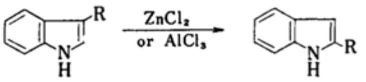
Twofold Wagner-Meerwein Type Rearrangement of 2, 3-Disubstituted Indoles

By Masao NAKAZAKI

(Received August 31, 1959)

Among various interesting reactions of indoles, little attention has been paid to Fischer's rearrangement, which is as old as the discovery of indole itself. In 1888, Fischer and Schmidt[1] reported the conversion of 3-phenylindole (Ia) into 2-phenylindole (IIa) when heated with zinc chloride. Recently, Clemo and Seaton[2] demonstrated the same type of migration of substituents from 3-position to 2-position of indoles on 3-(2-pyridylmethyl) indole (Ib), 3-benzylindole (Ic) and skatole (Id), using aluminum chloride instead of zinc chloride.



I a R = C_6H_5	II a R = C_6H_5
b R = 2-pyridylmethyl	b R = 2-pyridylmethyl
c R = $CH_2C_6H_5$	c R = $CH_2C_6H_5$
d R = CH_3	d R = CH_3

Fig. 1

These researchers, however, did not dare to inquire into the possible exchange reaction of substituents between 2- and 3-position of 2, 3-disubstituted indoles. This paper is concerned with the demonstration of such possibility.

As a simple representative of 2, 3-disubstituted indoles, the reaction of 2-methyl-3-phenylindole (III) with aluminum chloride was initially investigated.

2-Methyl-3-phenylindole (III) was prepared from phenylacetone phenylhydrazone by Fischer's method employing zinc chloride[3] or borontrifluoride[4] as catalyst, but the melting point (78~79°C) was inconsistent with the reported melting point (59~60°C) by Trenkler[3] or Ockenden and Schofield[4]. Because of such a great discrepancy of the melting points, an attempt was made to determine the structure of the indole (m. p. 78~79°C) by ozonolysis.

The melting point of *o*-acetoaminobenzophenone (IVa) obtained by ozonolysis of the indole (m. p. 78~79°C) was found 86~88°C in our hands, but Ockenden and Schofield[4] reported it as 71~73°C. There have been disputes about the melting point of IVa: von Auwers and Meyerburg[5] reported that their sample prepared by the acetylation of *o*-aminobenzophenone showed m. p. 72°C, but from the mother liquor there were obtained other crystals melting at 88.5~89°C, although the latter were the only crystals obtained in the repetitions of their experiment by themselves[6] and by others[7].

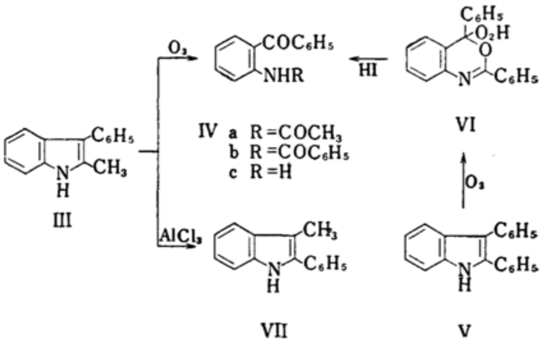


Fig. 2

To secure an authentic sample of *o*-acetoaminobenzophenone for comparison, IVa was synthesized by the process which involved the ozonolysis of 2,3-diphenylindole (V). Although Ockenden and Schofield[4] reported that 2, 3-diphenylindole was converted into *o*-benzaminobenzophenone (IVb) (m. p. 85~86°C, 56% yield) when ozone was passed into a solution of V in ethyl acetate at 0°C, our result was found to be another contradiction with their finding.

In our hands, the ozonide VI[8] (m. p. 152

---

[1] E. Fischer and T. Schmidt, *Ber.*, **21**, 1811 (1888).

[2] G. R. Clemo and J. C. Seaton, *J. Chem. Soc.* **1954**, 2582. An excellent review about the rearrangement reactions of indoles and indolenines are to be found in P. L. Julian, E. W. Meyer and H. C. Pring, "The Chemistry of Indoles" in R. Elderfield, "Heterocyclic Compounds", Vol. 3, John Wiley & Sons, Inc., New York (1952), p. 1.

