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## Michael Reactions of 4-Acylmethylene-1,3(2*H*,4*H*)-isoquinolinediones with Malononitrile

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2-Methyl-1,3(2*H*,4*H*)-isoquinolinedione (I) reacted with methylglyoxal to form 1,1-bis(2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetone (IV) in 58% yield. The Michael reaction of 2-methyl-4-phenacylidene-1,3(2*H*,4*H*)-isoquinolinedione (II) with malononitrile gave 1*H*-pyrano[2,3-*c*]isoquinoline (VI) and furo[2',3':2,3]furo[5,4-*c*]isoquinoline (VII) derivatives in a ratio of 2:3. In the reaction of IV with malononitrile, retrograde Michael reaction occurred and resulted in the formation of I, 1*H*-pyrano[2,3-*c*]isoquinoline (IX) and 4-3'-furyl-1,3(2*H*,4*H*)-isoquinolinedione (X) derivatives. X-Ray structure analyses of VII and IX were performed.

**Keywords**—2-methyl-1,3(2*H*,4*H*)-isoquinolinedione; 1,1-bis(1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-yl)acetone; 1*H*-pyrano[2,3-*c*]isoquinoline; furo[2',3':2,3]furo[5,4-*c*]isoquinoline; 4-3'-furyl-1,3(2*H*,4*H*)-isoquinolinedione; Michael reaction; retrograde Michael reaction; X-ray structure analysis

In a previous paper,<sup>1)</sup> we reported the synthesis of spiro[isoquinoline-4,4'-(4'*H*-pyran)] compounds by the Michael reaction of 1,3-dioxo-2*H*,4*H*-isoquinolin-4-ylidenemalononitrile with active methylene compounds. As the one of them was found to possess an anti-allergic activity, we next carried out similar reactions of 4-acylmethylene-1,3(2*H*,4*H*)-isoquinolinediones with malononitrile to obtain the homologous spiro compounds. Although we failed to obtain the desired compounds by these reactions, some interesting results were obtained and are reported in this paper.

2-Methyl-4-phenacylidene-1,3(2*H*,4*H*)-isoquinolinedione (II) was prepared by the condensation of 2-methyl-1,3(2*H*,4*H*)-isoquinolinedione (trivial; homophthalimide) (I) with phenylglyoxal according to the procedure of Bailey *et al.*<sup>2)</sup> The similar reaction of I with methylglyoxal, which was expected to produce the 4-acetonylidene compound (III), was carried out. The reaction at room temperature did not give III but resulted in the formation of an unexpected product IV as colorless crystals, mp 174—175 °C, in 58% yield. In this reaction, the use of less solvent or a higher reaction temperature caused polymerization. The product IV thus obtained showed C=O absorption bands at 1710, 1670—1660 and 1640 cm<sup>-1</sup> in its infrared (IR) spectrum, and the proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectrum showed signals due to three methine protons attributable to >CH<sub>b</sub>-CH<sub>a</sub>-CH<sub>c</sub>< at δ 4.32 (1*H*, q, *J*<sub>a,b</sub> = 5.6, *J*<sub>a,c</sub> = 2.0 Hz, >CH<sub>a</sub>-), 4.65 (1*H*, d, *J*<sub>a,c</sub> = 2.0 Hz, -CH<sub>c</sub><) and 4.84 (1*H*, d, *J*<sub>a,b</sub> = 5.6 Hz, >CH<sub>b</sub>-) along with signals due to COCH<sub>3</sub> (3*H*, s) and 2 × NCH<sub>3</sub> (6*H*, s), as well as aromatic protons (8*H*, m). From the above results and the analytical data, the structure of IV was supposed to be 1,1-bis(2-methyl-1,3-dioxo-tetrahydroisoquinolin-4-yl)acetone. However, the spectroscopic evidence could not be fully explained merely by the plane structure of IV. We have, therefore, made a stereochemical analysis of IV.

From the coupling constants (*J*<sub>a,b</sub> and *J*<sub>a,c</sub>) of the three methine protons in the <sup>1</sup>H-NMR spectrum of IV, two torsion angles, ∠H<sub>a</sub>, H<sub>b</sub> = 132° and ∠H<sub>a</sub>, H<sub>c</sub> = 114°, were obtained by

