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Spiro Heterocyclic Compounds. VI.[1] Synthesis of Spiro[imidazolidine-4,1′-isoindoline] and Related Compounds

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Nitrosation of 2-methylisoquinoline-1,3(2*H*,4*H*)-dione (I) with $NaNO_2$ in AcOH afforded the 4-nitroso compound (II) in almost quantitative yield. Catalytic reduction of II produced 4-imino-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (III) and a small amount of 4,4′-bi-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (IV). Acidic hydrolysis of III gave 2-methylisoquinoline-1,3,4(2*H*)-trione (V).

The hydrogenated mixture of II was allowed to react with methyl- and phenylisocyanate under an inert atmosphere to give 4-ureido compounds (VIIa, b) in yields of 79% (both). Dehydrogenation of VIIa,b with Pd-C afforded the 4-carbamoylimino compounds (VIIIa, b) in 60 and 87% yields, respectively.

When their methanol solutions were refluxed with base catalyst, the compounds (VIIIa, b) were transformed into spiro[imidazolidin-4,1′-isoindoline]-2,3′,5-triones (XIIa, b) in yields of 80 and 86%, respectively.

Keywords——nitrosation; 2-methyl-4-nitrosoisoquinoline-1,3-(2*H*,4*H*)-dione; catalytic reduction; 4-imino-2-methylisoquinoline-1,3(2*H*,4*H*)-dione; 4,4′-bi-2-methylisoquinoline-1,3(2*H*,4*H*)-dione; 2-methylisoquinoline-1,3,4(2*H*)-trione; 2-methyl-4-ureidoisoquinoline-1,3(2*H*,4*H*)-dione; 4-carbamoylimino-2-methylisoquinoline-1,3(2*H*,4*H*)-dione: spiro[imidazolidine-4,1′-isoindoline]-2,3′,5-trione; ethyl 2-methyl-1-(*N*′-methylureido)-3-oxo-isoindoline-1-carboxylate

4-Nitrosoisoquinoline-1,3(2*H*,4*H*)-dione (II) is easily accessible, but its chemistry has not been extensively investigated. We are interested in exploring its usefulness for the synthesis of new 4-substituted isoquinoline compounds by reducing the nitroso group. The present paper deals with the reduction of II and with some novel chemistry leading to the synthesis of spiro[imidazolidine-4,1′-isoindoline]compounds from the reduction product of II.

It is reported that the nitrosation of 2-methylisoquinoline-1,3(2*H*,4*H*)-dione (I) with sodium nitrite in hydrochloric acid ethanol solution produced II in 85% yield; the product was considered to be present as the hydroxyimino tautomer (II′) on the basis of spectral data.[2,3] We carried out the same reaction in acetic acid, and II was obtained in almost quantitative yield.

The catalytic reduction of II using Pd–C consumed two molar equivalents of hydrogen and gave pale brown crystals (III) in 60% yield. The filtrate after the separation of III showed a bright blue color upon exposure to air. The product (III) thus obtained showed the molecular ion peak (M^+) at *m/e* 188 in the mass spectrum (MS) and showed absorption bands due to an NH and two C=O groups at 3225, 1700 and 1660 cm^{-1}, respectively, in its infrared (IR) spectrum. The proton magnetic resonance (PMR) spectrum of III showed two singlets at δ 3.5 (3H) and 11.9 (1H, exchangeable with D_2O) due to NCH_3 and =NH protons, respectively, together with aromatic protons (4H, m). These results and analytical data supported the structure of III as 4-imino-2-methylisoquinoline-1,3-(2*H*,4*H*)-dione. This compound was easily converted to the isoquinoline-1,3,4(2*H*)-trione (V) by acidic hydrolysis in 70% yield.