[3] B. Trenkler, *Ann.*, **248**, 111 (1888).

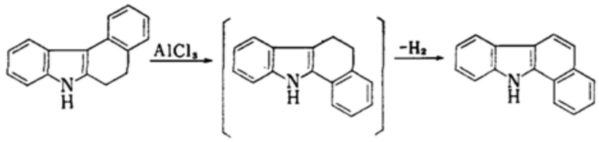
[4] D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, **1953**, 612.

[5] K. von Auwers and V. Meyerburg, *Ber.*, **24**, 2384 (1891).

[6] K. von Auwers, ibid., **29**, 1263 (1896).

[7] A. Bishler and D. Barad, ibid., **25**, 3081 (1892); R. Camps, *Arch. Pharm.*, **237**, 683 (1899).

[8] The stable ozonides of indole derivatives were first observed by G. Mentzer, D. Molho and Y. Berguer, *Bull. soc. chim.*, 555 (1950). For details see the exhaustive studies by Witkop on the ozonide of phenylskatole. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855 (1952); B. Witkop, J. B. Patrick and H. M. Kissman, *Chem. Ber.* **85**, 949 (1952). Remembering that 2-aryl indoles usually afford stable ozonides, it seems rather surprising that Ockenden and Schofield[4] obtained *o*-benzaminobenzophenone (IVb) directly from V. The stable ozonide from 2-(dibenzylmethyl)-3-benzylindole which does not possess the 2-aryl group was reported by M. Nakazaki and K. Tanno, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **77**, 952 (1956).



VIII IX X

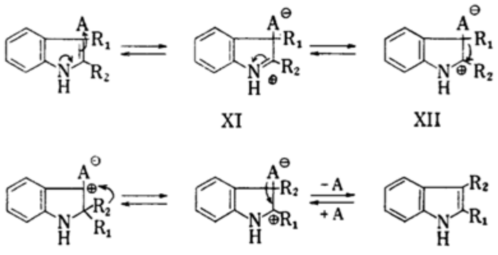
Fig. 3

~154°C, decomp.) of 2, 3-diphenylindole was the only compound isolated following their procedure (in ethyl acetate) or in the ozonolysis in acetic acid. The ozonide VI showed typical reactions of ozonide, and reductive hydrolysis⁹⁾ with hydroiodic acid in acetic acid converted it into benzoic acid and *o*-aminobenzophenone (IVc) which was acetylated with acetic anhydride to give *o*-acetoaminobenzophenone (m. p. 86~88°C) which was found identical with IV from 2-methyl-3-phenylindole by mixed melting point determination and comparison of their infrared absorption spectra. Thus being established the structure, 2-methyl-3-phenylindole (III) was subjected to rearrangement by heating with aluminum chloride at 220~240°C for 20 min. The product obtained was found to be identical with 2-phenyl-3-methylindole¹⁰⁾ (VII).

5, 6-Dihydro-7-benzo [*c*] carbazole¹¹⁾ (VIII) was the next indole derivative tried to demonstrate the analogous rearrangement reaction.

The tetrahydrocarbazole derivative VIII, which was provided from the phenylhydrazone of β-tetralone was heated at 220~240°C for 20 min. with aluminum chloride to give rise to 11-benzo [*a*] carbazole (X), apparently resulted by the dehydrogenation of the intermediate 5, 6-dihydro-11-benzo [*a*] carbazole (IX) with aluminum chloride.

Mechanistically, these rearrangements¹²⁾ can be explained by twofold Wager-Meerwein type rearrangement initiated by the electrophilic attack by the Lewis acid (A in Fig. 4.) on the 3-position of indoles (Fig. 4), and the equilibria XI $\rightleftarrows$ XII $\rightleftarrows$ XIII $\rightleftarrows$ XIV are completly parallel to the one to be found in rearrangement of indolenines¹³⁾ and Plancher's rearrangement of indolenium compounds¹⁴⁾.

