

## Synthesis of 5-Pyrazolylbarbituric Acid Derivatives

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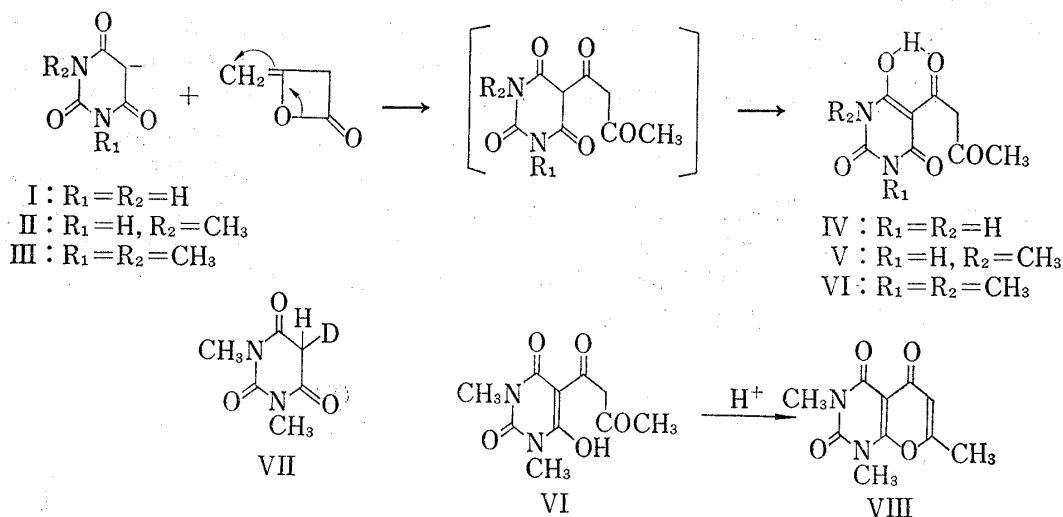
Diketene reacted with barbituric acids in the presence of the basic catalyst and gave the acetoacetyl derivatives (IV—VI) in excellent yields. Condensation of the 5-acetoacetylbarbituric acids with hydrazine and phenylhydrazine gave the pyrazole (IXa, Xa) and phenylpyrazole derivatives (XIa, XIIa) in quantitative yields, respectively.

Intramolecular cyclization of 1,3-dimethyl-5-acetoacetylbarbituric acid in the acidic conditions afforded the  $\gamma$ -pyrone derivative (VIII).

The direct electrophilic substitution reactions at the 5-position in barbituric acids are a little known. Diketene which is generally used for acetoacetylation of the protic functions<sup>2)</sup> was found to react smoothly with barbituric acids in the presence of the basic catalyst.

When 1-methyl- (II) and 1,3-dimethylbarbituric acids (III) were refluxed with two equivalent amounts of diketene in chloroform containing a catalytic amount of triethylamine, 5-acetoacetyl derivatives V and VI were obtained in above 70% yields, respectively. Similarly, barbituric acid (I) afforded 5-acetoacetylbarbituric acid (IV) in dioxane solvent.

The nuclear magnetic resonance (NMR) spectra of V and VI showed the acetyl peak at 2.21 and 2.34 ppm, and the methylene protons at 4.06 and 3.35 ppm, respectively, and lacked a methine proton which provided strong support for the enol structure.



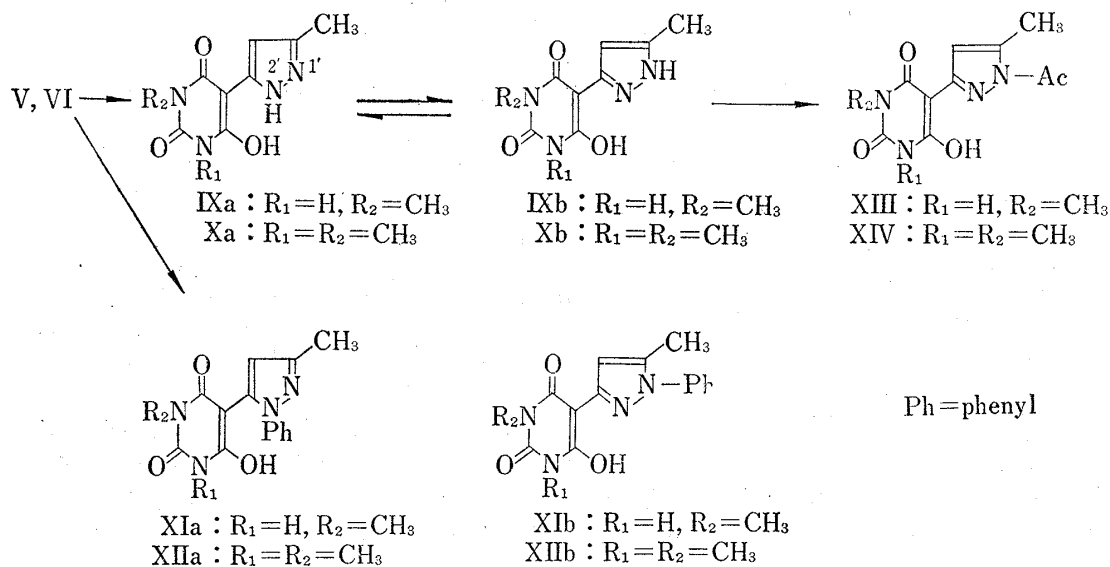
The 5-acetoacetylbarbituric acids underwent facile ketone-degradation to the parent barbituric acids by treatment in an alkaline solution. When the ketone-degradation of VI was carried out in deuterioxide, monodeuterio-1,3-dimethylbarbituric acid (VII) was obtained.

