[Chem. Pharm. Bull. 23(12)3151—3153(1975)]

UDC 547.384.04 : 547.288.1.04

Polycyclic N-Hetero Compounds. IX.[1] Reactions of Tetralones with Formamide or Trisformylaminomethane

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(Received April 15, 1975)

Condensation of 1-tetralone (I) with trisformylaminomethane gave 5,6-dihydrobenzo-[*h*]quinazoline (II) which was dehydrogenated with sulfur to benzo[*h*]quinazoline (III). Condensation of 2-tetralone (IV) with formamide or trisformylaminomethane gave 5,6-dihydrobenzo[*f*]quinazoline (V) which was dehydrogenated with sulfur to benzo[*f*]quinazoline (VI).

In the previous paper,[3] we reported that the reaction of phenylacetones or desoxybenzoins with formamide in the presence of phosphoryl chloride afforded 3-substituted isoquinolines or 4,5-disubstituted pyrimidines. On the other hand, Bredereck, *et al.*[4] described the synthesis of pyrimidines by heating ketones with trisformylaminomethane in formamide. Application of these pyrimidine ring-forming reactions to bicyclic aromatic ketones is now described to obtain fused pyrimidines.

As shown in Chart 1, 1-tetralone (I) and 2-tetralone (IV) were used as starting materials.

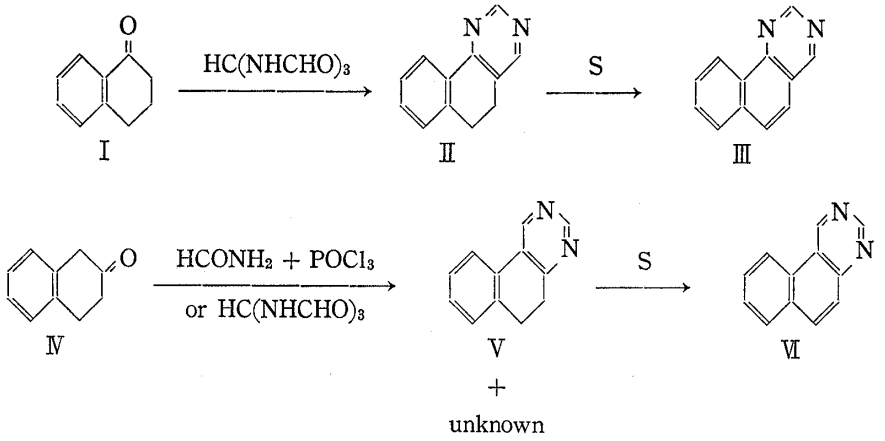

Chart 1

Modest, *et al.*[5] synthesized 2,4-diamino-5,6-dihydrobenzo[*h*]quinazoline or 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline by the condensation of I or II with dicyandiamide, respectively.

At first, condensation of I with trisformylaminomethane expectedly afforded 5,6-dihydrobenzo[*h*]quinazoline (II) in 40% yield. Wagner and Jutz[6] synthesized II from 1-dimethylamino-2-dimethylimoniomethyl-3,4-dihydronaphthalene tetrafluoroborate and formamidine

1) Part VIII: T. Koyama, T. Hirota, C. Bashou, Y. Satoh, Y. Watanabe, S. Matsumoto, Y. Shinohara, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2158 (1975).
2) Location: *1-1 Tsushima-naka 1-chome, Okayama, 700, Japan.*
3) T. Koyama, M. Toda, T. Hirota, and M. Yamato, *Yakugaku Zasshi*, **90**, 11 (1970); T. Koyama, Y. Katsuse, M. Toda, T. Hirota, and M. Yamato, *Yakugaku Zasshi*, **90**, 1207 (1970).
4) H. Bredereck, R. Gompper, and B. Geiger, *Chem. Ber.*, **93**, 1402 (1960).
5) E.J. Modest, S.K. Sengupta, S. Chatterjee, and H.K. Protopapa, *J. Org. Chem.* **37**, 1323 (1972).
6) R.M. Wagner and C. Jutz, *Chem. Ber.*, **104**, 2975 (1971).