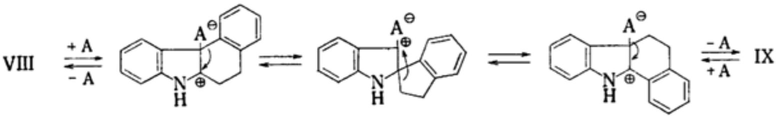


XI XII XIII XIV

Fig. 4

The *Spiro* type intermediate XV, analogous to the one postulated by Woodward¹⁴⁾ in the dienone-phenol rearrangement, would be the intermediate in the case of 5, 6-dihydro-7-benzo [*c*] carbazole.

Inspection of the ultraviolet spectra (Figs. 6, 7 and 8) and π-electron density in the indole



XV

Fig. 5

---

9) The reductive hydrolysis of the stable ozonide with hydrobromic acid in acetic acid was carried out on the ozonide of 2-(dibenzylmethyl)-3-benzylindole. M. Nakazaki and K. Tanno, Ref. 8.

10) The structure of 2-phenyl-3-methylindole was established by ozonolysis. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3861 (1952); cf. B. Witkop, J. B. Patrick and H. M. Kissman, *Chem. Ber.*, **85**, 949 (1952).

11) Dehydrogenation by heating with 5% palladium-charcoal at 250~260°C converted VIII into the known 7-benzo[*c*] carbazole, m. p. 135~136°C.

12) In Bishler's indole synthesis applied on α-bromo-β-phenylpropiophenone, there was found the formation of two isomeric indoles, i. e. 2-phenyl-3-benzylindole and 2-benzyl-3-phenylindole. [P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945); P. L. Julian and J. Pikl, ibid., **55**, 2105 (1953)]. But from a mechanistical standpoint which was worked out recently by Wygand and Richter [*Chem. Ber.*, **88**, 499 (1955)], it is highly improbable to assume the mutual interconversion of these two indoles under the reaction condition *after* they are formed.

13) See the author's papers on Plancher's rearrangement which follow.

14) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950). For the dienone-phenol rearrangements of the compounds possessing *spiro* structure, see R. T. Arnold, J. B. Buckley and R. M. Dodson, ibid., **72** 3553 (1950); E. N. Marvell and A. O. Geiszler, ibid., **74**, 1259 (1952). Also it is noteworthy to compare the smooth conversion of VIII into X with the dienone-phenol rearrangement of 2-keto-4a-methyl-2, 4a, 5, 6-tetrahydrobenzo[*c*] phenathrene in which the transformation which requires a *spiro* intermediate is inhibited. C. Djerassi and T. T. Grossnickle, *J. Am. Chem., Soc.*, **76**, 1741 (1954).