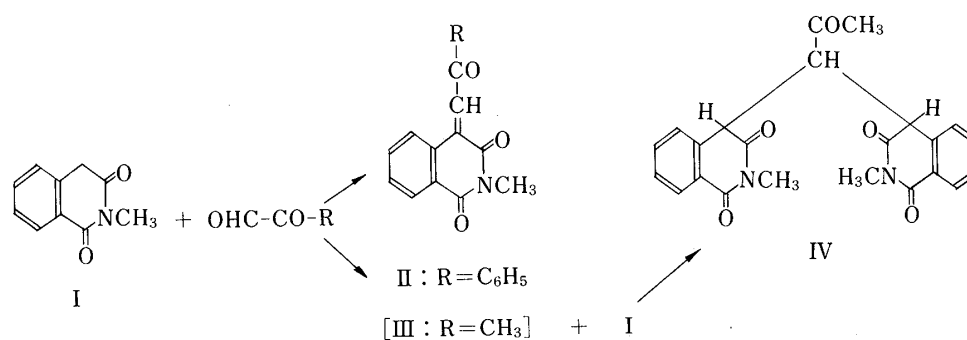


Chart 1

the use of Karplus' equation. In the stereo-structure constructed with these angles, hydrogen-bonding between H<sub>b</sub> and the 3'-C=O group of the other ring is considered to be possible. In the IR spectrum of IV, the C=O band at the lowest frequency (1640 cm<sup>-1</sup>) is assigned to this hydrogen-bonded C=O group. In the <sup>1</sup>H-NMR spectrum of IV, the different chemical shifts of H<sub>b</sub> and H<sub>c</sub> may also be due to this hydrogen-bonding. The mass spectrum (MS) of IV lacks the molecular ion peak (M<sup>+</sup>) at *m/z* 404 and the fragmentation begins with a peak at 229 corresponding to the mass of IV with loss of a homophthalimide (I) moiety. It is also considered that the transfer of H<sub>b</sub> to the 3'-C=O group favors the appearance of I. The fragmentation process of IV can be rationalized as illustrated in Chart 2.

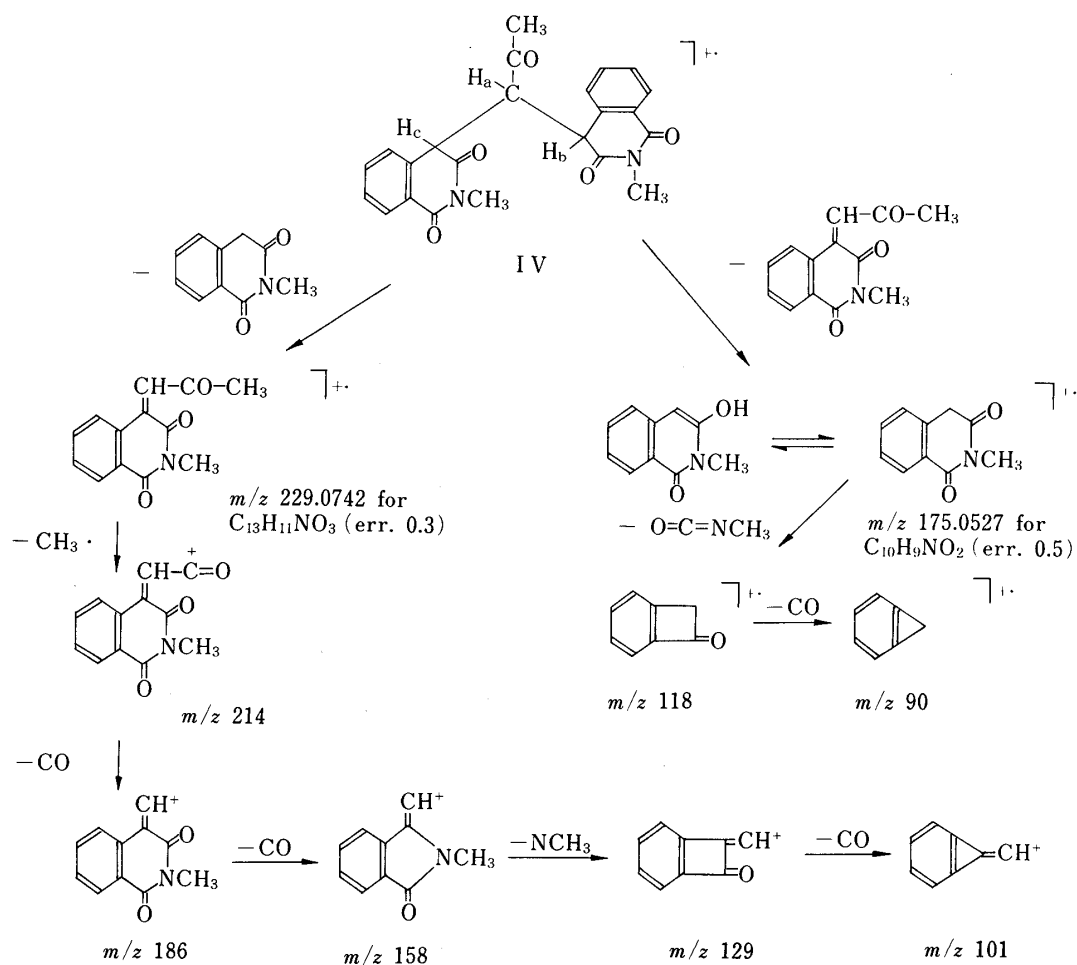


Chart 2

Next, the Michael reactions of II and IV with malononitrile will be described. Compound II reacted with malononitrile in the presence of diethylamine as a catalyst to give a pale yellow solid which yielded two products, pale yellow granular crystals, mp 224 °C (VI) and colorless prisms, mp 211 °C (VII), in a ratio of 2:3, on fractional recrystallization. Both VI and VII showed the same  $M^+$  at  $m/z$  357 corresponding to the normal Michael adduct, and they showed the absorptions of NH and conjugated CN in their IR spectra. These observations suggested that the initially formed Michael adducts were transformed into these compounds having an  $NH_2$  group and a conjugated CN group, by analogy with similar reactions previously reported.<sup>1,3,4)</sup>