in 80% yield. Melting point and nuclear magnetic resonance (NMR) spectrum of our specimen agreed with those of the authentic sample.[6] Dehydrogenation of II with sulfur gave benzo[*h*]quinazoline (III) in 86.5% yield. Perkampus and Bluhm[7] obtained III by the photolysis of 5-styrylpyrimidine in 37% yield. Melting point and NMR spectrum of our specimen agreed with those of the authentic sample.[8]

Secondly, reaction of IV with formamide in the presence of phosphoryl chloride gave 5,6-dihydrobenzo[*f*]quinazoline (V) in poor yield. The structure of V is supported from its elemental analysis, absence of carbonyl absorption in the infrared spectrum, and the molecular weight determination by mass spectroscopy. Moreover, its NMR spectrum exhibited a four-proton singlet at δ 3.20 attributable two methylene groups, three-proton multiplet centered around δ 7.35 of aromatic protons, one-proton multiplet of C_{10}-proton at δ 7.78 shifted to down field from normal aromatic protons by anisotropic effect of pyrimidine ring, and two singlets attributable pyrimidine ring protons at δ 8.98 and 9.00. As by-product, pale brown needles was isolated (mp 227—229°), and its molecular formula was determined $C_{31}H_{23}N$ from its elemental analysis and the molecular weight determination by mass spectroscopy, but the structure could not be confirmed because of poor yield.

Condensation of IV with trisformylaminomethane at 160—165° afforded V in 30% yield, identical with the specimen prepared from the method with formamide. Dehydrogenation of V with sulfur gave benzo[*f*]quinazoline (IV) in 72.2% yield. VI was already synthesized by Modest, *et al.*[5] with dechlorination of 1,3-dichlorobenzo[*f*]quinazoline and by Perkampus and Bluhm[7] with photolysis of 4-styrylpyrimidine.

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value). Mass spectra were taken on a Shimadzu-LKB 9000 spectrometer with a direct inlet system. Ultraviolet (UV) spectra were taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH.

Reaction of 1-Tetralone (I) with HC(NHCHO)$_3$——A mixture of 6 g of I, 11.9 g of $HC(NHCHO)_3$, 8.0 ml of $HCONH_2$, and 0.4 g of *p*-toluenesulfonic acid was heated at 160—165° for 6 hr. The reaction mixture was made alkaline with 2N NaOH and extracted with *n*-hexane. The *n*-hexane extract was washed with H_2O, dried, and evaporated. The residue was recrystallized from *n*-hexane to give 3.0 g (40%) of 5,6-dihydrobenzo[*h*]quinazoline (II) as pale yellow needles, mp 54—55° (reported mp 53—54°)[6]. *Anal.* Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.25; H, 5.41; N, 15.23. NMR spectrum of II agreed with that of authentic sample.[6]

Dehydrogenation of II——A mixture of 182 mg of II and 64 mg of sulfur was heated at 230—240° for 1.5 hr in a long test tube (*ca.* 40 cm). The reaction mixture was subjected to high vacuum sublimation at 120—130° then recrystallized from petro. ether to give 157 mg (86.5%) of benzo[*h*]quinazoline (III) as colorless scales, mp 102—103° (reported mp 103—104°[7]). *Anal.* Calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.48; N, 15.15. Found: C, 79.88; H, 4.52; N, 15.28. NMR ($CDCl_3$): 7.68—8.01 (5H, multiplet, C_{5-9}–H), 9.30 (1H, multiplet, C_{10}–H), 9.36, 9.54 (each 1H, singlet, C_2, C_4–H). UV λ_{max}^{EtOH} nm (log ε): 216 (3.98), 233 (4.24), 253 (4.31), 258 (4.30), 290 (3.60), 319 (3.11), 334 (3.30), 350 (3.34).

