

Polycyclic *N*-Hetero Compounds. XL. Reaction of Cyclic Ketones with Trisformylaminomethane

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Reactions of cyclic ketones such as α -tetralone, 1,3-cyclohexanedione, or naphthalenedione with formamide or trisformylaminomethane (TFAM) have shown to form polycyclic fused pyrimidines by us. Reactions of terpene ketones like *l*-menthone, *d*-camphor, *l*-carvone with TFAM were performed, and 8-isopropyl-5-methyl-5,6,7,8-tetrahydroquinazoline, borno[2,3-*d*]pyrimidine, and 5-isopropenyl-8-methyl-5,6-dihydroquinazoline were expectedly obtained from three terpenes. Minor products of 5-isopropenyl-8-methyl-5,6,7,8-tetrahydroquinazoline and 5-isopropenyl-8-methylquinazoline were formed with 5-isopropenyl-8-methyl-5,6-dihydroquinazoline by disproportionation reaction of *l*-carvone. Furthermore, *N*-formylmenthylamine, *N*-formylbornylamine, and *N*-formylcarvylamine were obtained as the Leuckart-type products of terpene ketones in these reactions. The reaction of *N*-benzyl-4-piperidone with TFAM gave desired 6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. The reaction of diethyl succinylsuccinate with TFAM afforded tricyclic 4,9-dioxo-3,4,8,9-tetrahydropyrimido[4,5-*g*]quinazoline. Above compounds were determined by the measurements of their instrumental analyses.

Key Words : Cyclic ketone, Trisformylaminomethane, Fused pyrimidine, Cyclization, Reductive amination

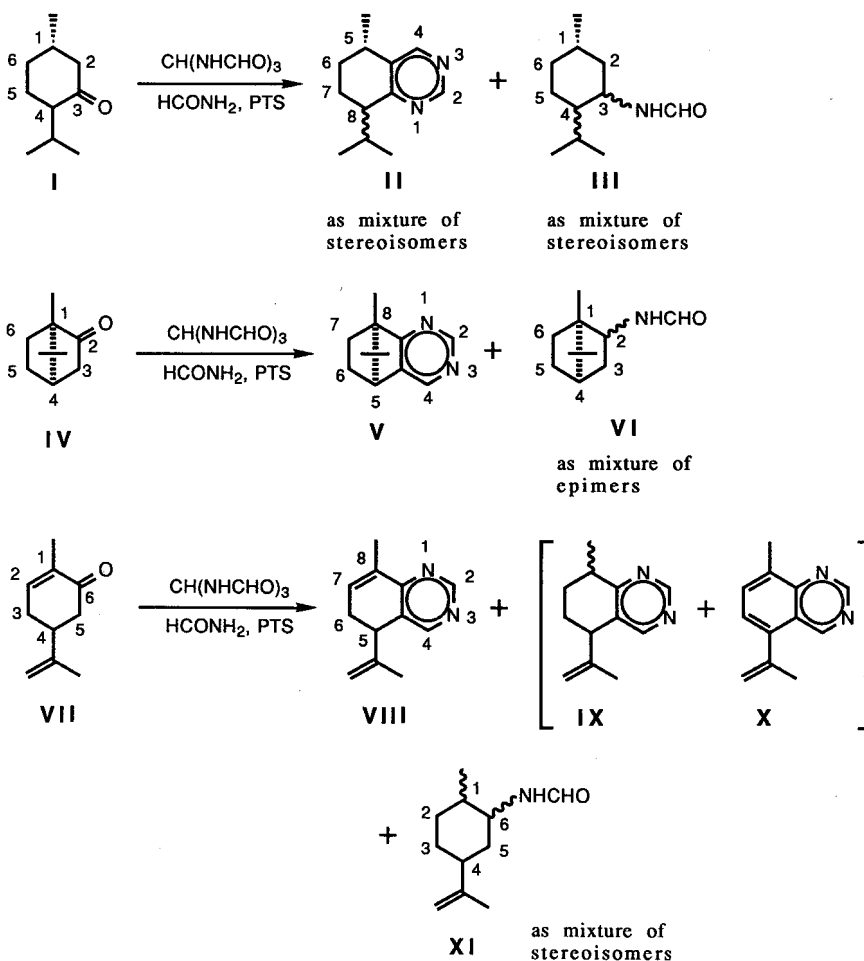
There are two major routes for the preparation of pyrimidine. One of them is the method corresponding to the type of C-C-C + N-C-N and the other is the type of N-C-C-C-N + C.¹⁾ In the previous paper,²⁾ we have reported the syntheses of polycyclic fused pyrimidines by the reaction of cyclic ketones like cyclohexanone or cyclohexanedione derivatives with formamide (FA) or trisformylaminomethane (TFAM). Similar syntheses of pyrimidines by heating ketones with TFAM were reported in the review by Brederick *et*

*al.*³⁾ In this paper, we would like to describe the application of this pyrimidine ring-formation to terpene and other some cyclic ketones.