Concerning the electronic character of compound II, two nucleophilic centers have to be considered, the carbon at the 4-position and the *exo*-methylene carbon, as shown in Chart 3. If nucleophilic attack by the carbanion of malononitrile took place at C-4 of II, a Michael adduct V would be obtained predominantly.<sup>1)</sup> However, the  $^1H$ -NMR spectrum of the crude products showed no olefin proton signal reflecting the formation of such a compound. The attack by the carbanion of malononitrile on the *exo*-methylene carbon of II would produce

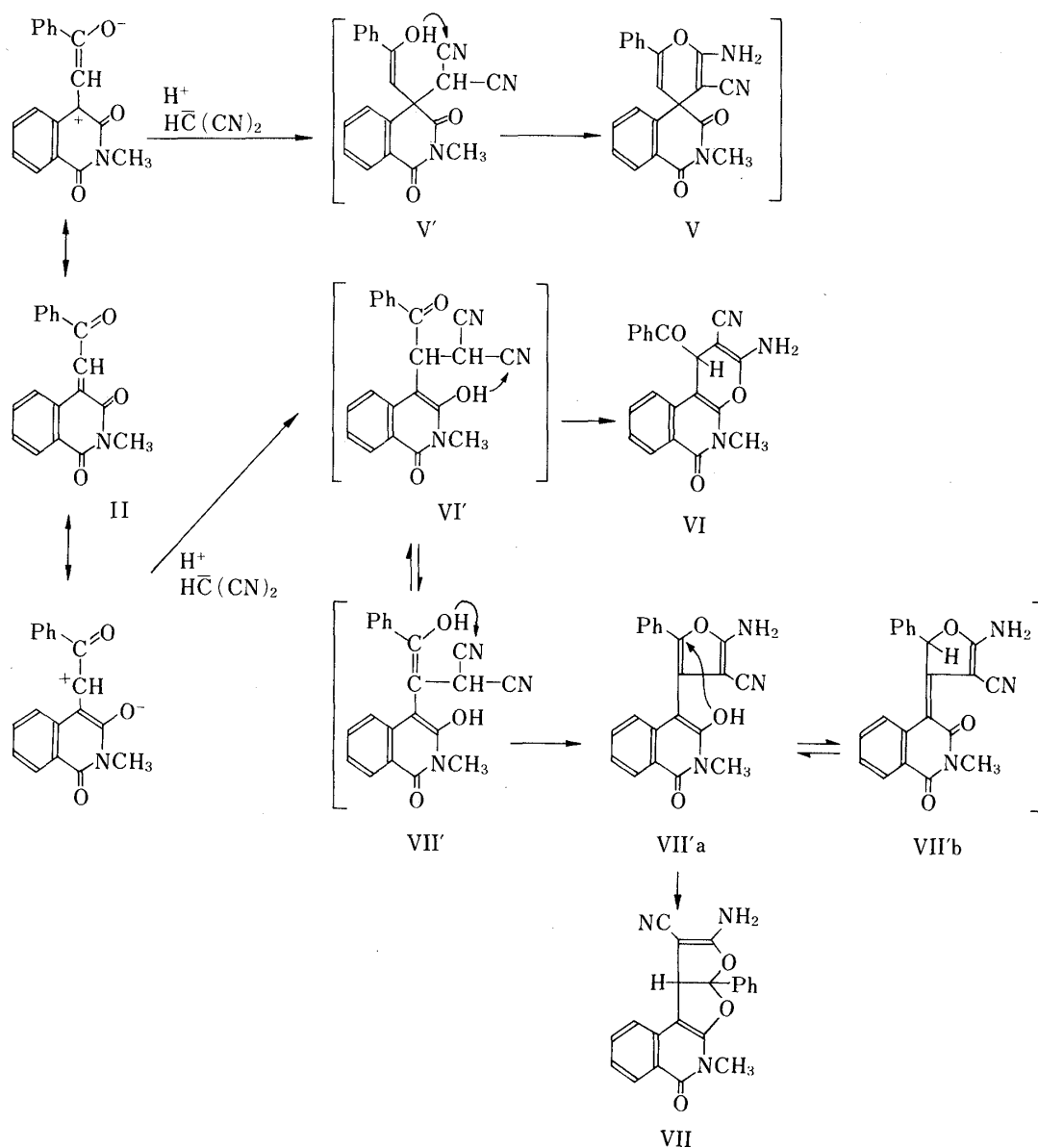


Chart 3

the normal Michael adduct VI', which could undergo cyclo-addition between the OH and CN groups to form VI. In contrast to this, another enol form VII' of the Michael adduct would be transformed to the cyclized product VII'a or VII'b, as reported in the preceding paper.<sup>3)</sup>