Refluxing of 1,3-dimethyl-5-acetoacetylbarbituric acid (VI) in methanol containing concentrated sulfuric acid gave a crystalline product VIII, mp 155°, in 99% yield. The elemental analysis and mass spectrum measurement of VIII established the composition,  $C_{10}H_{10}O_4N_2$ . The ultraviolet (UV) absorption spectrum of VIII exhibited maxima at 227 nm ( $\epsilon$  24300) and 260 nm ( $\epsilon$  12100). The structure of VIII was proven to be a  $\gamma$ -pyrone deriva-

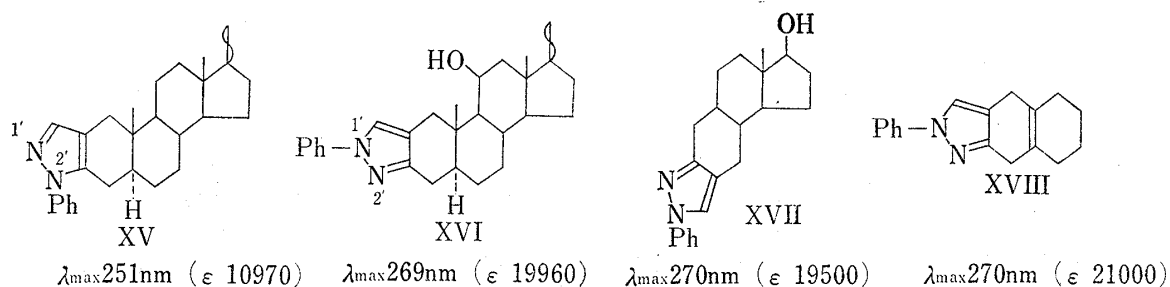
1) Location: Aobayama, Sendai.

2) Cf. T. Kato, *J. Synth. Org. Chem. Japan*, **26**, 311 (1968); *idem*, *Kagaku no Ryoiki, Suppl.*, **92**, 203 (1970).

tive by its NMR spectrum which showed a vinyl-methyl group at 2.48 ppm and an olefinic proton at 6.19 ppm as well as two N-methyl groups.



Condensation of the 5-acetoacetyl derivatives, V and VI, with hydrazine in refluxing methanol yielded the pyrazole derivatives IX and X in excellent yields, respectively. The molecular ion peak in the mass spectra of these pyrazole derivatives was consistent with the expected composition. The combustion analysis showed the adduct with hydrazine. When the condensations were performed in acetic acid, the free pyrazole derivatives were obtained. The NMR spectrum of IX showed a proton at 6.72 ppm which is assignable to the ring proton of pyrazole, a singlet methyl at 2.20 ppm and a N-methyl signal at 3.07 ppm. X displayed an aromatic proton at 6.49 ppm, a singlet methyl at 2.10 ppm and two N-methyl signal at 3.22 ppm. IX and X gave the monoacetates, XIII and XIV. The 1'-acetyl substitution was supported by the diamagnetic shift of the vinyl-methyl signals of XIII and XIV in the diagnostic analysis of the NMR spectra. V and VI analogously gave the N-phenylpyrazole derivatives XI and XII on condensation with phenylhydrazine, respectively. Although two isomeric pyrazoles, 2'- (XIa, XIIa) and 1'-substituents (XIb, XIIb), are possible, a single isomer was preferentially isolated in this experiment.