As shown in Scheme 1, the heating reaction of *l*-menthone (**I**)⁴⁾ in FA with TFAM in the presence of *p*-toluenesulfonic acid (PTS) gave 8-isopropyl-5-methyl-5,6,7,8-tetrahydroquinazoline (**II**) and *N*-formylmenthylamine (**III**), each of which was a mixture of stereoisomers. The same isomeric mixture of **II** was already synthesized from menthone *via* 2-hydroxymethylenementhone and 2-ami-

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Scheme 1.

nomethylenementhone by Breitmaier⁵⁾ and Spohn *et al.*⁶⁾ Compound **II** was prepared from **I** in one-step by us. It had a parent peak at m/z 190 in the mass spectrum and showed two doublets ($J = 6.0$ Hz, δ 0.64 and 0.71 ppm, C_5 -methyl protons), four doublets ($J = 7.0$ Hz, δ 1.00, 1.07, 1.23, and 1.30 ppm, isopropyl methyl protons) and two singlets (δ 8.35 and 8.45 ppm, C_4 -proton) in the pmr spectrum. These assignments supported that **II** was a mixture of stereoisomers. Elementary analyses also supported the structures of **II** and its picrate.

Compound **III** had a parent peak at m/z 183 in the mass spectrum and showed two multiplets (one proton, δ 3.80 and 4.40 ppm, C_3 -proton), two broad singlets (one proton, each signal was exchangeable with D_2O , δ 5.80 and 6.10 ppm, amino proton), and two broad singlets (one proton, δ 7.79 and 8.13 ppm, formyl proton) in the pmr spectrum. Read *et al.*⁷⁾ have already obtained *N*-formyl-*d*-neomenthylamine by heating **I** with dry ammonium formate for 40 hours, and also obtained *N*-formyl-*d*-(or *l*-)menthylamine from *d*-(or *l*-)isomenthone by the similar

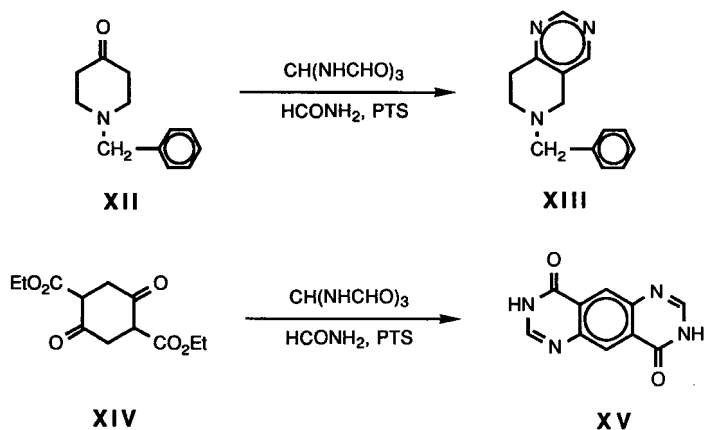
manner. Cope *et al.*⁸⁾ have prepared *N*-formyl-*d*-neomenthylamine by heating a mixture of *l*-menthone and *d*-isomenthone with ammonium formate for 48 hours. Wallach⁹⁾ has also reported the preparation of *l*-menthylamine and *d*-neomenthylamine by heating *l*-menthone with ammonium formate. Ammonium formate is well known to be formed by heating FA or TFAM.^{3,10)} Therefore, it was considered that **III** was a mixture of stereoisomers and formed by the Leuckart-Wallach reaction of **I** similar to the above stereoisomeric results.⁷⁻⁹⁾

