[Chem. Pharm. Bull.
23(9)2158—2161(1975)]

UDC 547.572.04 : 547.233.04

Polycyclic N-Hetero Compounds. VIII.[1] Reactions of Ketones with Trisformylaminomethane

Takaji Koyama, Takashi Hirota, Chizuko Bashou, Yoshiko Satoh, Yasuko Watanabe, Sachiko Matsumoto, Yurie Shinohara, Shinji Ohmori, and Masatoshi Yamato

Faculty of Pharmaceutical Sciences, Medical School, Okayama University[2]

(Received January 25, 1975)

Reactions of ketones with trisformylaminomethane were described. Except pyrimidine derivatives reported by Bredereck, *et al.*,[3] few by-products were obtained. Thus methyl ethyl ketone (I) gave 4-ethylpyrimidine (III) and 5-methyl-4-(5-pyrimidinyl)pyrimidine (IV), diethyl ketone (V) gave 4-amino-3,5-dimethylpyridine (VII), cyclohexanone (VIII) gave bis(5,6,7,8-tetrahydro-8-quinazolinylidenemethyl)amine (X). 4-Methyl-5-phenylpyrimidine (XII) and 8-phenyl-5,6,7,8-tetrahydroquinazoline (XIV) were obtained from phenylacetone (XI) and 2-phenylcyclohexanone (XIII) respectively. Dehydrogenation of (XIV) with sulfur afforded 8-phenylquinazoline (XV).

In the previous paper,[1] it was reported that the reaction of phenylacetone with formamide in the presence of phosphoryl chloride (called modified Vilsmeier reaction) gave 4-methyl-5-phenylpyrimidine and 5-phenyl-4-(5-pyrimidinyl)pyrimidine. The latter was obtained from the former with the same reaction. To study the pyrimidine ring formation of the active alkyl group of 4-alkylpyrimidines under the modified Vilsmeier reaction, the authors planned synthesis of 4-alkylpyrimidines. According to the method of Bredereck, *et al.*,[3] that is, on heating ketones with trisformylaminomethane (TFM), 4-alkylpyrimidines were synthesized.

As shown in Chart 1, methyl ethyl ketone (I), diethyl ketone (V), cyclohexanone (VIII), phenylacetone (XI), and 2-phenylcyclohexanone (XIII) were used as ketones. The reactions of (I), (V), and (VIII) with TFM were already reported by Bredereck, *et al.*[3] yielding 4,5-dimethylpyrimidine (II), 4-ethyl-5-methylpyrimidine (VI), and 5,6,7,8-tetrahydroquinazoline (IX) respectively, but we obtained other products than the pyrimidines. Bredereck, *et al.*[3] did not report the reactions of XI and XIII with TFM. The present paper describes the main and minor products of Bredereck's method starting from the above ketones.

On heating I with TFM afforded 4,5-dimethylpyrimidine (II), 4-ethylpyrimidine (III), and 5-methyl-4-(5-pyrimidinyl)pyrimidine (IV). Only II was reported by Bredereck, *et al.*[3] (III) was not isolated but its existence was suggested by the nuclear magnetic resonance (NMR) of the resulting mixture of II and III. The formation of IV is similar to that of the reaction of phenylacetone with formamide in the presence of phosphoryl chloride to 5-phenyl-4-(5-pyrimidinyl)pyrimidine,[1] that is, initially formed II reacted furthermore with TFM to IV.

On heating V with TFM afforded 4-ethyl-5-methylpyrimidine (VI) as reported by Bredereck, *et al.*[3] and 4-amino-3,5-dimethylpyridine (VII). The presumed formation process of VII is shown in Chart 2.

On heating VIII with TFM afforded 5,6,7,8-tetrahydroquinazoline (IX) as reported by Bredereck, *et al.*[3] and bis(5,6,7,8-tetrahydro-8-quinazolinylidenemethyl)amine (X). The

---

[1] Part VII: T. Koyama, T. Hirota, Y. Shinohara, S. Matsumoto, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), 23, 2029 (1975).

[2] Location: *1-1, Tsushima-naka 1-chome, Okayama, 700, Japan.*

[3] H. Bredereck, R. Gompper, and B. Geiger, *Chem. Ber.*, 93, 1402 (1960).

formation of X is similar to that of IV and the presumed process is shown in Chart 2. Although Bredereck, *et al.*[3] did not report for XI or XIII, XI and XIII were heated with TFM to obtain 4-alkylpyrimidines. 4-Methyl-5-phenylpyrimidine (XII) or 5,6,7,8-tetrahydro-8-phenylquinazoline (XIV) was obtained respectively. The latter (XIV) was dehydrogenated with sulfur to give 8-phenylquinazoline (XV).