Reaction of 2-Tetralone (IV) with $HCONH_2$——A mixture of 5.7 ml of $HCONH_2$ and 26 ml of $POCl_3$ was stirred at room temperature for 0.5 hr keeping free from atmospheric moisture. To the colloidal mixture, 6.9 g of IV in 30 ml of toluene was added dropwise under stirring. After addition was completed, stirring was continued for 9 hr, then the reaction mixture was heated at 80° for 6 hr. Ice water was added to the reaction mixture and the solution was extracted with ether followed by $CHCl_3$. The water layer was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. Each extract was washed with H_2O, dried, and evaporated independently. The benzene-soluble fraction of the first ether and $CHCl_3$ extracts was combined (same spots on thin-layer chromatography (TLC)) and chromatographed over alumina. The benzene eluate was fractionated with preparative TLC (Merck, Kieselguhr, benzene: cyclohexane=2: 1) and collected the fraction of *Rf* value *ca.* 0.4 which had violet fluorescence with PAN UV-lamp. Recrystallization of the fraction from dil. EtOH gave 13.5 mg of unknown pale brown needles, mp 227—229°. *Anal.* Calcd. for $C_{31}H_{23}N$: C, 90.92;

7) H.H. Perkampus and T. Bluhm, *Tetrahedron*, **28**, 2099 (1972).
8) H.H. Perkampus, T. Bluhm, and J.V. Knop, *Z. Naturforsch.*, **27a**, 310 (1972).

H, 5.66; N, 3.42. Found: C, 90.45; H, 5.79; N, 3.37. Mass Spectrum: *m/e* (M^+)=409. NMR ($CDCl_3$): 2.81—3.78 (12H, multiplet), 7.25—7.65 (9H, multiplet), 8.04 (1H, broad doublet), 8.80 (1H, multiplet). The $CHCl_3$ eluate was fractionated with preparative TLC (Merck, Kieselguhr, benzene: ether=1: 1). The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from petro. ether to give 0.12 g (1.5%) of 5,6-dihydrobenzo[*f*]quinazoline (V) as colorless needles, mp 85.5—86.5°. *Anal.* Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.30; H, 5.42; N, 15.51. NMR ($CDCl_3$): 3.02 (4H, singlet, CH_2CH_2), 7.35 (3H, multiplet, C_7, C_8, C_9–H), 7.78 (1H, multiplet, C_{10}–H), 8.98, 9.00 (each 1H, singlet, C_1, C_3–H). Mass Spectrum: *m/e* (M^+)=182.

Reaction of 2-Tetralone with $HC(NHCHO)_3$——A mixture of 6.0 g of IV, 11.9 g of $HC(NHCHO)_3$, 8.0 ml of $HCONH_2$, and 0.4 g of *p*-toluenesulfonic acid was heated at 160—165° for 6.5 hr. The reaction mixture was made alkaline with 2N NaOH and extracted with *n*-hexane. The *n*-hexane extract was washed with H_2O, dried, and evaporated. The residue was recrystallized from *n*-hexane to give 1.95 g (26%) of V as colorless needles, mp 85.5—86.5°, identical with the specimen prepared from the above method.

Dehydrogenation of V——A mixture of fine powdered 182 mg of V and 64 mg of sulfur was heated at 220—230° for 45 min in a long test tube (*ca.* 40 cm). The reaction mixture was subjected to high vaccum sublimation at 130—150° to give 130 mg (72.2%) of benzo[*f*]quinazoline (VI) as pale yellow needles, mp 107—108° (reported mp 107.5—108.5°[7]). *Anal.* Calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.48; N, 15.15. Found: C, 79.78; H, 4.55; N, 15.42. NMR ($CDCl_3$) 7.55—8.20 (5H, multiplet, C_{5-9}–H), 8.65 (1H, multiplet, C_{10}–H), 9.40 (1H, singlet, C_3–H), 10.03 (1H, singlet, C_1–H).

Acknowledgement The authors are grateful to Mr. A. Iwadoh for microanalyses and measurement of mass spectra.