The similar reaction of *d*-camphor (**IV**) gave borno[2,3-*d*]pyrimidine (**V**) and an epimeric mixture of *N*-formylbornylamine (**VI**). Instrumental analyses of **V** supported the structure. Compound **VI** had a parent peak at *m/z* 181 in the mass spectrum. The pmr spectrum of **VI** showed the following characteristic signals; δ 0.70, 0.76, 0.78, 0.82, 0.87, and 0.89 ppm (nine protons, each singlet, 3 x methyl protons), 3.07 and 4.07 ppm (one proton, each multiplet, C₂-proton), 7.58 and 7.84 ppm (one proton, each broad singlet, exchangeable with D₂O, amino proton), 7.95 and 8.02 ppm (one proton, each broad singlet, formyl proton). McKenna *et al.*¹¹⁾ prepared *N*-formylbornylamine by heating *d*-bornylamine with 98% formic acid for 12 hours, and also obtained a mixture of *N*-formylbornylamine and *N*-formylneobornylamine by the Leuckart-Wallach reaction of *d*-camphor. A mixture of stereoisomers, **III**, was produced from **I** by heating with TFAM as mentioned above. Therefore, **VI** is also considered to be an epimeric mixture consisting of *N*-formylbornylamine and *N*-formylneobornylamine. The former has the formylamino group of endo-form and the latter has that of exo-form. Instrumental data of **VI**

supported the structure.

The reaction of *l*-carvone (**VII**) with TFAM in the presence of PTS gave desired 5-isopropenyl-8-methyl-5,6-dihydroquinazoline (**VIII**) and a stereoisomeric mixture of *N*-formyl-1,2-dihydrocarvylamine (**XI**). Instrumental data of **VIII** supported the structure. In the mass spectrum of **XI**, the parent peak was observed at *m/z* 181. The signal of C₁-methyl protons in the pmr spectrum was observed at δ 0.88 and 0.98 ppm as each three protons doublet ($J = 6.5$ Hz). Similarly, isopropenyl methyl protons, C₆-proton, amino proton, and formyl proton were observed at δ 1.63 and 1.66 ppm (each three protons singlet), 3.58 and 4.27 ppm (each one proton multiplet), 5.68 and 6.50 ppm (each one proton broad singlet, exchangeable with D₂O), 8.04 and 8.17 ppm (each one proton doublet, $J = 5.5$ Hz), respectively. Thus, **XI** obtained here was determined to be a stereoisomeric mixture similar to **III** and **VI**. In the purification of **VIII** obtained as viscous oil, the formation of 5-isopropenyl-8-methyl-5,6,7,8-tetrahydroquinazoline (**IX**) and 5-isopropenyl-8-methylquinazoline (**X**) was confirmed as shown in bracket of Scheme 1. Gas-chromatographic result of the oil showed that the relative ratio of **VIII**, **IX**, and **X** was 6 to 2 to 1, respectively. In the GC-mass spectrum of the oil, compound **IX** had a parent peak at *m/z* 188 and **X** at *m/z* 184. Both fragment patterns of **IX** and **X** were close to that of **VIII**. The pmr measurement of the viscous oil also supported their structures.

As shown in Scheme 2, the reaction of *N*-benzyl-4-piperidone (**XII**) with TFAM in the presence of PTS was performed to obtain *N*-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (**XIII**). The instrumental analyses sup-



Scheme 2.

ported the structures of **XIII** and its picrate.

Finally, the reaction of diethyl succinylsuccinate (**XIV**) as a cyclic diketone with TFAM in the presence of PTS was performed to give linear cyclic 4,9-dioxo-3,4,8,9-tetrahydropyrimido[4,5-*g*]quinazoline (**XV**). The instrumental analyses supported the structure.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90-MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard. The signals are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet doublet. The mass spectra were taken on a Shimadzu LKB-9000 instrument. Optical rota-

tions were measured in ethanol ($c = 0.01$) on a JASCO DIP-4 polarimeter.

Reaction of **I** with TFAM

A mixture of 15.4 g (0.1 mol) of **I**, 29.0 g (0.2 mol) of TFAM, 10 ml of FA, and 0.9 g of PTS was heated at 160–170°C for 4 hours under stirring. After cooling, the reaction mixture was made alkaline with aq. ammonia and extracted with cyclohexane. The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The viscous oily residue was cooled to precipitate the solid, which was collected on a filter. The solid was recrystallized from cyclohexane to give 3.5 g (19.1%) of **III** as colorless prisms, mp 116–116.5°C; $[\alpha]_D^{20} +65.4^\circ$; ir (KBr): 3310 (O-H), 1685 (C=O) cm^{-1} ; pmr (CDCl_3): 0.82–0.93 (9H, m, 3 x CH_3), 3.80 and 4.40 (1H, each m, $\text{C}_3\text{-H}$), 5.80 and 6.10 (1H, each br s, exchangeable with D_2O , NH), 7.97 and 8.13 (1H, each br s, CHO). For elemental analysis, small amounts of the crystals were sublimated under vacuum (105°C/8 mmHg). Data of mass spectrum are stated in the text. *Anal.* Calcd. for $\text{C}_{11}\text{H}_{21}\text{NO}$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.13; H, 11.49; N, 7.75. The viscous oil obtained