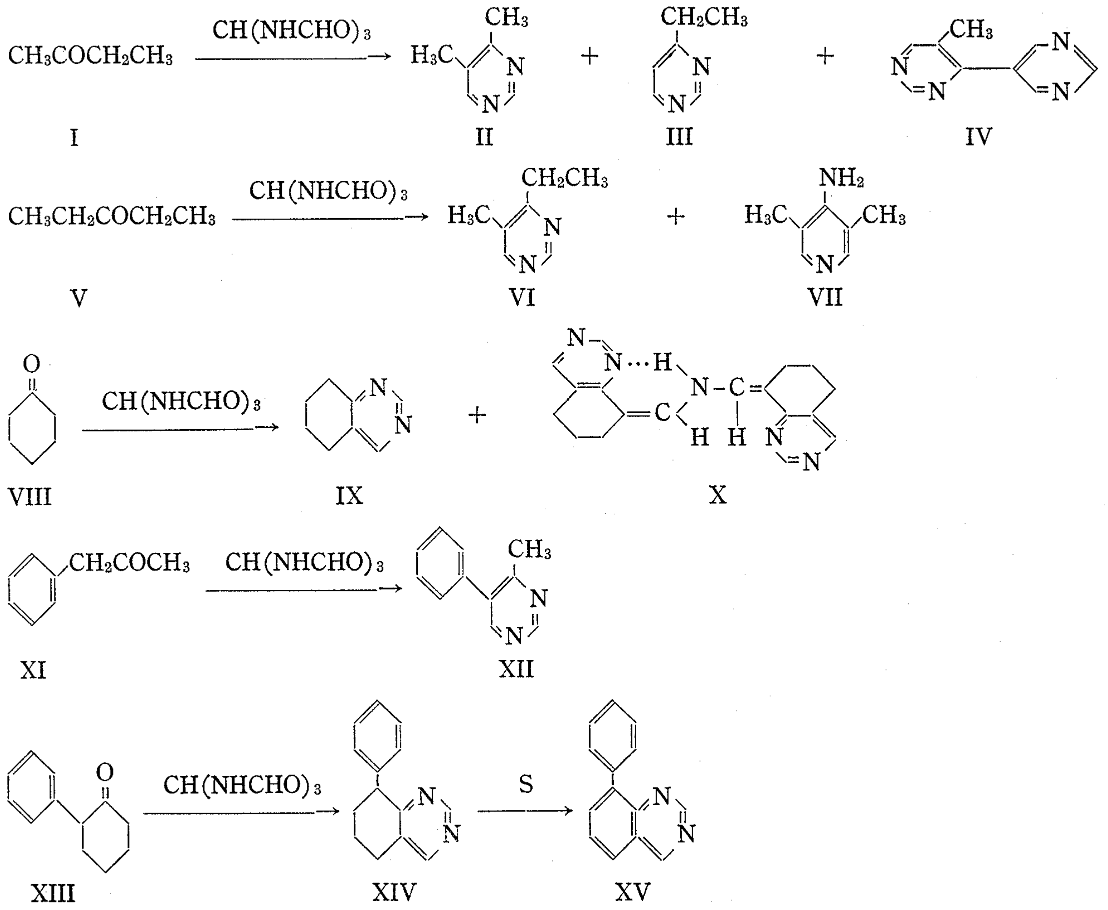

Chart 1

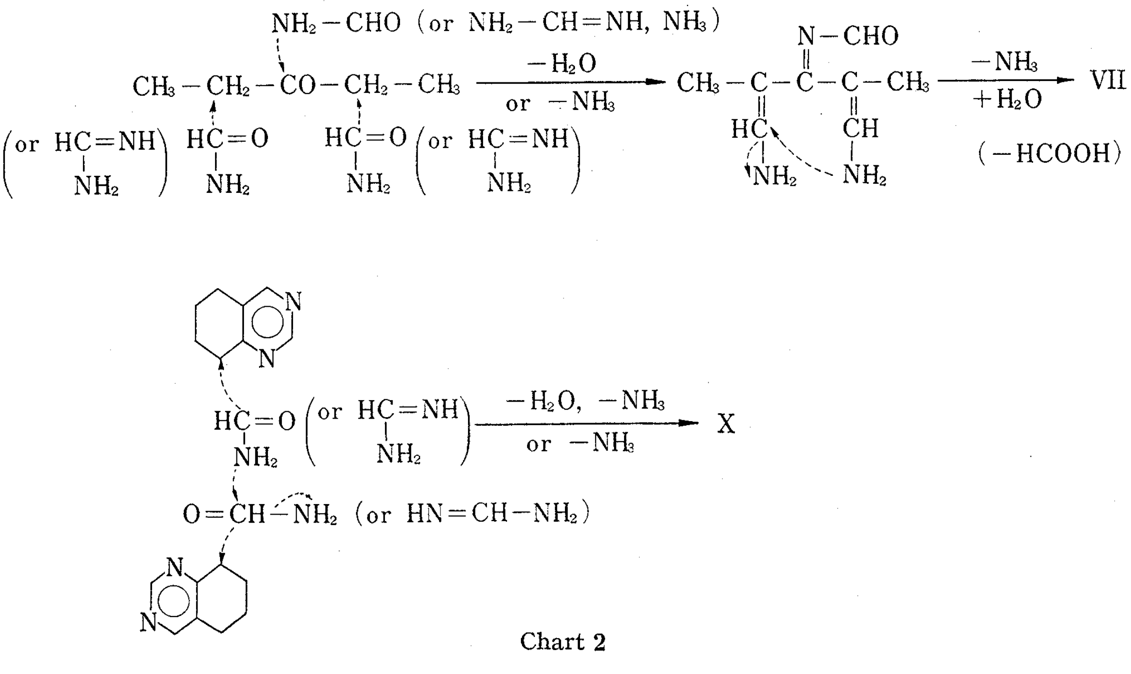

Chart 2

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) in $CDCl_3$ with tetramethysilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Infrared (IR) spectra were recorded on a Nihon Bunko Model IR-G spectrometer in KBr disk. UV spectra were taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH. Mass spectra were taken on a Shimadzu LKB-9000 spectrometer with a direct inlet system.

Reaction of Methyl Ethyl Ketone (I) with Trisformylaminomethane (TFM)——A mixture of 14.2 g of I, 57 g of TFM, 29.4 ml of $HCONH_2$, and 1.5 g of *p*-toluenesulfonic acid was heated at 150—160° for 8 hr in an electromagnetic autoclave. After treatment as described by Bredereck, *et al.*,[3] the $CHCl_3$ extract was subjected to reduced fractional distillation. The result was as follows; (1) bp ~56°/17—13 mmHg (2.4 g) as slightly pale yellow liquid (two spots on TLC), (2) bp 56—62°/12—10 mmHg (7.6 g) as slightly pale yellow liquid (two spots on TLC), (3) bp 62—78°/10—7 mmHg (1.6 g) as slightly pale yellow liquid (two spots on TLC, which was similar to (1) and (2) but the upper spot was more larger than (I) and (2)), and (4) bp 78—81°/7—6 mmHg (7.6 g) as pale yellow liquid, which was almost $HCONH_2$. The fraction (1) and (2) were combined and subjected to the second fractional distillation *in vacuo*. The result was