The <sup>1</sup>H-NMR spectrum of VI showed signals at  $\delta$  3.58 (3H, s) and 5.38 (1H, s) assigned to NCH<sub>3</sub> and methine protons, respectively, as well as  $\delta$  7.51 (2H, s) due to NH<sub>2</sub> protons (disappeared with D<sub>2</sub>O), and aromatic protons (9H, m). Aromatic signals (integrated 3H) were clearly observed at lower field. One of them was assigned to H-8 of the homophthalimide moiety and the others were the two ortho protons of the benzoyl group (based on the magnetic anisotropy effect of the adjacent C=O groups). The presence of the benzoyl C=O group could not be confirmed in the carbon-13 nuclear magnetic resonance (<sup>13</sup>C-NMR) spectrum because of the poor solubility of VI. This product corresponds well to the compound IX, described later, in all spectroscopic respects (IR, <sup>1</sup>H-NMR and MS). The above results and analytical data supported the structure 3-amino-1-benzoyl-5-methyl-6-oxo-5,6-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-2-carbonitrile for VI.

On the other hand, the <sup>1</sup>H-NMR spectrum of VII also showed signals due to NCH<sub>3</sub> ( $\delta$  3.51, 3H, s), >CH- (5.06, 1H, s) and NH<sub>2</sub> (7.61, 2H, s) along with 9H (m) of aromatic protons. In the <sup>13</sup>C-NMR spectrum of VII, the absence of a signal due to benzoyl C=O carbon (usually seen at below 200 ppm) suggests the formula VII'a or VII'b for the product VII. Since further confirmation of the structural assignment could not be obtained from spectroscopic data, an X-ray crystallographic analysis of VII was performed. Bond lengths and angles for VII are listed in Table I, and a perspective drawing of VII is shown in Fig. 1. Thus, VII was found to contain a novel ring system; its structure is 9-amino-6-methyl-5-oxo-7a-phenyl-5,6,7a,10a-tetrahydrofuro[2',3':2,3]furo[5,4-*c*]isoquinoline-10-carbonitrile. The formation of this unexpected tetracyclic compound can be rationalized as shown in Chart 3.

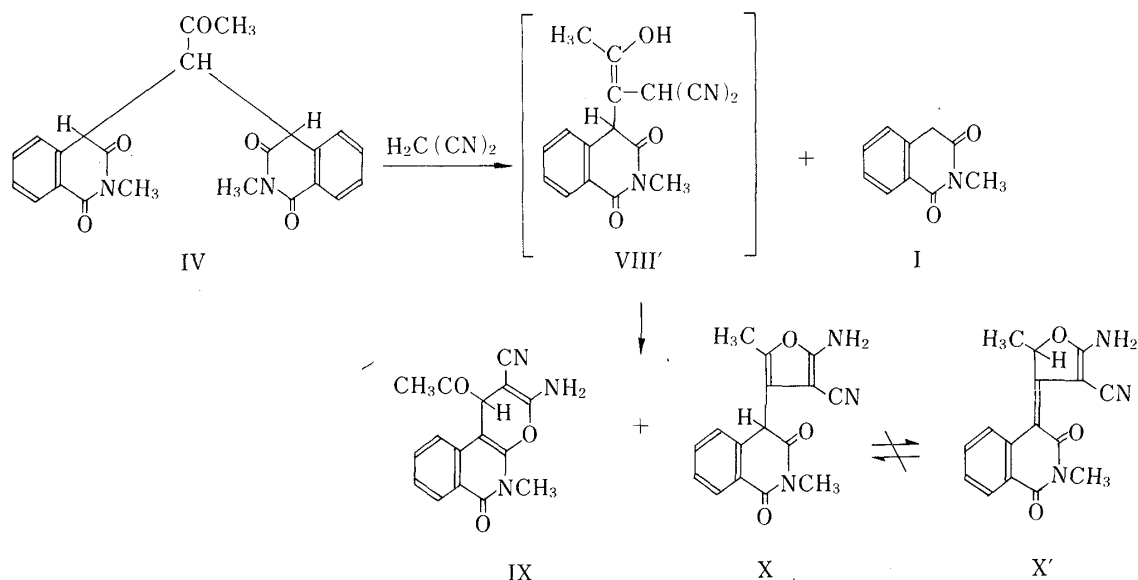


Chart 4

Finally, the reaction of IV with malononitrile in the presence of diethylamine as a catalyst was carried out. The reaction product was a mixture of three compounds which could be isolated by fractional recrystallization. The first product, obtained as colorless needles, was found to be the starting material (I). The second product, yellow prisms of mp 230 °C (IX), and the last one, colorless silky needles, mp 224 °C (X), showed the same  $\text{M}^+$  at  $m/z$  295. The spectral features of IX were very similar to those of VI. A 1*H*-pyrano[2,3-*c*]isoquinoline structure for the product IX was confirmed by X-ray crystallographic analysis. Atomic

parameters and a perspective drawing for IX are presented in Table II and Fig. 2, respectively.