from the filtrate mentioned above was dissolved in ethanol. Saturated solution of picric acid in ethanol was added to prepare the picrate of **II**. The picrate was recrystallized from ethanol to give yellow needles, mp 134-135°C. *Anal.* Calcd. for $C_{18}H_{21}N_5O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.56; H, 5.10; N, 16.67. The picrate was cloven with concd. ammonia to give free **II**. Compound **II** was extracted with diethyl ether, and the organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The residual viscous oil was distilled under vacuum (65-74°C/0.003 mmHg) to give 2.6 g (13.7%) of **II** as colorless oil; $[\alpha]_D^{15} -14.7^\circ$; pmr ($CDCl_3$): 0.64 and 0.71 (3H, each d, $J = 6.0$ Hz, C_5-CH_3), 1.00, 1.07, 1.23, and 1.30 (6H, each d, $J = 7.0$ Hz, isopropyl CH_3), 1.85 (4H, m, 2 x CH_2), 2.75 (3H, m, C_5 - and C_8 -H and isopropyl CH), 8.35 and 8.45 (1H, each s, C_4 -H), 8.90 (1H, s, C_2 -H). Data of mass spectrum is stated in the text. *Anal.* Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.49; H, 9.38; N, 14.62.

Reaction of **IV** with TFAM

A mixture of 7.6 g (0.05 mol) of **IV** ($[\alpha]_D^{18} +42.5^\circ$), 14.5 g (0.1 mol) of TFAM, 5 ml of FA, and 0.45 g of PTS was heated at 160-170°C for 9 hours under stirring. After cooling, the reaction mixture was made alkaline with aq. ammonia and extracted with cyclohexane. The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The viscous oily residue was cooled to precipitate the solid, which was collected on a filter. The solid was recrystallized from petro. ether to give 2.8 g (30.6%) of **VI** as colorless plates, mp 69-71°C; $[\alpha]_D^{17} -26.2^\circ$; ir (KBr): 3270 (N-H), 1670 (C=O) cm^{-1} ; pmr ($DMSO-d_6$): 0.70,

0.76, 0.78, 0.82, 0.87 and 0.89 (9H, each s, 3 x CH_3), 1.00-1.30 (6H, m, 3 x CH_2), 1.80 (1H, m, C_4 -H), 3.07 and 4.07 (1H, each m, C_2 -H), 7.58 and 7.84 (1H, each br s, exchangeable with D_2O , NH), 7.95 and 8.02 (1H, each br s, CHO); Data of mass spectrum are stated in the text. *Anal.* Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.77; H, 10.64; N, 7.87. The viscous oil obtained from the above filtrate was dissolved in chloroform and the solution was extracted with 2N-HCl. The aqueous layer was made alkaline with aq. ammonia and furthermore extracted with chloroform. The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The viscous oily residue was distilled under vacuum (61-63°C/2 mmHg) to give 122 mg (1.3%) of **V**; $[\alpha]_D^{18} +32.0^\circ$; mass: m/z 188 (M^+); pmr ($CDCl_3$): 0.58, 1.03, and 1.31 (each 3H, each s, 3 x CH_3), 2.03 (4H, m, 2 x CH_2), 2.91 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 5.0$ Hz, C_5 -H), 8.31 (1H, s, C_4 -H), 8.92 (1H, s, C_2 -H). *Anal.* Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.32; H, 8.45; N, 14.80.