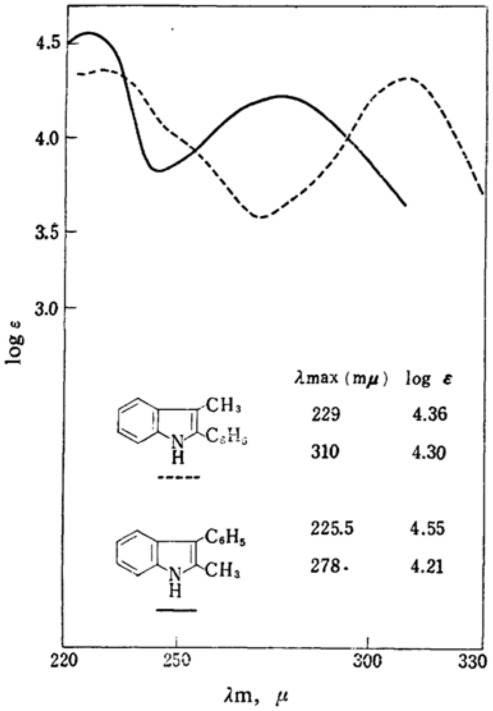


Fig. 6

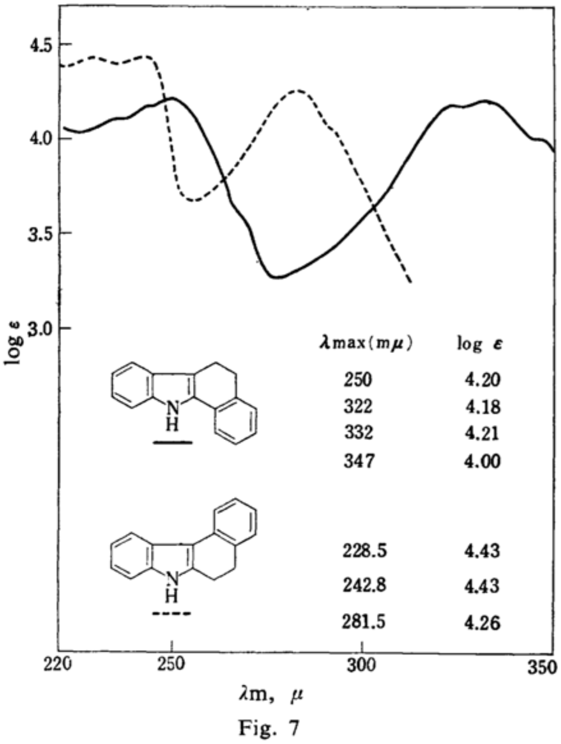


Fig. 7

nucleus[15] (1.059 at 2-position, 1.066 at 3-position) suggest that the driving force of these rearrangement reactions could be sought in the mesomeric stabilization of the products (VII,

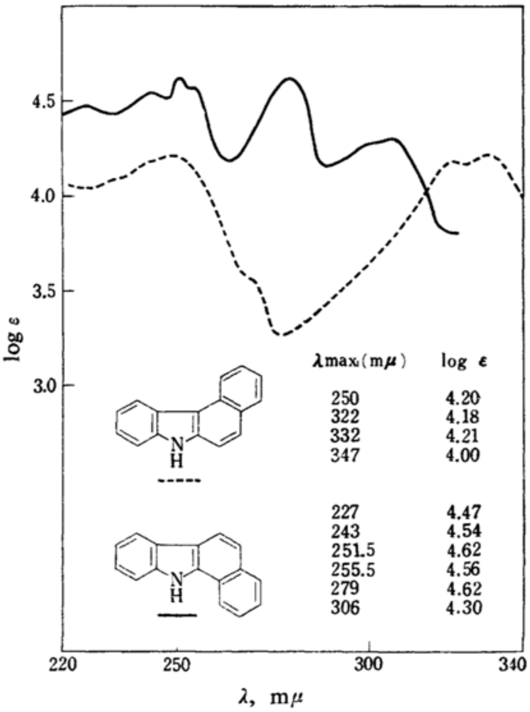


Fig. 8

IX and X) by the phenyl group at 2-position rather than at 3-position.

The same reasoning could be applied to interprete Fischer's rearrangement[1] (migration of hydrogen anion), and the hyperconjugation effect[16] would be the stabilization factor in the case of the rearrangements of the indoles studied by Clemo and Seaton[2].

Experimental[17]

2-Methyl-3-phenylindole (III).—*By borontrifluoride etherate method*[4].—To a solution of 7.0 g. of phenylacetone phenylhydrazone (m. p. 82~83°C) in 70 cc. of acetic acid, 5.1 g. borontrifluoride etherate was added, and the mixture was refluxed on an oil bath for 3 hr. The color of the solution changed from yellow to brown→green→brown. Water was added into the reaction mixture and was extracted with ether. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a viscous brown

---

[15] K. Higasi and H. Baba, "Quantum Organic Chemistry (Ryoshi Yuki Kagaku)", Asakura Publishers, Tokyo (1956), p. 406.

[16] The formation of *spiro*-(cyclopentane-1, 3′-*pseudo*-2′-methyl-indole) instead of 11-methyltetrahydrocarbazolenine from *spiro*-(cyclopentane-1, 2′-*pseudo*indoxyl) by the action of methyl/magnesium iodide could be interpreted on the same reason. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* 75, 2572 (1953).

