^{10,1}$ is transmitted to $\Delta^{9,10}$ to yield III, which infrared absorption spectrum is identified with that of the authentic sample.[5]



When a indolenine derivative (III) is acylated, a 10–hydroxy compound (IV) is obtained as a intermediate, which was dehydrated to give II. Heating of the compound (III) with benzoyl chloride causes the formation of 9–benzoyl–10–hydroxy–11–methyl–1,2,3,4,10,11–hexahydrocarbazole (IV), the structure of which is supported by the nuclear magnetic resonance (NMR) spectrum which contained peaks due to hydrogen of OH at 4.81τ and 8 hydrogens of $-CH_2-CH_2-CH_2-CH_2-$ at 7.65—8.7τ, its infrared absorption spectrum which is suggested a OH group at $3440\ cm^{-1}$ and a carbonyl group at $1630\ cm^{-1}$, and its elementary analysis.

---

[5] K.H. Pausacker and C.I. Schubert, *J. Chem. Soc.*, **1949**, 1384.

Further, heating of the compound (IV) under reduced pressure gave the compound (IIb), the structure of which is confirmed by showing identical infrared absorption spectrum and thin-layer chromatograph with those of an authentic sample (Chart 3).

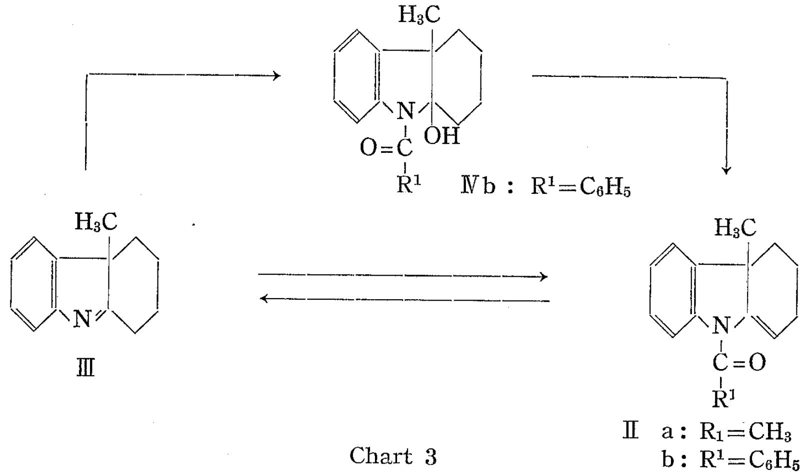


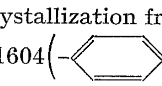
Chart 3

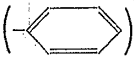
Experimental

Melting points were not corrected. Infrared absorption spectra were recorded on a Simazu IR–27G spectrophotometer and NMR spectra were taken on a Varian A–60 spectrophotometer.

9-Acetyl-11-methyl-2,3,4,11-tetrahydrocarbazole (IIa) and 11-Methyl-1,2,3,4-tetrahydrocarbazolenine (III) ——To a mixture of 4.9 g of N¹–acetylphenylhydrazine hydrochloride and 15 ml of glacial acetic acid was added dropwise 2.95 g of 2–methylcyclohexanone for 10 min with stirring. Thereafter, the stirring was continued for additional 1 hr with heating to 70—75°. Then, the reaction solution was concentrated to an oliy residue, which was added to 10% hydrochloric acid under cooling and promptly extracted with benzene. After the benzene layer was dried on anhydrous sodium sulfate, it was distilled to give 2.4 g of a brown liquid. The aqueous layer made alkaline with sodium carbonate was extracted with ether, and etheral layer was washed with water and dried on anhydrous sodium sulfate, and then distilled to give 1.8 g of a reddish brown liquid. Vaccum distillation of the reddish brown liquid obtained from the aqueous layer was afforded 1.2 g of III, bp 75—80° (0.05—0.06 mmHg). IR $\nu_{\text{liq.}}$ cm^{-1}: 1613, 1582, 775, 750. The picrate: mp 170—171° (ethanol).