Reaction of **VII** with TFAM

A mixture 7.5 g (0.05 mol) of **VII**, 14.5 g (0.1 mol) of TFAM, 5 ml of FA, and 0.45 g of PTS was heated at 160-170°C for 8 hours. After cooling, the reaction mixture was made alkaline with aq. ammonia and extracted with benzene. The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on silica gel. The eluate of cyclohexane-benzene (1:2) gave reddish brown viscous oil, which was dissolved in chloroform and extracted with 2N-HCl. The aqueous layer was made alkaline with 2N-

ammonia and extracted with dichloromethane. The dichloromethane layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The resulting oily residue was submitted to gas-chromatography (column; OV-17, 2%, 2 m; column temp. 90 to 220°C, 4°C/min.; inject. temp. 220°C; sep. temp. 250°C; carrier gas, argon; flow rate, 24 ml/min.). The chromatogram showed three peaks consisting of **VIII**, **IX**, and **X**. Relative ratio of the intensity of the three was 6 (**VIII**, $R_t = 15.5$ min.): 2 (**IX**, $R_t = 13.5$ min.): 1 (**X**, $R_t = 16.5$ min.). In the GC-MS of this oil, each parent peak of these peaks was observed at m/z 186 (**VIII**), 188 (**IX**), and 184 (**X**). The oil was attempted to separate with preparative TLC (Merck, Kieselgel 60 PF₂₅₄, solvent system; chloroform : diethyl ether = 1:1). The fraction with R_f value of around 0.6, which showed deep blue fluorescence with PAN-UV lamp, gave **VIII** as viscous oil. However, separation of **IX** and **X** was unsuccessful. Data of **VIII** are as follows; yield: 109 mg (1.2%); bp 118°C/4 mmHg; $[\alpha]_D^{16} +84.8^\circ$; mass: m/z 186 (M^+); pmr (CDCl₃): 1.69 (3H, d, $J = 1.5$ Hz, C₈-CH₃), 2.07 (3H, dd, $J_1 = 2.5$ Hz, $J_2 = 2.0$ Hz, isopropenyl CH₃), 2.44 (2H, m, C₆-H), 3.53 (1H, t, $J = 8.0$ Hz, C₅-H), 4.72 and 4.89 (each 1H, each br s, isopropenyl CH₂), 6.22 (1H, m, C₇-H), 8.21 (1H, s, C₄-H), 8.89 (1H, s, C₂-H). *Anal.* Calcd. for C₁₂H₁₄N₂: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.09; H, 7.63; N, 14.72. Pmr (CDCl₃) of the mixture of **IX** and **X** are as follows; **IX**: 1.32 (3H, d, $J = 7.0$ Hz, C₈-CH₃), 1.61 (3H, br s, isopropenyl CH₃), 1.82 (4H, m, 2 x CH₂), 3.40 (1H, m, C₈-H), 3.56 (1H, t, $J = 8.0$ Hz, C₅-H), 4.47 and 4.60 (each 1H, each br s, isopropenyl CH₂), 8.26 (1H, s, C₄-H), 8.85 (1H, s, C₂-H); **X**: 2.68 and 2.71 (each 3H, each br

s, 2 x CH₃), 5.00 and 5.45 (each 1H, each br s, isopropenyl CH₂), 7.29 and 7.59 (each 1H, AB q, $J = 5$ Hz, C₆- and C₇-H), 9.20 (1H, s, C₂-H), 9.47 (1H, s, C₄-H). The above residual chloroform solution, which was extracted with 2*N*-HCl, was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The obtained viscous oil was submitted to preparative TLC (Merck, Kieselgel 60 PF₂₅₄, solvent system; chloroform: diethyl ether = 1:1). The fraction with R_f value of 0.5, which adsorbed iodine, was collected and extracted with chloroform. The extract was distilled under vacuum (166-168°C/4 mmHg) to give 317 mg (3.5%) of **XI** as colorless oil; $[\alpha]_D^{16} +2.0^\circ$; ir (KBr): 3260 (N-H), 1660 (C=O) cm⁻¹; pmr (CDCl₃): 0.88 and 0.93 (3H, each d, $J = 6.5$ Hz, C₁-CH₃), 1.63 and 1.66 (3H, each br s, isopropenyl CH₃), 1.70 (6H, m, C₂-, C₃-, and C₅-H), 2.00 (2H, m, C₁- and C₄-H), 3.58 and 4.27 (1H, each m, C₆-H), 5.68 and 6.50 (1H, each br s, exchangeable with D₂O, NH), 8.04 and 8.17 (1H, each d, $J = 5.5$ Hz, CHO). Data of mass spectrum are stated in the text. *Anal.* Calcd. for C₁₁H₁₉NO: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.59; H, 10.40; N, 7.79.