The product X showed  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectral patterns similar to those of VII. These observations suggested a tetracyclic structure like that of VII for X. However, the IR spectrum of X showed two strong  $\text{C}=\text{O}$  bands at  $1680$  and  $1660\text{ cm}^{-1}$ ; their absorption mode

TABLE I. Bond Lengths and Angles for VII with Estimated Standard Deviations in Parentheses

| Bond length | (Å)        | Bond angle     | (°)        |
|-------------|------------|----------------|------------|
| C1-C2       | 1.397 (23) | C2-C1-C10c     | 118.3 (19) |
| C1-C10c     | 1.418 (46) | C1-C2-C3       | 121.1 (19) |
| C2-C3       | 1.414 (26) | C2-C3-C4       | 120.3 (15) |
| C3-C4       | 1.391 (45) | C3-C4-C4a      | 119.5 (20) |
| C4-C4a      | 1.400 (24) | C4-C4a-C5      | 118.3 (19) |
| C4a-C5      | 1.454 (47) | C4-C4a-C10c    | 120.5 (19) |
| C4a-C10c    | 1.412 (21) | C5-C4a-C10c    | 121.2 (13) |
| C5-N6       | 1.388 (22) | C4a-C5-N6      | 118.2 (19) |
| C5-O11      | 1.233 (20) | C4a-C5-O11     | 122.7 (13) |
| C6a-N6      | 1.367 (20) | N6-C5-O11      | 119.1 (19) |
| C6a-O7      | 1.363 (20) | C5-N6-C6a      | 118.3 (19) |
| C6a-C10b    | 1.336 (43) | C5-N6-C12      | 120.5 (17) |
| C7a-O7      | 1.424 (20) | C6a-N6-C12     | 121.1 (12) |
| C7a-O8      | 1.444 (13) | N6-C6a-O7      | 117.2 (19) |
| C7a-C10a    | 1.576 (48) | N6-C6a-C10b    | 126.4 (12) |
| C7a-C13     | 1.490 (15) | O7-C6a-C10b    | 116.4 (19) |
| C9-O8       | 1.363 (31) | C6a-O7-C7a     | 106.4 (21) |
| C9-C10      | 1.369 (31) | O7-C7a-O8      | 105.7 (11) |
| C9-N19      | 1.325 (15) | O7-C7a-C10a    | 108.6 (19) |
| C10-C10a    | 1.497 (14) | O7-C7a-C13     | 111.2 (11) |
| C10-C20     | 1.378 (40) | O8-C7a-C10a    | 105.8 (7)  |
| C10a-C10b   | 1.516 (22) | O8-C7a-C13     | 109.6 (11) |
| C10b-C10c   | 1.436 (24) | C10a-C7a-C13   | 115.4 (7)  |
| C12-N6      | 1.480 (49) | C7a-O8-C9      | 109.8 (14) |
| C13-C14     | 1.374 (23) | O8-C9-C10      | 112.3 (19) |
| C13-C18     | 1.398 (17) | O8-C9-N19      | 115.1 (13) |
| C14-C15     | 1.405 (19) | C10-C9-N19     | 132.6 (9)  |
| C15-C16     | 1.366 (19) | C9-C10-C10a    | 110.1 (15) |
| C16-C17     | 1.399 (30) | C9-C10-C20     | 124.7 (18) |
| C17-C18     | 1.430 (20) | C10a-C10-C20   | 125.2 (8)  |
| C20-N21     | 1.157 (35) | C7a-C10a-C10   | 101.1 (10) |
|             |            | C7a-C10a-C10b  | 99.8 (11)  |
|             |            | C10-C10a-C10b  | 115.7 (8)  |
|             |            | C6a-C10b-C10a  | 108.7 (10) |
|             |            | C6a-C10b-C10c  | 118.7 (19) |
|             |            | C10a-C10b-C10c | 132.6 (15) |
|             |            | C1-C10c-C4a    | 120.3 (13) |
|             |            | C1-C10c-C10b   | 122.5 (19) |
|             |            | C4a-C10c-C10b  | 117.2 (19) |
|             |            | C7a-C13-C14    | 118.6 (10) |
|             |            | C7a-C13-C18    | 120.1 (14) |
|             |            | C14-C13-C18    | 121.2 (11) |
|             |            | C13-C14-C15    | 120.1 (12) |
|             |            | C14-C15-C16    | 120.3 (18) |
|             |            | C15-C16-C17    | 120.6 (14) |
|             |            | C16-C17-C18    | 119.7 (12) |
|             |            | C13-C18-C17    | 118.2 (16) |
|             |            | C10-C20-N21    | 175.7 (10) |