as follows; (a) bp 50—60°/16—13 mmHg (6.8 g) as colorless liquid (two spots on TLC), (b) bp 60—71°/13 mmHg (0.8 g) as colorless liquid (two spots on TLC), and bp 71—71.5°/13 mmHg (0.6 g) as colorless liquid (two spots on TLC). Since the NMR spectrum of the fraction (a) showed the mixture of 4,5-dimethylpyrimidine (II) and 4-ethylpyrimidine (III) (*ca.* 3: 1 ratio), it was purified by formation of picrate. The fractional crystallization of the picrate from AcOEt–EtOH (1: 1) gave 9.0 g of 4,5-dimethylpyrimidine picrate as yellow needles, mp 160—161° (reported mp 162°). *Anal.* Calcd. for $C_{12}H_{11}O_7N_5$: C, 42.73; H, 3.29; N, 20.77. Found: C, 42.91; H, 3.34; N, 20.64. NMR (Me_2SO-d_6): 2.23, 2.42 (each 3H, s, 2-CH_3), 8.51, 8.88 (each 1H, s, pyrimidine-H), 8.59 (2H, s, picric acid-H). 6.5 g of the picrate was treated with aq. ammonia and the $CHCl_3$ extract was distilled to give 1.5 g (76%) of free base II as colorless liquid, bp 71°/21 mmHg (reported bp 169—171°/750 mmHg). NMR: 2.23, 2.45 (each 3H, s, 2-CH_3), 8.38, 8.89 (each 1H, s, pyrimidine-H). Although purification of 4-ethylpyrimidine picrate failed, the NMR data of the mixture of free base II and III suggested the existence of III, that is, 1.31 (3H, t, $J=7.5$ Hz, $C\underline{H}_3CH_2$), 2.79 (2H, q, $C\underline{H}_2CH_3$), 7.21 (1H, dd, $J=5$ Hz, $J=1.5$ Hz, C-5-H), 8.60 (1H, d, $J=5$ Hz, C-6-H), 9.11 (1H, d, $J=1.5$ Hz, C-2-H).