Reaction of **XII** with TFAM

A mixture of 2.4 g (13 mmol) of **XII**, 3.7 g (26 mmol) of TFAM, 3 ml of FA, and 0.2 g of PTS was heated at 130-140°C for 2.5 hours under N₂ stream. The reaction mixture was made alkaline with aq. ammonia and extracted with benzene. The organic layer was washed with sat. brine, dried over anhydrous sodium sulfate, and evaporated. The chloroform solution of the viscous oily residue was extracted with 2*N*-HCl. The aqueous layer was made alkaline with aq. ammonia

and extracted with chloroform. The organic layer was worked up usually and the resulting viscous oil was converted to picrate, which was fractionally recrystallized from ethanol to give picrate of **XIII**, mp 170-172°C. *Anal.* Calcd. for C₂₀H₁₈N₆O₇: C, 52.86; H, 3.99; N, 18.50. Found: C, 53.01; H, 3.78; N, 18.60. The picrate was treated with concd. ammonia and extracted with chloroform. The organic layer was worked up usually and the resulting viscous oil was distilled under vacuum (125-127°C/0.01 mmHg) to give 375 mg (12.9%) of **XIII** as colorless oil; mass: m/z 225 (M⁺); pmr (CDCl₃): 2.78-3.10 (4H, m, C₇- and C₈-H), 3.59 (2H, br s, C₅-H), 3.72 (2H, s, CH₂-phenyl), 7.38 (5H, s, phenyl H), 8.33 (1H, s, C₄-H), 8.97 (1H, s, C₂-H). *Anal.* Calcd. for C₁₄H₁₅N₃: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.39; H, 6.70; N, 18.59.

Reaction of **XIV** with TFAM

A mixture of 12.8 g (0.05 mol) of **XIV**, 21.8 g (0.15 mol) of TFAM, 8 ml of FA, and 0.7 g of PTS was heated at 160-170°C for 5 hours. After cooling, precipitated solid was collected on a filter. The solid was triturated with 2*N*-NaOH and the soluble fraction was acidified with acetic acid. Precipitated solid was recrystallized from methanol to give 598 mg (5.6%) of **XV** as pale yellow powders, mp > 300°C; mass: m/z 214 (M⁺); ir (KBr): 3200 (broad, N-H), 1690 (C=O) cm⁻¹; pmr (DMSO-*d*₆): 8.08 and 8.27 (each 2H, each s, C₂- and C₇-H and C₅- and C₁₀-H). *Anal.* Calcd. for C₁₀H₆N₄O₂: C, 56.07; H, 2.82; N, 26.16. Found: C, 56.31; H, 2.84; N, 26.09.

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要 約

α -テトラロン, 1,3-シクロヘキサジオン, ナフタレンジオン等の環式ケトン類とホルムアミド或はトリスホルミルアミノメタン (TFAM) との反応により, 多環式縮合ピリミジン誘導体を容易に合成できる事は既に報告した。この反応の一環として環式ケトンに *l*-メントン, *d*-カンファ, *l*-カルボン等の生理活性を有するテルペンケトン及び *N*-ベンジル-4-ピペリドンとジエチルサクシニルサクシネートを用いて TFAM との反応を検討した。3種のテルペンケトン類からは予期した縮合ピリミジンとして 8-イソプロピル-5-メチル-5,6,7,8-テトラヒドロキナゾリン (II), ボルノ [2,3-*d*]ピリミジン (V), 及び 5-イソプロペニル-8-メチル-5,6-ジヒドロキナゾリン (VIII) を得た。VIII の分離の際に VIII の不均化化合物である 5-イソプロペニル-8-メチル-5,6,7,8-テトラヒドロキナゾリン (IX) 及び 5-イソプロペニル-8-メチルキナゾリン (X) の生成を GC-MS 及び pmr で確認したが, それらの単離には到らなかった。又, テルペンケトン類から Leuckart 型反応生成物と考えられる *N*-ホルミルメンチルアミン (III), *N*-ホルミルボルニルアミン (VI) 及び *N*-ホルミルカルビルアミン (XI) を得た。

N-ベンジル-4-ピペリドンと TFAM との反応では, 6-ベンジル-5,6,7,8-テトラヒドロピリド [4,3-*d*]ピリミジン (XIII) が得られた。

最後に, 環式ジケトンジエステルであるジエチルサクシニルサクシネートと TFAM との反応に於いては一挙に三環性の 4,9-ジオキソ-3,4,8,9-テトラヒドロピリミド [4,5-*g*]キナゾリン (XV) を得ることが出来た。得られた化合物の構造は ir, mass, pmr, 元素分析等で決定した。

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