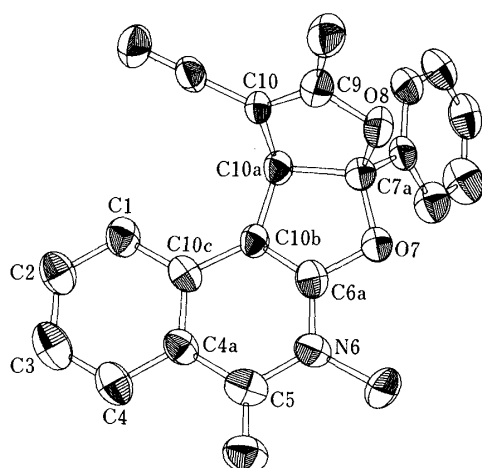


Fig. 1. A Perspective Drawing of VII

TABLE II. Bond Lengths and Angles for IX with Estimated Standard Deviations in Parentheses

| Bond length | (Å)        | Bond angle    | (°)       |
|-------------|------------|---------------|-----------|
| C1-C2       | 1.513 (8)  | C2-C1-C10b    | 108.4 (6) |
| C1-C10b     | 1.516 (10) | C2-C1-C11     | 109.9 (5) |
| C1-C11      | 1.539 (15) | C10b-C1-C11   | 109.9 (5) |
| C2-C3       | 1.354 (12) | C1-C2-C3      | 124.1 (6) |
| C2-C14      | 1.418 (10) | C1-C2-C14     | 118.6 (7) |
| C3-O4       | 1.368 (9)  | C3-C2-C14     | 117.3 (6) |
| C3-N16      | 1.348 (8)  | C2-C3-O4      | 121.4 (5) |
| C4a-N5      | 1.379 (9)  | C2-C3-N16     | 128.2 (7) |
| C4a-C10b    | 1.338 (11) | O4-C3-N16     | 110.3 (7) |
| C4a-O4      | 1.371 (7)  | C3-O4-C4a     | 117.9 (6) |
| C6-N5       | 1.380 (7)  | O4-C4a-N5     | 110.5 (6) |
| C6-C6a      | 1.451 (12) | O4-C4a-C10b   | 124.7 (6) |
| C6-O18      | 1.227 (10) | N5-C4a-C10b   | 124.8 (5) |
| C6a-C7      | 1.405 (8)  | C4a-N5-C6     | 120.8 (6) |
| C6a-C10a    | 1.400 (10) | C4a-N5-C17    | 121.1 (5) |
| C7-C8       | 1.388 (14) | C6-N5-C17     | 118.1 (6) |
| C8-C9       | 1.410 (13) | N5-C6-C6a     | 116.6 (6) |
| C9-C10      | 1.387 (9)  | N5-C6-O18     | 119.2 (7) |
| C10-C10a    | 1.413 (11) | C6a-C6-O18    | 124.2 (6) |
| C10a-C10b   | 1.448 (8)  | C6-C6a-C7     | 117.7 (7) |
| C11-O12     | 1.203 (11) | C6-C6a-C10a   | 121.6 (6) |
| C11-C13     | 1.507 (12) | C7-C6a-C10a   | 120.8 (7) |
| C14-N15     | 1.138 (11) | C6a-C7-C8     | 119.5 (7) |
| C17-N5      | 1.484 (12) | C7-C8-C9      | 120.0 (7) |
|             |            | C8-C9-C10     | 120.7 (8) |
|             |            | C9-C10-C10a   | 119.6 (7) |
|             |            | C6a-C10a-C10  | 119.4 (6) |
|             |            | C6a-C10a-C10b | 118.4 (7) |
|             |            | C10-C10a-C10b | 122.2 (6) |
|             |            | C1-C10b-C4a   | 121.7 (5) |
|             |            | C1-C10b-C10a  | 120.6 (6) |
|             |            | C4a-C10b-C10a | 117.8 (6) |
|             |            | C1-C11-O12    | 118.9 (6) |
|             |            | C1-C11-C13    | 119.6 (9) |
|             |            | O12-C11-C13   | 121.4 (7) |
|             |            | C2-C14-N15    | 179.1 (8) |

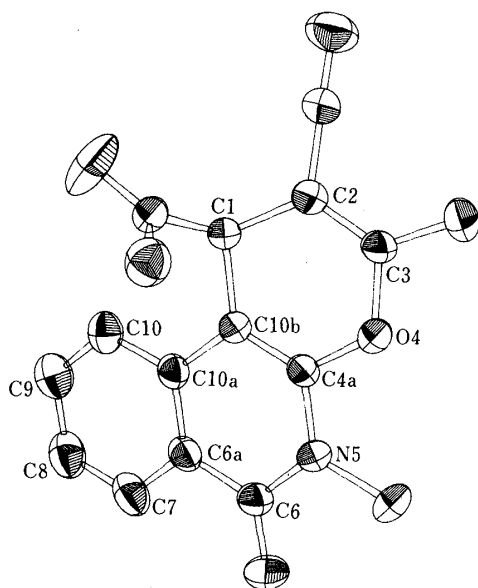


Fig. 2. A Perspective Drawing of IX

differed from those of VII and IX, and strongly suggested a 4-substituted 1,3(2*H*,4*H*)-isoquinolinedione structure.<sup>1)</sup> Formula X' was ruled out by the absence of methyl-methine proton signals in the <sup>1</sup>H-NMR spectrum. In view of the above results, the structure of X was concluded to be 4-5'-amino-2'-methyl-3'-furyl-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4'-carbonitrile. X-Ray analysis could not be done since a suitable single crystal of X could not be obtained.