The dark brown residue of the first fractional distillation was allowed to stand 1 week and the deposited crystalline solid was collected. Sublimation of the solid *in vacuo* gave 40 mg (0.1%) of 5-methyl-4-(5-pyrimidinyl)pyrimidine (IV) as colorless needles, mp 146°. *Anal.* Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 62.74; H, 4.68; N, 32.28. Mass Spectrum *m/e*: (M^+)=172. NMR: 2.46 (3H, s, CH_3), 8.75 (1H, s, C-6-H), 9.14 (2H, s, C-4′, C-6′-H), 9.26, 9.41 (each 1H, s, C-2, C-2′-H). UV λ_{max}^{EtOH} mμ (log ε): 208 (4.20), 223 (4.11), 263 (4.05).

Reaction of Diethyl Ketone (V) with TFM——A mixture of 17 ml of V, 45 g of TFM, 30 ml of $HCONH_2$, and 0.8 g of *p*-toluenesulfonic acid was heated at 120—130° for 8 hr then at 150—160° for 8 hr. After treatment of the reaction mixture as described by Bredereck, *et al.*,[3] the $CHCl_3$ extract was subjected to reduced fractional distillation. The result was as follows; (1) bp 75—78°/13 mmHg (5.68 g) as colorless liquid (one spot on TLC), this fraction was VI (reported bp 72°/11 mmHg),[3] (2) bp 98—107°/18 mmHg (7.53 g) as pale yellow liquid (five spots on TLC), and (3) bp 110—112°/18 mmHg (0.51 g) as pale yellow liquid (four spots on TLC). The fraction (2) was fractionated again by reduced distillation to give 0.25 g of VI, total yield of VI 5.93 g (30.4%) (reported yield 37%).[3] Mass Spectrum *m/e*: (M^+)=122.083 (calcd. for $C_7H_{10}N_2$: 122.0844). NMR: 1.25 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 2.26 (3H, s, CH_3), 2.75 (2H, q, $C\underline{H}_2CH_3$), 8.42, 8.97 (each 1H, s, pyrimidine-H). Purification of the other fraction of (2) failed. The dark brown residue of the first fractional distillation was recrystallized from benzene-cyclohexane to give 0.49 g (2.5%) of 4-amino-3,5-dimethylpyridine (VII) as colorless needles, mp 104—106°. *Anal.* Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.99; H, 8.11; N, 22.80. Mass spectrum *m/e*: (M^+)=122. IR ν_{max}^{KBr} cm^{-1}: 3400, 3225, 1660 (N–H). NMR: 2.10 (6H, s, 2-CH_3), 3.99 (2H, b, NH_2, disappeared with D_2O exchange), 8.00 (2H, bs, pyridine C-2, C-5-H).

Reaction of Cyclohexanone (VIII) with TFM——A mixture of 21.6 g of VIII, 63.6 g of TFM, 23 ml of $HCONH_2$, and 2.2 g of *p*-toluenesulfonic acid was heated at 160—165° for 7 hr. After treatment of the reaction mixture as described by Bredereck, *et al.*,[3] the $CHCl_3$ extract was concentrated *in vacuo* and allowed to stand 2 days at room temperature. The deposited dark brown solid was filtered and recrystallized from EtOH followed by benzene to give 0.17 g (2%) of bis(5,6,7,8-tetrahydro-8-quinazolinylidenemethyl)amine (X) as slightly yellowish brown needles, mp 189—192°. *Anal.* Calcd. for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.94. Found: C, 70.68; H, 6.20; N, 22.87. Mass spectrum *m/e*: (M^+)=305. NMR: 1.89 (4H, m, 2-CH_2), 2.62 (8H, m, 4-CH_2), 6.35, 7.88 (each 1H, bd, $J=11$ Hz, $J=12$ Hz, 2-N-CH=, changed to broad singlet with D_2O exchange), 8.22, 8.30, 8.73, 8.90 (each 1H, s, pyrimidine-H), 11.7 (1H, b, NH, disappeared with D_2O exchange). The unequivalency of vinyl protons and pyrimidine ring protons suggested the structure X.