The blue filtrate after the separation of III gave a small amount of colorless crystals (IV) whose IR spectrum was superimposable on that of 2-methylisoquinoline-1,3(2*H*,4*H*)-dione (I). The PMR spectrum of IV showed a significant singlet at δ 4.75 (1H) along with signals due to NCH_3 (3H, s) and aromatic protons (4H, m). The MS of IV showed M^+ at *m/e* 348 and a

diagnostic peak at 174 ($M^+/2$) corresponding to the mass of 2-methylisoquinoline-1,3(2*H*,4*H*)-dione (I) with loss of one hydrogen radical. Accordingly, the product IV should be a dimer of I, and the relative intensity of the PMR spectrum of IV must be double the observed values. Thus the singlet at δ 4.75 was assigned to a >CH–CH< unit in the molecule. Based on the above results and the analytical data, the structure of IV was concluded to be 4,4′-bi-2-methylisoquinoline-1,3(2*H*,4*H*)-dione. The mechanism for the formation of the dimer (IV) by catalytic reduction of the nitroso compound (II) remains unclear.

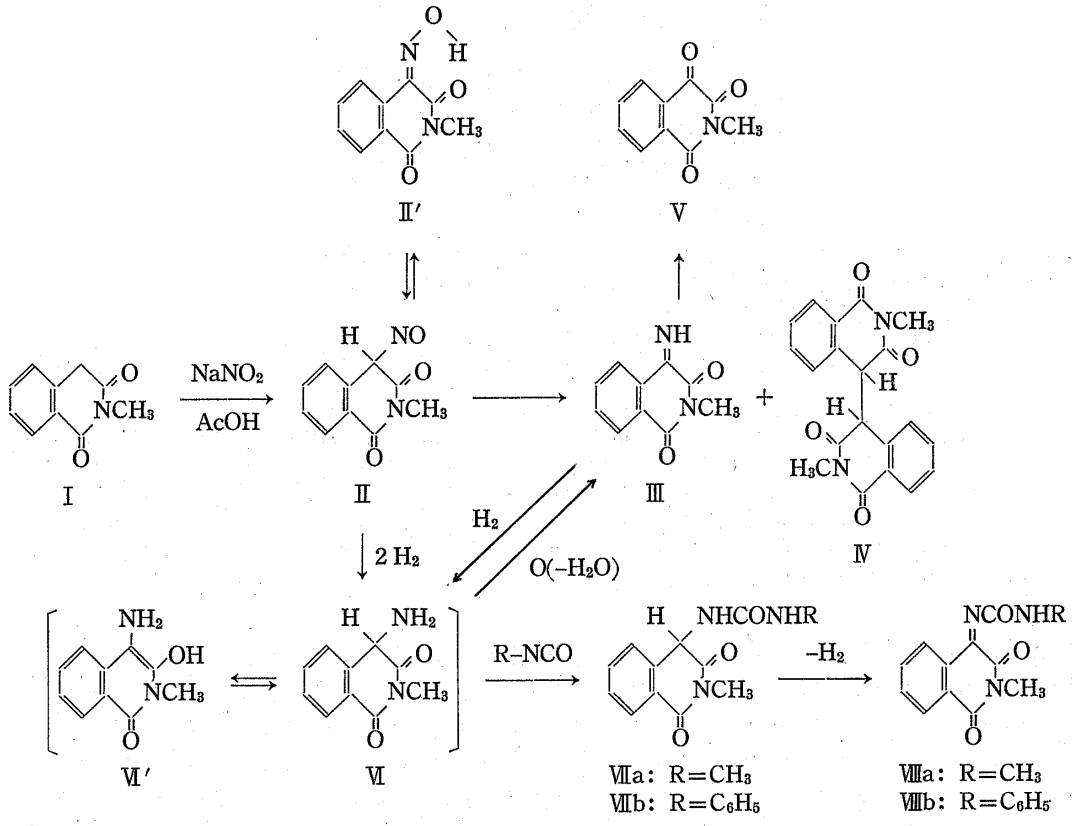

Chart 1

A tetrahydrofuran (THF) solution of III catalytically absorbed one molar equivalent of hydrogen. However, the 4-amino compound (VI or VI′) was not obtained in a pure state by recrystallization in the usual manner. It appears that the amino compound (VI) is very unstable and readily undergoes air-oxidation to form the imino compound (III), and the foregoing blue coloration suggested the formation of a quinhydrone compound consisting of III and VI. Therefore, a reduction treatment was necessary to prevent air-oxidation before carrying out the next procedure. Compound II in THF was reduced catalytically and, without isolation, the 4-amino compound was allowed to react with methyl- and phenylisocyanate