This reaction can best be explained by assuming the initial occurrence of retrograde Michael reaction between IV and malononitrile, as shown in Chart 4; *viz.* one of the homophthalimide moieties of IV is replaced by malononitrile to afford a normal Michael adduct VIII' and I, then VIII' cyclizes to give IX and X, in the same way as in the formation of VI and VII'a.

### Experimental

All melting points were taken in a capillary and are uncorrected. IR spectra were measured with a Hitachi 215 spectrometer and MS with a JEOL LMS-D300 spectrometer. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded on a JEOL JNM-FX100 FT NMR with tetramethylsilane as a internal standard. The lattice constants and intensity data were collected on a Rigaku AFC-5FOS diffractometer using MoK $\alpha$  radiation monochromated by means of a graphite plate.

**1,1-Bis(2-methyl-1,3-dioxo-tetrahydroisoquinolin-4-yl)actone (IV)**—A solution of I (2.4 g) in EtOH (100 ml) was added in small portions to a stirred solution of methylglyoxal (40%, 2.4 g) and 10 drops of diethylamine in EtOH (350 ml) at room temperature. As stirring was continued for 1 h, the reaction mixture became green, and the crystals that separated were collected. Yield, 1.6 g (58%). Colorless granular crystals, mp 174–175°C (CHCl<sub>3</sub>). IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 1710 (CH<sub>3</sub>CO), 1670–1660 (3-CO, 1-CO), 1640 (hydrogen-bonded 3'-CO). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.58 (3H, s, CH<sub>3</sub>CO), 2.92 (6H, s, 2  $\times$  NCH<sub>3</sub>), 4.32 (1H, dd,  $J_{ab}$  = 5.6,  $J_{ac}$  = 2.0 Hz, CH<sub>a</sub>), 4.65 (1H, d,  $J_{ac}$  = 2.0 Hz, CH<sub>c</sub>), 4.84 (1H, d,  $J_{ab}$  = 5.6 Hz, CH<sub>b</sub>), 7.35–8.16 (8H, m, Ar-H). Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>: C, 68.30; H, 4.99; N, 6.93. Found: C, 68.30; H, 4.93; N, 6.76.

**Reaction of II with Malononitrile: Formation of VI and VII**—A solution of malononitrile (0.93 g) in benzene (20 ml) was added in small portions to a stirred solution of II (4.0 g) in a mixed solvent of benzene (80 ml) and EtOH (80 ml) containing 6 drops of diethylamine at 60°C. Stirring was continued for 1 h, then the solvent was removed *in vacuo*. The product solidified on trituration with a small amount of EtOH. Recrystallization of the whole product (2.2 g) from AcOEt permitted the separation of VI (0.4 g) and VII (0.6 g).

**3-Amino-1-benzoyl-5-methyl-6-oxo-5,6-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-2-carbonitrile (VI)**—Yellow granular crystals, mp 224°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3380, 3320 (NH<sub>2</sub>), 2180 s (CN), 1690 (PhCO), 1680 (6-CO). MS  $m/z$ : 357 (M<sup>+</sup>). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 3.58 (3H, s, NCH<sub>3</sub>), 5.83 (1H, s, CH), 7.51 (2H, s, NH<sub>2</sub>, exchanged with D<sub>2</sub>O), 7.28–8.27 (9H, m, Ar-H). Anal. Calcd for C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.70; H, 4.01; N, 11.41.

**9-Amino-6-methyl-5-oxo-7a-phenyl-5,6,7a,10a-tetrahydrofuro[2',3':2,3]furo[5,4-c]isoquinoline-10-carbonitrile (VII)**—Colorless prisms, mp 211 °C. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3300, 3150 ( $\text{NH}_2$ ), 2175 s (CN), 1670, 1655 sh (5-CO). MS  $m/z$ : 357 ( $\text{M}^+$ ).  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 3.51 (3H, s,  $\text{NCH}_3$ ), 5.06 (1H, s, CH), 7.61 (2H, s,  $\text{NH}_2$ , exchangeable), 7.36–8.17 (9H, m, Ar-H).  $^{13}\text{C-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 28.8 (q,  $\text{NCH}_3$ ), 52.5 (s, C-10), 55.2 (d, C-10a), 93.0 (s, C-10b), 118.5 (s, CN)\*, 118.7 (s, C-7a)\*, 150.3 (s, C-9), 161.2 (s, C-6a), 166.5 (s, C-5). (\* Assignments are interchangeable.) *Anal.* Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_3$ : C, 70.58; H, 4.32; N, 11.76. Found: C, 70.33; H, 4.54; N, 11.39.