The brown liquid obtained from the benzene layer was chromatographed on alumina, and eluted with dichloromethane to give 1.08 g of an oily substance. Vaccum distillation (0.02—0.03 mmHg) of the solvent yielded 0.8 g of a pure oily substance, which was crystallized under cooling. Recrystallization from ether gave white needles of IIa, mp 101—102°. IR $\nu_{\text{max}}^{\text{paraffin}}$ cm^{-1}: 1665 $\left(\rangle\text{N}-\underset{\text{O}}{\underset{\|}{\text{C}}}-\right)$. NMR (in CDCl_3): singlet (3H) at 8.77 τ ($\text{C}\underline{\text{H}}_3$–), multiplet (6H) at 7.67—8.80 τ ($-\text{C}\underline{\text{H}}_2-\text{C}\underline{\text{H}}_2-\text{C}\underline{\text{H}}_2-$), singlet (3H) at 7.62 τ ($\text{C}\underline{\text{H}}_3$–), triplet (1H) at 4.59τ $\left(J=3.5\text{ cps},\ \rangle\text{C}=\text{C}\underset{\underline{\text{H}}}{\langle}\right)$, multiplet (4H) at 1.88—3.0 τ (benzene ring). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{17}\text{ON}$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.01; H, 7.37; N, 6.51.

9-Benzoyl-11-methyl-2,3,4,11-tetrahydrocarbazole (IIb)——A mixture of 5.0 g of N¹–benzoylphenylhydrazine hydrochloride and 20 ml of glacial acetic acid was stirred, while 2.25 g of 2–methylcyclohexanone was added dropwise to the mixture for 10 min. Then the mixture was stirred for additional 1.5 hr with heating to 70—75°. After allowing to stand overnight, acetic acid was distilled to an oily residue, to which was added water and the mixture was extracted with benzene, and then the benzene solution was dried on anhydrous sodium sulfate. The solution was distilled to give a brown oily substance, which was chromatographed on 91 g of alumina and eluted with dichloromethane to yield 2.0 g of IIb. Recrystallization from ether gave 1.7 g of colorless prisms, mp 131—133°. IR $\nu_{\text{max}}^{\text{paraffin}}$ cm^{-1}: 1653 $\left(\rangle\text{N}-\underset{\text{O}}{\underset{\|}{\text{C}}}-\right)$, 1604 . NMR (in CDCl_3): singlet (3H) at 8.59τ ($\text{C}\underline{\text{H}}_3$–), multiplet (6H) at 7.8—8.4 τ ($-\text{C}\underline{\text{H}}_2-\text{C}\underline{\text{H}}_2-\text{C}\underline{\text{H}}_2-$), triplet (1H) at 5.19 τ $\left(J=3.5\text{ cps},\ \rangle\text{C}=\text{C}\underset{\underline{\text{H}}}{\langle}\right)$, multiptlet (9H) at 1.97—3.0 τ (benzene ring). *Anal.* Calcd. for $\text{C}_{20}\text{H}_{19}\text{ON}$; C, 83.01; H, 6.62; N, 4.84. Found: C, 82.50; H, 6.74; N, 5.42.

6-Methoxy-9-(*p*-chlorobenzoyl)-11-methyl-2,3,4,11-tetrahydrocarbazole (IIc)——A mixture of 9.4 g of N¹–(*p*–chlorobenzoyl)–*p*–methoxyphenylhydrazine hydrochloride and 3.4 g of 2–methylcyclohexanone was added to 10 ml of glacial acetic acid, and the reaction mixture was slowly heated with stirring in a nitrogen gas. When the reaction began to proceed vigorously, the mixture was cooled to keep the temperature below 40° for 30 min, then was gently heated to 70—75° for 3 hr with stirring. A resultant precipitate (ammonium chloride) was filtered, and the filtrate was concentrated *in vacuo* to an oily residue. Water was added to the residue and the mixture was extracted with benzene. After drying on anhydrous sodium sulfate, distillation of benzene gave an oily substance, which chromatographed on 100 g of alumina and eluted with benzene to yield 1.3 g of crystals of IIc. Recrystallization from ether gave 0.8 g of light yellow prisms of pure IIc, mp 144—145°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 1644 $\left(>\text{N}-\underset{\overset{\|}{\text{O}}}{\text{C}}-\right)$, 1598 (). NMR (in $CDCl_3$): singlet (3H) at 8.57 τ ($-C\underline{H}_3$), multiplet (6H) at 7.79—8.33 τ ($-C\underline{H}_2-C\underline{H}_2-C\underline{H}_2-$), singlet (3H) at 6.22 τ ($-C\underline{H}_3$), triplet (1H) at 5.22 τ $\left(J=4\ \text{cps},\ >\text{C}=\underset{\text{H}}{\text{C}}<\right)$, multiplet (7H) at 2.07—3.30 τ (benzene ring). *Anal.* Cacld. for $C_{21}H_{20}O_2NCl$: C, 71.29; H, 5.66; N, 3.93. Found: C, 71.02; H, 5.66; N, 4.33.