under nitrogen at room temperature to provide colorless products (VIIa, b) in the same yield of 79%. The MS of VIIa gave M^+ at *m/e* 247 and the IR spectrum showed absorption bands due to an NH at 3320 and three C=O groups at 1720, 1650 and 1630 cm^{-1}. The PMR spectrum of VIIa showed a singlet at δ 3.2 (3H) for NCH_3, mutually coupled signals at δ 2.56 (3H, d, J=4 Hz, changed to s. in D_2O) and 6.2 (1H, q, J=4 Hz, disappeared in D_2O) due to $NHCH_3$, and two doublets at δ 5.4 (1H, J=8 Hz, exchang. with D_2O) and 7.1 (1H, J=8 Hz, changed to s. in D_2O) which could be assigned to >CH–NH– protons, as well as a multiplet (4H) of aromatic protons. These results and the analytical data were consistent with the structure 2-methyl-4-(*N*′-methylureido)isoquinoline-1,3(2*H*,4*H*)-dione (VIIa). VIIb was similarly identified as

the 4-(*N'*-Phenylureido) compound. A small amount of the foregoing product (IV) was also obtained from the filtrates after the separations of VIIa, b.

These ureido compounds VIIa, b were stable to air, but were expected to be oxidized rather easily into imino compounds. When THF solutions of VIIa, b were stirred with Pd–C (10%) at 40°C for 3 h, the corresponding products VIIIa, b were obtained in yields of 60 and 87%, respectively. The PMR spectra of both VIIIa, b showed signals due to NCH_3 (3H, s) and CONH– (1H, s, exchang. with D_2O) protons and the absence of coupling signals due to a >CH–NH– unit, while in their MS the molecular ions were each two mass units (2H) less than those of VIIa, b. In view of these results and the analytical data, the products VIIIa, b were determined to be 4-(methylcarbamoylimino)- and 4-(phenylcarbamoylimino)isoquinoline-1,3-(2*H*, 4*H*)-dione, respectively.