The above filtrate was subjected to reduced fractional distillation, but each fraction had 3 or 4 spots on TLC. The fraction of bp 121—124°/25 mmHg, which was similar to that of 5,6,7,8-tetrahydroquinazoline (IX) reported by Bredereck, *et al.*,[3] was purified by the formation of its picrate. Recrystallization of the picrate from EtOH gave 14.24 g of IX picrate as yellow needles, mp 106—107° (reported mp 106—108°).

After decomposition of the picrate with NH_4OH, the $CHCl_3$ extract was distilled under reduced pressure to give 3.23 g (11%) of IX as colorless liquid, bp 113°/16 mmHg (reported bp 106—112°/15 mmHg).³⁾ *Anal.* Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.55; H, 7.60; N, 20.79.

Reaction of Phenylacetone (XI) with TFM——A mixture of 6.7 g of XI, 15 g of TFM, 10 ml of $HCONH_2$, and 0.5 g of *p*-toluenesulfonic acid was heated at 150—160° for 8 hr and allowed to stand overnight at room temperature. The reaction mixture was made alkaline with 2N NaOH and extracted with benzene–ether (1: 1). The organic layer was washed with H_2O, dried, and evaporated. The residue was recrystallized from petr. ether to give 3.1 g (36%) of 4-methyl-5-phenylpyrimidine (XII) as pale yellow needles, mp 76—76.5°, identical with the specimen prepared from the method with $HCONH_2$.¹⁾ *Anal.* Calcd. for $C_{11}H_{10}N_2$: C, 77.65; H, 5.88; N, 16.47. Found: C, 77.90; H, 5.78; N, 16.44. NMR: 2.45 (3H, s, CH_3), 7.39 (5H, m, C_6H_5), 8.42 (1H, s, pyrimidine C-6-H), 8.93 (1H, s, pyrimidine C-2-H).

Reaction of 2-Phenylcyclohexanone (XIII) with TFM——A mixture of 5.22 g of XIII, 13.15 g of TFM, 7.7 ml of $HCONH_2$, and 0.5 g of *p*-toluenesulfonic acid was heated 160—165° for 14 hr. After cooling, the reaction mixture was made alkaline with NH_4OH and extracted with ether. The ether extract was washed with H_2O, dried, and evaporated. The residue was chromatographed over alumina and eluted with benzene, and benzene–CH_2Cl_2. The benzene–CH_2Cl_2 (3: 1) eluate gave 1.57 g (25%) of 8-phenyl-5,6,7,8-tetrahydroquinazoline (XIV) as viscous oil, which was purified by the formation of the picrare (mp 173—175°), identical with the specimen prepared from the method with $HCONH_2$.¹⁾ *Anal.* Calcd. for $C_{20}H_{17}O_7N_5$ (picrate): C, 54.67; H, 3.90; N, 15.94. Found: C, 54.50; H, 3.75; N, 15.80. After decomposition of the picrate with NH_4OH, the $CHCl_3$ extract was distilled under reduced pressure, bp 250—260°/0.05—0.07 mmHg. NMR of the free base: 1.75—2.45 (4H, m, C-6, C-7-H), 2.84 (2H, bt, $J=6$ Hz, C-5-H), 4.21 (1H, bt, $J=7$ Hz, C-8-H), 6.98—7.50 (5H, m, C_6H_5), 8.53 (1H, s, C-4-H), 8.97 (1H, s, C-2-H).

The EtOH eluate was recrystallized from benzene–EtOH (4: 1) to give 230 mg of colorless plates, mp 237—239.5°, but the structure was unknown.

Dehydrogenation of XIV——A mixture of 106 mg of XIV and 65 mg of sulfur was heated at 200—230° for 1 hr in a long test tube (ca. 40 cm). Reduced sublimation of the dark brown solid at 124—135°/0.001 mmHg gave 18 mg (18.5%) of 8-phenylquinazoline (XV) as pale yellow fine crystals, mp 107—108°. *Anal.* Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.68; H, 4.80; N, 13.42.

Acknowledgement The authors are grateful to Mr. A. Iwadoh for microanalyses and mass spectral measurements.