[17] All melting points are not corrected. All ultraviolet spectra were measured by an EPS-2 Hitachi autorecording spectrophotometer and infrared spectra on a Perkin Elmer Model 12C. The analyses were performed in the Microanalytical Laboratory of the Institute of Polytechnics, Osaka City University.

liquid which was distilled in vacuo to afford a pale yellow liquid, b. p. 196~200°C/3 mmHg, 6.2 g. (57.5% yield). The distilate solidified gradually and was recrystallized from petroleum ether (b. p. 60°C) to give crystals, m. p. 78~79°C (literature[3,4]: 59~60°C).

Found: C, 86.77; H, 6.54. Calcd. for $C_{15}H_{13}N$: C, 86.99; H, 6.32%.

U.V. spectrum[18]: λ_{max} mμ (log ε), 225.5 (4.55), 278 (4.21). λ_{min} 245.5 mμ (log 3.82) in methanol (Fig. 6). I.R. spectrum: 2.95 μ.

The picrate was recrystallized from ethanol to give brown needles, m. p. 139~140°C (literature[3,4]: 141~142°C).

Found: C, 57.42; H, 3.84; N, 12.25. Calcd. for $C_{21}H_{16}O_7N_4$: C, 57.80; H, 3.70; N, 12.84%.

By zinc chloride method.— Following Trenkler's procedure[3], III was obtained in a yield of 34.6%, m. p. 78~79°C.

Ozonolysis of 2-Methyl-3-phenylindole (III)[4]. —To a mixture of 0.7 g. of 2-methyl-3-phenylindole and 35 cc. of acetic acid, a stream of ozone (approximately 5%) was passed for 45 min. at room temperature, during which time the color of the solution was observed to change from yellow to red and then pale yellow again. After water was added, the solution was extracted with ether thrice and the combined ethereal extract was washed with water followed by 5% sodium carbonate solution and saturated sodium chloride solution. Removal of the solvent yielded a viscous residue which could be brought to crystallization by trituration. The crystals were collected and recrystallized from petroleum ether to give crystals melting at 70~72°C (0.291 g.). The melting point was raised to 86~88°C by further recrystallization from water-ethanol.

Found: C, 75.20; H, 5.78. Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48%.

Stable Ozonide of 2, 3-Diphenylindole VI. — *In acetic acid solution.*—A stream of ozone (approximately 5%) was passed into a mixture of 1.4 g. of 2, 3-diphenylindole (V) and 40 cc. of acetic acid for 1 hr. at room temperature. Completion of the reaction was estimated by the usual color change of the reaction mixture: yellow→red→yellow. Water was added to the reaction mixture to precipitate crystals which were collected and washed with water.

Recrystallization from water-ethanol and ethanol gave colorless crystals (0.47 g.) which darkened in color at 140°C and decomposed at 152~153°C. On the addition of solid potassium iodide to a solution of VI in acetic acid, the formation of iodine was observed.

In ethyl acetate solution[4]. — Into a mixture of 2.7 g. of 2, 3-diphenylindole and 75 cc. of ethyl acetate, a stream of ozone (approximately 5%) was passed for 1.5 hr. at 0°C. The color of the solution changed from yellow to brown and then to yellow again. After the excess of ozone was blown out by a stream of nitrogen, the solvent was removed in vacuo to give a viscous residue which crystallized by trituration with ethanol.

The crude ozonide (decomp. 148°C) weighed 1.5 g., and was recrystallized from ethanol to afford crystals which decomposed at 152°C.

Found: C, 75.37; H, 5.12; N, 4.54. Calcd. for $C_{20}H_{15}O_3N$: C, 75.69; H, 4.72; N, 4.41%.

Reductive Hydrolysis of the Ozonide VI. — A mixture of 1.50 g. of the ozonide VI, 30 cc. of acetic acid and 10 cc. of constant boiling hydroiodic acid solution was refluxed for 5 hr. After water was added, the reaction mixture was extracted with ether, to separate basic and acidic fractions.