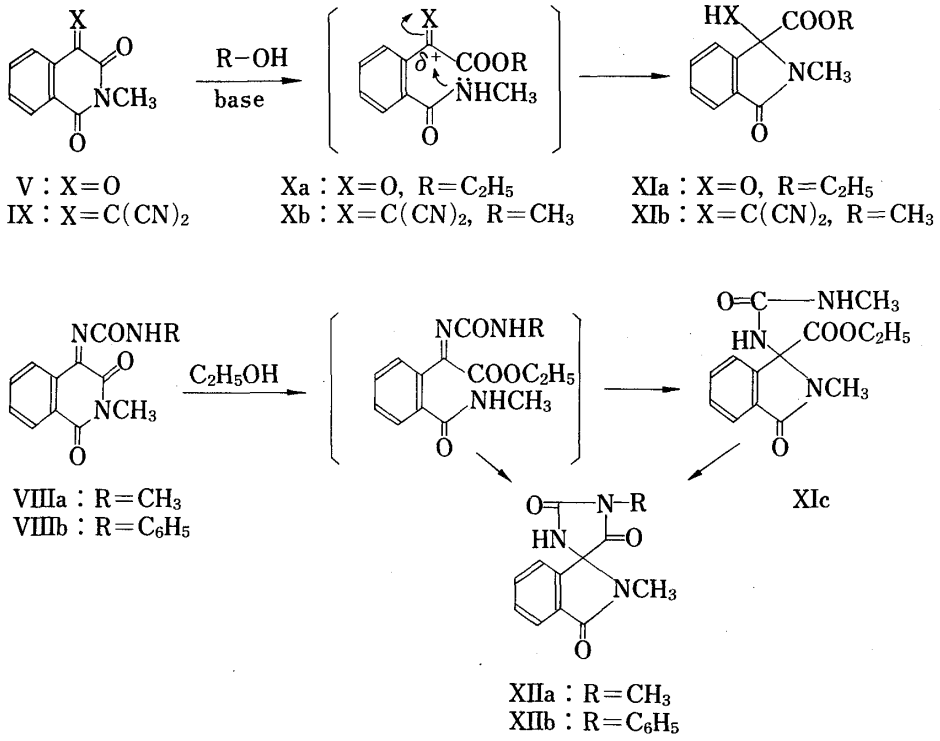

Chart 2

Next, the transformations of VIIIa, b into spiro[imidazolidine-4,1'-isoindoline] compounds will be described.

Recently, isoquinoline-1,3,4(2*H*)-trione (V) was transformed into an isoindolinone derivative (XIa) in ethanol solution with a base catalyst by Peterson *et al.*[4] On the other hand, we have also obtained an analogous isoindolinone compound (XIb) from 4-dicyanomethyleneisoquinoline-1,3(2*H*,4*H*)-dione (IX).[1] A possible mechanism for these ring transformations is shown in Chart 2; *viz.* the C-4 carbon of compound V or IX is conjugated with a strong electron-attracting group and its electron density is reduced. First, the alcoholysis of V or IX results in ring-cleavage of the 2—3 bond, affording a ring-opened intermediate Xa or Xb, followed by recyclization involving the attack of the $NHCH_3$ lone pair on the strongly cationic benzylidene carbon to form the isoindolinone compound (XI). From the similarity of the electron contribution, we anticipated that homologous ring transformations would occur on the compounds VIIIa, b and the ureido and ester groups would form an imidazolidinedione ring at the 1-position of isoindolinone.

Refluxing an ethanol solution of VIIIa with a catalytic amount of triethylamine afforded a colorless product (XIIa) in 80% yield. The MS of XIIa showed the same M^+ at *m/e* 245 as

that of VIIIa and the IR spectrum showed absorption bands due to an NH at 3275 and three C=O bands at 1790, 1730 and 1670 cm^{-1}. The C=O band at the highest region suggests the presence of an imidazolidine-2,4-dione ring.[5] The C=O absorption of an isoindolinone ring usually appears at below 1700 cm^{-1}.[4,6] The PMR spectrum of XIIa showed signals of two NCH_3 at δ 2.9 and 3.1 (each of 3H, s) and a CONH– at δ 9.1 (1H, s, exchang. with D_2O), together with 4H (m) of aromatic protons. These results and the analytical data were in good accord with the proposed 1,2′-dimethylspiro[imidazolidine-4,1′-isoindoline]-2,3′,5-trione structure. In one run with a reaction time of 5 min, an intermediate (XIc), which on refluxing with a trace of triethylamine in ethanol afforded XIIa, was obtained in 83% yield. It was identified as ethyl 2-methyl-1-(*N*′-methylureido)-3-oxo-isoindoline-1-carboxylate (XIc) from the following spectral data. The MS of XIc gave M^+ at *m/e* 291. The PMR spectrum showed signals due to OCH_2CH_3 (δ 1.2, 3H, t, and 3.5, 2H, q; J=7 Hz), $NHCH_3$ (δ 2.95, 3H, d, J=4 Hz, chang. to s. in D_2O and 6.1, 1H, q, dull, disappear. in D_2O), NCH_3 (δ 3.15, 3H, s) and NHCO protons (δ 7.75, 1H, s, exchang. with D_2O), together with aromatic protons (4H, m). The ^{13}C nuclear magnetic resonance (CMR) spectrum of XIc indicated the presence of one quaternary (δ 89.71), one methylene (59.40) and three each of methyl (14.66, 24.41 and 26.75) and C=O (154.42, 171.24 and 171.71) carbons in the molecule, as well as six aromatic carbons. The IR spectrum of XIc showed absorption bands due to two NH at 3300 and 3400 and three C=O bands at 1790, 1720 and 1640 cm^{-1}. The C=O band at 1790 cm^{-1} (abnormally high frequency) is considered to be due to the ureido C=O group including a distorted NH–CO bond like that of an unsaturated five-membered lactam as a result of the ionic interactions between the $NHCH_3$ and ester C=O groups.