It has been reported<sup>3-5)</sup> that the steroidal 2'-phenyl[3,2-c]pyrazole (XV) which has restricted rotation around the N-phenyl axis shows maximal absorption at the shorter wave-

- 3) R. Hirschmann, P. Buchschacher, N.G. Steinberg, J.H. Fried, R. Ellis, G.J. Kent, and M. Tishler, *J. Am. Chem. Soc.*, **86**, 1520 (1964).
- 4) K. Wiedhaup, A.J.H. Nolle, J.G. Korsloot, and H.O. Huisman, *Tetrahedron*, **24**, 771 (1968).
- 5) L.J. Chinn, *J. Org. Chem.*, **36**, 1597 (1971).

length as comparison with those of unhindered phenylpyrazole derivatives, XVI, XVII and XVIII. The UV absorption spectra of pyrazole IX and X showed the absorption maxima at 272–274 nm, while the N-phenylpyrazoles XI and XII exhibited the absorption maxima at 253–255 nm. The fact suggested that the coplanarity of the pyrazole ring and the barbituric acid chromophore and/or the phenyl group was inhibited owing to the bulkiness of the phenyl ring. As additional evidence the vinyl-methyl resonances of XI and XII were little affected by diamagnetic shielding of the phenyl group. Consequently, XI and XII were best represented by the 2'-phenylpyrazole structures, XIa and XIIa, respectively.

### Experimental<sup>6)</sup>

**1,3-Dimethyl-5-acetoacetylbarbituric Acid (VI)**—To a solution of 3.12 g of 1,3-dimethylbarbituric acid (III) in 20 ml of  $\text{CHCl}_3$  was added 3.36 g of freshly distilled diketene and 0.25 ml of triethylamine. The mixture was refluxed for 3 hr. The solvent was evaporated under reduced pressure and added MeOH. The deposit was recrystallized from MeOH to afford colorless plates, mp 124–126°. Yield: 3.63 g (75.6%). *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_5\text{N}_2$ : C, 50.00; H, 5.04; N, 11.66. Found: C, 49.86; H, 5.18; N, 12.02. Mass Spectrum  $m/e$ : 240 ( $\text{M}^+$ ). NMR ( $\text{CDCl}_3$ ) ppm: 2.34 (3H, s,  $-\text{COCH}_3$ ), 3.26 (6H, s,  $2 \times =\text{N}-\text{CH}_3$ ), 3.35 (2H, s,  $-\text{CH}_2-\text{CO}-$ ). UV  $\lambda_{\text{max}}^{\text{EtOH}}$  nm ( $\epsilon$ ): 277 (10600). IR (KBr)  $\text{cm}^{-1}$ : 1728 (sh), 1708, 1658.

**1-Methyl-5-acetoacetylbarbituric Acid (V)**—To a solution of 2.13 g of 1-methylbarbituric acid (II) in 20 ml of  $\text{CHCl}_3$  was added 1.89 g of diketene and a few drops of triethylamine. The reaction mixture was worked up in the same manner as described above. Recrystallization from MeOH gave colorless plates, mp 186–188°. Yield: 3.1 g (92.4%). *Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{O}_5\text{N}_2$ : C, 47.79; H, 4.46; N, 12.39. Found: C, 47.71; H, 4.44; N, 12.57. Mass Spectrum  $m/e$ : 226 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.21 (3H, s,  $-\text{COCH}_3$ ), 3.07 (3H, s,  $=\text{N}-\text{CH}_3$ ), 4.06 (2H, s,  $-\text{COCH}_2-$ ). UV  $\lambda_{\text{max}}^{\text{EtOH}}$  nm ( $\epsilon$ ): 243 (6000), 277 (12300). IR (KBr)  $\text{cm}^{-1}$ : 3420, 1717, 1691.

**5-Acetoacetylbarbituric Acid (IV)**—To a solution of 1.28 g of barbituric acid (I) in dioxane was added 1.68 g of diketene and three drops of triethylamine. The mixture was allowed to react on a water bath for 3 hr and then worked up in the same manner as described above. The residue was recrystallized from MeOH to afford needles, mp 205–207° (decomp.). Yield: 1.73 g (85.6%). Mass Spectrum  $m/e$ : 212 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.22 (3H, s,  $-\text{COCH}_3$ ), 4.10 (2H, s,  $-\text{COCH}_2\text{CO}-$ ).