Acidic fraction.—The ether layer was washed with sodium thiosulfate solution to discharge the color of iodine, and was extracted with 2 N sodium hydroxide solution. The alkaline solution was acidified with 2 N hydrochloric acid solution to precipitate benzoic acid, 0.381 g. Recrystallization from water gave crystals which melted at 120~121°C, alone and admixed with an authentic specimen of benzoic acid.

Basic fraction.—The aqueous layer was washed with ether, and was made basic with 2 N sodium hydroxide solution to precipitate *o*-aminobenzophenone (IVc). Extraction with ether afforded 0.81 g. of golden yellow crystals, m. p. 101~104.5°C, which was recrystallized from ethanol-water to give yellow prisms, m. p. 103~105°C (literature[5-7]: 105~106°C).

Found: C, 78.88; H, 5.68. Calcd. for $C_{13}H_{11}ON$: C, 79.16; H, 5.62%.

***o*-Acetoaminobenzophenone (IVa)**.—After a mixture of 0.287 g. of *o*-aminobenzophenone (IVc) and 3 cc. of acetic anhydride was heated on a water bath for 2 hr., water was added to the reaction mixture and was allowed to stand overnight. The precipitate was collected (0.270 g., m. p. 70~75°C) and was recrystallized from ethanol-water to give crystals melting at 86~88°C, alone and admixed with *o*-acetoaminobenzophenone (m. p. 86~88°C) obtained by the ozonolysis of 2-methyl-3-phenylindole (III) mentioned above. The identity was further comfirmed by the comparison of their infrared spectra.

Rearrangement of 2-Methyl-3-phenylindole (III). —A mixture of 0.8 g. of 2-methyl-3-phenylindole, 0.8 g. of aluminum chloride and 0.1 g. of sodium chloride was heated at 220°C for 15 min. and at 220~240°C for 5 min. After water was added to the resulted brown solid mass, the mixture was extracted with ether and the ether extract was washed with water and dried over anhydrous potassium carbonate. After the removal of the solvent, the residue was distilled in vacuo to afford 0.482 g. of a viscous oil, b. p. 194~195°C/2 mmHg., which crystallized on standing. Recrystallization from ethanol-water gave crystals, m. p. 89~90°C, which were found identical with 2-phenyl-3-methylindole[19] by mixed melting point determination and the comparison of infrared

---

[18] Ultraviolet spectrum of phenylskatole: λ_{max}(log ε), 229 mμ (4.36), 310 mμ (4.30), λ_{min}271.5 mμ (3.58) in ethanol (Fig. 6). Cf. R. Huisgen and I. Ugi, *Ann.*, **610**, 57 (1957); B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855 (1952).

[19] Prepared from propiophenonephenylhydrazone. Fischer's method employing zinc chloride was found to give better yield than the polyphosphoric acid method and borontrifluoride method. [H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952); B. Witkop and J. B. Patrick, ibid, **74**, 3858 (1952)].

spectrum with an authentic specimen. Also, the picrate, m. p. 144～145°C (from ethanol) was prepared to confirm their identity.

5, 6-Dihydro-11-benzo[*a*]carbazole (IX)[20]. — 5,6-Dihydro-11-benzo[*a*]-carbazole was synthesized following the procedure of Organic Syntheses, **30**, 90 (1950), m. p. 163～164°C (from methanol).

U. V. specrum. λ_{max} (log ε), 250 mμ (4.20), 332 mμ (4.21); λ_{min} (log ε), 227 mμ (4.04), 276 mμ (3.26) in ethanol (Fig. 7).

The picrate was recrystallized from ethanol to give black needles, m. p. 153～154°C.

Found: N, 12.79. Calcd. for $C_{22}H_{16}O_7N_4$: N, 12.50%.

11-Benzo[*a*]carbazole (X)[20].—A mixture of 0.5 g. of 5,6-dihydro-11-benzo[*a*]carbazole and 0.1 g. of 5% palladium-charcoal was heated at 250～260°C for 20 min. 11-Benzo[*a*]carbazole which resulted was recrystallized from benzene to yield crystals melting at 227～229°C. (literature[21]: 225°C).