While, dichloroethane eluted 0.8 g of crystals, which were recrystallized from ethyl acetate to give 0.5 g of white needles of V, mp 178—181.5°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 3270 (NH), 1712 (C=O), 1647 $\left(>\text{N}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\right)$. NMR (in $CDCl_3$): doublet (3H) at 8.94τ ($J=6$ cps, $C\underline{H}_3-$), multiplet (8H) at 7.3–8.2 τ ($-C\underline{H}-C\underline{H}_2-CH_2-C\underline{H}_2-C\underline{H}-$), singlet (3H) at 6.22 τ ($C\underline{H}_3-$), multiplet (7H) at 2.2–3.3 τ (benzene), singlet (1H) at 1.89 τ (–NH). *Anal.* Calcd. for $C_{21}H_{22}O_3NCl$: C, 67.83; H, 5.92; N, 3.77. Found: C, 68.09; H, 5.66; N, 3.93.

9-Acetyl-11-methyl-2,3,4,11-tetrahydrocarbazole (IIa) from 11-Methyl-1,2,3,4-tetrahydrocarbazolenine (III)——To a mixture of 10 ml of acetic anhydride and 0.8 g of sodium acetate was added 1.03 g of III and the mixture was heated at 100° for 1 hr with stirring. The solvent was distilled *in vaccuo* to an oily residue, to which was added water. The resultant crystals were filtered and dried to give 1.08 g of crystals. Recrysstallization from a mixture of ether and petr. ether gave 0.9 g (71%) of white needles, mp 101—102°, undepressed when admixed with an authentic sample. Identical infrared absorption spectra were obtained from this material and authentic sample.

11-Methyl-1,2,3,4-tetrahydrocarbazolenine (III) from 9-Acetyl-11-methyl-2,3,4,11-tetrahydrocarbazole (IIa)——The mixture of 0.24 g IIa and 5 ml of glacial acetic acid was heated at 75—80° for 1 hr with stirring. Thereafter, acetic acid was distilled *in vacuo,* and water was added to the resultant residue. It was extractd with chloroform, and dried on anhydrous sodium sulfate, and then chloroform was distilled to give a crude product, which was gaschromatographed to give 20.4% of III and 79.6% of IIa.

9-Benzoyl-11-methyl-2,3,4,11-tetrahydrocarbazole (IIb) from 11-Methyl-1,2,3,4-tetrahydrocarbazolenine (III)——The mixture of 3.7 g of III and 5 ml of benzoyl chloride was heated at 100° for 2 hr with stirring. After cooling, ice water was added to the reaction mixture, and it was extracted with ether. An etheral layer was washed with 5% sodium hydrogen carbonate and with water twice, and then dried on anhydrous sodium sulfate. Ether was distilled to give 3.8 g (62%) of white crystals. Recrystallization from *n*–hexane gave 3.2 g of white prisms of 9–benzoyl–10–hydroxy–11–methyl–1,2,3,4,10,11–hexahydrocarbazole (IVb), mp 108—109°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 3440 (–OH), 1630 (>N–C=O). NMR (in $CDCl_3$): singlet (3H) at 8.69 τ ($C\underline{H}_3-$), multiplet (8H) at 7.65—8.7 τ ($-C\underline{H}_2-C\underline{H}_2-C\underline{H}_2-C\underline{H}_2-$), singlet (1H) at 4.81$\tau$ ($O\underline{H}$, disappeared by D_2O), multiplet (9H) at 2.3—3.36 τ (benzene ring). *Anal.* Cacld. for $C_{20}H_{21}O_2N$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.68; H, 7.09; N, 4.94. Under reduced pressure (25—30 mmHg) 1.0 g of IVb was heated for 30 min in a bath of 175—180°. After cooling, the reactant was dissolved in a solvent mixture of one part of ether and five parts of *n*–hexane and the solution was allowed to stand at the room temperature overnight. Then, white crystals were precipitated, filtered, and dried to give 0.95 g of white needles of IIb. The melting point was undepressed when admixed with an authentic sample. Identical infrared absorption spectra and thin-layer chromatographs (*Rf*) were obtained from this material and from an authentic sample.