**Alkaline Degradation of VI**—a) A solution of 500 mg of VI in 10%  $\text{Na}_2\text{CO}_3$  was heated on a water bath for 1 hr. After neutralization with 10% HCl the reaction mixture was evaporated *in vacuo*. The residue was extracted with  $\text{CHCl}_3$ , and the solvent was removed to give a crystalline mass. Recrystallization from MeOH afforded colorless plates, mp 123°. This material was identical with an authentic specimen of 1,3-dimethylbarbituric acid (III) by direct comparison.

b) The same reaction was carried out in 10%  $\text{Na}_2\text{CO}_3\text{-D}_2\text{O}$ . The reaction mixture was worked up as the same manner. 5-Deuterio-1,3-dimethylbarbituric acid (VII) was obtained as colorless plates, mp 123°. Mass Spectrum  $m/e$ : 157 ( $\text{M}^+$ ).

**1,3-Dimethyl-5-[3-methyl-5(1H)pyrazolyl]barbituric Acid (Xa)**—To a solution of 500 mg of VI in 10 ml of MeOH was added 2 ml of hydrazine hydrate. After refluxing for 3 hr the reaction mixture was cooled, whereupon the 1:1 hydrazine adduct crystallized. Recrystallization from MeOH gave colorless needles, mp 270°. Yield: 505 mg (90.5%). *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_4 \cdot \text{N}_2\text{H}_4$ : C, 44.77; H, 6.01; N, 31.33. Found: C, 44.47; H, 6.33; N, 31.03. Mass Spectrum  $m/e$ : 236 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.10 (3H, s, vinyl  $\text{CH}_3$ ), 3.22 (6H, s,  $2 \times =\text{N}-\text{CH}_3$ ), 6.49 (1H, s, olefinic proton), 7.37 (4H, br. s,  $\text{N}_2\text{H}_4$ ). UV  $\lambda_{\text{max}}^{\text{EtOH}}$  nm ( $\epsilon$ ): 274 (23500).

When the above condensation was performed in acetic acid as the solvent, colorless needles was obtained. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_4$ : C, 50.84; H, 5.12; N, 23.72. Found: C, 50.65; H, 5.29; N, 23.12. UV  $\lambda_{\text{max}}^{\text{EtOH}}$  nm ( $\epsilon$ ): 265 (infl.) (16000), 286 (20100) ( $c$ ,  $3.6405 \times 10^{-4}\text{M}$ ); 262 (20800), 288 (24300) ( $c$ ,  $7.281 \times 10^{-4}\text{M}$ );  $\lambda_{\text{max}}^{0.01\text{N KOH-EtOH}}$  nm ( $\epsilon$ ): 274 (24000);  $\lambda_{\text{max}}^{0.01\text{N HCl}}$  nm ( $\epsilon$ ): 260 (14000), 292 (23000). IR (KBr)  $\text{cm}^{-1}$ : 3375 (br.), 1688, 1618.

**Xa Acetate (XIV)**—To a solution of 200 mg of Xa in 1 ml of AcOH was added 1 ml of acetic anhydride. The mixture was refluxed for 2 hr and evaporated to dryness *in vacuo*. The acetate was washed with water and recrystallized from MeOH to yield colorless needles, mp 235° (decomp.). Yield: quantitatively. *Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_4\text{N}_4$ : C, 51.79; H, 5.07; N, 20.48. Found: C, 51.73; H, 5.46; N, 20.48. Mass Spectrum  $m/e$ : 278 ( $\text{M}^+$ ). NMR ( $\text{CDCl}_3\text{-CD}_3\text{OD}$ ) ppm: 2.63 (3H, s, vinyl  $\text{CH}_3$ ), 2.68 (3H, s,  $-\text{COCH}_3$ ), 3.40 (6H, s,

6) Melting points are uncorrected and were taken on a Yamato melting point apparatus. Nuclear magnetic resonance spectra were obtained on a Hitachi R-60 spectrometer. Ultraviolet absorption spectra were measured on a Hitachi 124 spectrophotometer in 95% ethanol. Infrared absorption spectra were obtained on a Shimadzu Grating spectrophotometer IR-27G. Mass spectra recorded on a Hitachi mass spectrometer RMU-7 at 80 eV.

$2 \times =N-\underline{CH}_3$ ), 7.11 (1H, s, olefinic proton). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 268 (infl.) (18200), 285 (21400). IR (KBr)  $\text{cm}^{-1}$ : 1735, 1706.