U.V. spectrum[21]: λ_{max} mμ (log ε), 227 (4.47), 243 (4.54), 251 (4.62), 279 (4.62), 306 (4.30). λ_{min} mμ (log ε), 234 (4.42), 248.5 (4.51), 263 (4.18), 289 (4.17) in ethanol (Fig. 8).

5,6-Dihydro-7-benzo[*c*]carbazole (VIII)[20].—Considerable generation of heat was observed when 15 cc. of acetic acid was added to a mixture of 2.9 g. of β-tetralone[22] and 2.2 g. of phenylhydrazine, and the reaction mixture was refluxed for 1 hr. After being kept at room temperature overnight, the crystals precipitated were filtered and washed with methanol. Recrystallization from methanol gave 2.4 g. of crystals, m. p. 102～103°C.

Found: C, 87.91; H, 6.15; N, 6.31. Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39%.

U.V. spectrum: λ_{max} mμ (log ε), 228.5 (4.43), 281.5 (4.26); λ_{min} 253.5 mμ (log ε 3.68) in ethanol (Fig. 7).

The picrate was recrystallized from ethanol to give black needles, m. p. 129～132°C.

Found: C, 59.11; H, 3.76; N, 12.82. Calcd. for $C_{22}H_{16}O_7N_4$: C, 58.93; H, 3.60; N, 12.50%.

7-Benzo[*c*]carbazole[20].—A mixture of 0.5 g. of 5,6-dihydro-7-benzo[*c*]carbazole and 0.1 g. of 5% palladium-charcoal was heated at 250～260°C for 30 min. The reaction mixture was extracted with boiling benzene. After the solvent was removed, the residue was recrystallized from benzene-ligroin to give 0.27 g. of crystals, m. p. 135～136°C (literature[23]: 135°C). U.V. spectrum: λ_{max} mμ (log ε), 265 (4.69), 285.5 (4.02), 326 (4.09), λ_{min} mμ (log ε), 237 (4.21), 282 (3.86), 295 (3.45) in ethanol (Fig. 8).

Rearrangement of 5, 6-dihydro-7-benzo[c]carbazole (VIII).—A mixture of 1.0 g. of VIII, 1 g. of aluminum chloride and 0.1 g. of sodium chloride was heated at 220°C for 10 min. and at 220～240°C for 5 min. Water was added to the reaction mixture and extracted with ether. The yellow ethereal solution, which exhibited green fluorescence, was washed with water followed with sodium bicarbonate solution and was dried over anhydrous magnesium sulfate. Distillation of the solvent gave a residue which was recrystallized from carbon tetrachloride to give 0.206 g. of crystals, m. p. 210°C. Recrystallization from benzene improved the melting point to 227～228°C which was undepressed when admixed with an authentic specimen of 11-benzo[*c*]carbazole. The identity was further confirmed by the comparison of their infrared spectra which could be overlapped in every detail.

The author is very grateful to Dr. Itaru Mita for his generous supply of phenylacetone. He also feels indebted to Mr. Satosi Kamei for his technical assistance; to Mr. Sachihiko Isoe who kindly measured the ultraviolet absorption spectra.

Institute of Polytechnics
Osaka City University
Kita-ku, Osaka

---

[20] Nomenclature followed A. M. Patterson and L. T. Capell, "The Ring Index", Reinhold Publishing Corp., New York (1940), p. 331.

[21] R. Huisgen and I. Ugi, *Ann.*, **616**, 63 (1957).

[22] M. D. Soffer et. al., "Organic Syntheses", Vol. 32, John Wiley & Sons, Inc., New York (1952), p. 97.

[23] F. R. Japp and W. M. Maitland, *J. Chem. Soc.*, **83**, 270 (1903); H. T. Bucherer and F. Seyde, *J. Prakt. Chem.*, (2) 77. 406 (1908); S. G. P. Plant and S. H. Oakeshott, *J. Chem. Soc.*, **1928**, 1843.