**X-Ray Structure Analysis of VII**—The crystal data are: monoclinic, space group  $P2_1/c$ ,  $a=10.795$  (3),  $b=16.118$  (3),  $c=16.508$  (4) Å,  $\beta=142.03$  (1)°,  $V=1767.3$  (9) Å<sup>3</sup>,  $z=4$ ,  $D_c=1.343$  g·cm<sup>-3</sup>. A total of 1522 independent reflections were measured with  $2\theta$  less than 46° as being above the  $2\sigma(F)$  level, and were used in the structural analysis. The structure was solved by the direct method and refined by the block-diagonal least-squares method. The final  $R$  factor without hydrogen atoms was 0.090.

**Reaction of IV with Malononitrile: Formation of I, IX and X**—A solution of malononitrile (1.0 g) in benzene (20 ml) was added to a stirred solution of IV (3.5 g) in a mixed solvent of benzene (50 ml), MeOH (50 ml) and  $\text{CHCl}_3$  (50 ml) containing diethylamine (10 drops), and the mixture was warmed at 50 °C for 1 h. The reaction mixture was kept standing overnight at room temperature, then the solvent was removed. The product was solidified by treatment with a small amount of MeOH. Fractional recrystallization of the whole product (1.5 g) from MeOH was repeated twice, and the three compounds, I (0.28 g), IX (0.15 g) and X (0.2 g), were isolated. The product I was found to be the starting material by IR comparison and mixed mp determination.

**1-Acetyl-3-amino-5-methyl-6-oxo-5,6-dihydro-1H-pyranof[2,3-c]isoquinoline-2-carbonitrile (IX)**—Yellow prisms, mp 230 °C. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3410, 3340 ( $\text{NH}_2$ ), 2180 s (CN), 1720 ( $\text{CH}_3\text{CO}$ ), 1680 (6-CO). MS  $m/z$ : 295 ( $\text{M}^+$ ), 252 ( $\text{M}^+ - \text{COCH}_3$ ).  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 2.13 (3H, s,  $\text{CH}_3$ ), 3.53 (3H, s,  $\text{NCH}_3$ ), 4.49 (1H, s, CH), 7.63 (2H, s, exchangeable), 7.39–8.27 (4H, m, Ar-H).  $^{13}\text{C-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 26.2 (q,  $\text{CH}_3$ ), 28.5 (q,  $\text{NCH}_3$ ), 45.6 (d, C-1), 51.3 (s, C-2), 88.0 (s, C-10b), 119.3 (s, CN), 143.0 (s, C-4a), 160.2 (s, C-3)\*, 160.5 (s, C-6)\*, 206.1 (s,  $\text{COCH}_3$ ). (\* Assignments are interchangeable.) *Anal.* Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 65.08; H, 4.44; N, 14.23. Found: C, 65.14; H, 4.05; N, 14.50.

**X-Ray Structure Analysis of IX**—The crystal data are: monoclinic, space group  $P2_1/c$ ,  $A=10.164$  (2),  $b=14.466$  (1),  $c=10.941$  (1) Å,  $\beta=122.57$  (1)°,  $V=1355.7$  (4) Å<sup>3</sup>,  $z=4$ ,  $D_c=1.45$  g·cm<sup>-3</sup>. A total of 1615 independent reflections were measured with  $2\theta$  less than 48° as being above the  $2\sigma(F)$  level, and were used in the structure analysis. The structure was solved by the direct method and refined by the block-diagonal least-squares method. The final  $R$  factor without hydrogen atoms was 0.083.

**4'-5'-Amino-2'-methyl-3'-furyl-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4'-carbonitrile (X)**—Colorless silky needles, mp 224 °C. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3350, 3200 ( $\text{NH}_2$ ), 2185 s (CN), 1680, 1660 (1-CO, 3-CO). MS  $m/z$ : 295 ( $\text{M}^+$ ).  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 1.82 (3H, s,  $\text{CH}_3$ ), 3.41 (3H, s,  $\text{NCH}_3$ ), 4.78 (1H, s, CH), 7.42 (2H, s,  $\text{NH}_2$ , exchangeable), 7.2–8.19 (4H, m, Ar-H).  $^{13}\text{C-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 23.6 (q,  $\text{CH}_3$ ), 29.0 (q,  $\text{NCH}_3$ ), 52.3 (d, C-4), 52.83 (s, C-4'), 93.6 (s, C-3'), 119.4 (s, CN), 120.2 (s, C-2'), 150.4 (s, C-5'), 161.5 (s, C-3), 166.3 (s, C-1). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 65.08; H, 4.44; N, 14.23. Found: C, 65.13; H, 4.40; N, 14.21.

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