**1-Methyl-5-[3-methyl-5(1H)pyrazolyl]barbituric Acid (IXa)**—IXa was prepared by the procedure described above from 500 mg of V and 2 ml of hydrazine hydrate. Recrystallization from MeOH gave colorless needles, mp 270°. Yield: 421 mg. *Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{O}_3\text{N}_4 \cdot \text{N}_2\text{H}_4$ : C, 42.51; H, 5.55; N, 33.06. Found: C, 42.22; H, 6.00; N, 33.16. Mass Spectrum  $m/e$ : 222 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.20 (3H, s, vinyl  $\underline{CH}_3$ ), 3.07 (3H, s,  $=N-\underline{CH}_3$ ), 6.72 (1H, s, olefinic proton), 6.92 (4H, br. s,  $\text{N}_2\text{H}_4$ ). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 273 (23500).

**IXa Acetate (XIII)**—XIII was prepared by the usual procedure. Recrystallization from MeOH gave 170 mg (85%) of colorless needles, mp 254° (decomp.). *Anal.* Calcd. for  $\text{C}_{11}\text{H}_{12}\text{O}_4\text{N}_4$ : C, 50.00; H, 4.58; N, 21.20. Found: C, 49.84; H, 4.87; N, 21.20. Mass Spectrum  $m/e$ : 264 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.58 (3H, s, vinyl  $\underline{CH}_3$ ), 2.65 (3H, s,  $-\text{CO}\underline{CH}_3$ ), 3.18 (3H, s,  $=N-\underline{CH}_3$ ), 7.04 (1H, s, olefinic proton). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 262 (18800), 293 (19700).

**1,3,7-Trimethyl-2,4,5-trioxo-1,2,3,4-tetrahydro-5H-pyrano[2,3-d]pyrimidine (VIII)**—To a solution of 500 mg of VI in 5 ml of MeOH was added dropwise 3 ml of conc.  $\text{H}_2\text{SO}_4$  under the mechanical agitation. The reaction mixture was allowed to stand for 1 hr, neutralized with NaOH aq. and then extracted repeatedly with  $\text{CHCl}_3$ . The solvent was concentrated to deposit colorless needles, mp 155° (decomp.). Yield: quantitatively. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_4\text{N}_2$ : C, 54.05; H, 4.54; N, 12.61. Found: C, 53.54; H, 4.67; N, 12.73. Mass Spectrum  $m/e$ : 222 ( $\text{M}^+$ ). NMR ( $\text{D}_2\text{O}$ ) ppm: 2.48 (3H, s, vinyl  $\underline{CH}_3$ ), 3.27 (3H, s,  $=N-\underline{CH}_3$ ), 6.19 (1H, s, olefinic proton). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 227 (24300), 260 (12100).

**1,3-Dimethyl-5-[3-methyl-1-phenyl-5-(1H)pyrazolyl]barbituric Acid (XIIa)**—To a solution of 500 mg of VI in 10 ml of MeOH was added 4 ml of phenylhydrazine. The reaction mixture was refluxed for 3 hr. Most of the solvent was evaporated and the white solid precipitated was filtered off. Recrystallization from MeOH gave colorless needles, mp 202–203°. Yield: quantitatively. *Anal.* Calcd. for  $\text{C}_{18}\text{H}_{16}\text{O}_3\text{N}_4 \cdot \text{C}_6\text{H}_8\text{N}_2$ : C, 62.84; H, 5.75; N, 19.99. Found: C, 62.56; H, 5.92; N, 19.70. Mass Spectrum  $m/e$ : 312 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.15 (3H, s, vinyl  $\underline{CH}_3$ ), 2.98 (6H, s,  $2 \times =N-\underline{CH}_3$ ), 5.80 (1H, s, olefinic proton), 6.70–7.50 (10H, m, aromatic proton of XIIa and phenylhydrazine). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 255 (17000). IR (KBr)  $\text{cm}^{-1}$ : 1670, 1604.

**1-Methyl-5-[3-methyl-1-phenyl-5-(1H)pyrazolyl]barbituric Acid (XIa)**—XIa was prepared by the procedure described above. Recrystallization from MeOH afforded colorless needles, mp 211–212°. Yield: quantitatively. *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{14}\text{O}_3\text{N}_4 \cdot \text{C}_6\text{H}_8\text{N}_2$ : C, 62.05; H, 5.46; N, 20.68. Found: C, 61.78; H, 5.89; N, 20.56. Mass Spectrum  $m/e$ : 298 ( $\text{M}^+$ ). NMR ( $\text{DMSO}-d_6$ ) ppm: 2.16 (3H, s, vinyl  $\underline{CH}_3$ ), 2.91 (3H, s,  $=N-\underline{CH}_3$ ), 5.85 (1H, s, olefinic proton), 6.73–7.50 (10H, m, aromatic protons of XIa and phenylhydrazine). UV  $\lambda_{\max}^{\text{EtOH}}$  nm ( $\epsilon$ ): 253 (28000).

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