The similar reaction of VIIIb gave the homologous spiro compound (XIIb) in 86% yield. In this case, an intermediate corresponding to XI was not obtained even at a short reaction time.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 215 instrument and MS with a JEOL D300 machine at 70 eV. PMR and CMR spectra were taken on a JEOL FX-100 spectrometer using tetramethylsilane as the internal standard. Solutions were concentrated on rotary evaporators *in vacuo*.

2-Methyl-4-nitrosoisoquinoline-1,3(2*H*,4*H*)-dione (II)——$NaNO_2$ (6.8 g) was added in small portions to a solution of I (5.0 g) in AcOH (50 ml) over 10 min at room temperature under stirring. The stirring was continued for 2 h at 40°C, and the pale yellow solid (II) that separated was collected and washed with water. The filtrate was poured into ice-water to give another crop of II. Total yield, 5.8 g, (99.5%). Pale yellow needles, mp 210—212°C (dec.) (from acetone). (lit.,[3] mp 201—203°C, (dec.)). MS *m/e* 204 (M^+). Spectral data coincided well with the literature values.

4-Imino-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (III)——A mixture of II (4.0 g) and Pd-C (10%, 0.2 g) in MeOH (100 ml) was stirred under a hydrogen atmosphere at room temperature. When two molar equivalents of hydrogen had been consumed, the mixture turned greenish-grey and muddy. A dark solid, mixed with Pd-C, was collected, dissolved in benzene, and filtered to remove the catalyst. The solution was concentrated to give III. Yield, 2.2 g (60%). Pale brown needles, mp 117—119°C (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3325 (NH), 1700, 1660 (C=O). PMR ($CDCl_3$) δ: 3.5 (3H, s, NCH_3), 7.7—8.5 (4H, m, Ar–H), 11.9 (1H, s, exchangeable with D_2O, =NH). MS *m/e* 188 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.26; N, 14.89. Found: C, 63.93; H, 4.17; N, 14.76.

The filtrate from the separation of III, or from the recrystallization of III becomes bright blue on exposure to air.

4,4′-Bi-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (IV)——In the above hydrogenation of II, the blue filtrate obtained after the separation of III was concentrated to dryness. The solid was recrystallized from MeOH to give IV as colorless prisms, mp 223—224°C. Yield, 0.4 g (5.9%). IR ν_{max}^{Nujol} cm^{-1}: 1710, 1650 (2 C=O). PMR ($CDCl_3$) δ: 3.2, s, NCH_3), 4.75 (1H, s, –CH<), 6.9—8.5 (4H, m, Ar–H), (relative intensity was observed as that of the monomer of IV). MS *m/e*: 348 (M^+), 100%), 174 (M^+/2, 40). *Anal.* Calcd for $C_{20}H_{16}N_2O_4$: C, 68.97; H, 4.60; N, 8.05. Found: C, 68.60; H, 4.51; N, 8.00.

Hydrolysis of III: 2-Methylisoquinoline-1,3,4(2*H*)-trione (V)——A solution of III (0.1 g) in HCl–MeOH (1: 1, 4 ml) was heated at 60°C for 1 h. After the reaction, MeOH was removed and the residual mixture

was cooled to give yellow needles, mp 186°C. Yield, 0.07 g (70%). This compound was identical with a sample of 2-methylisoquinoline-1,3,4(2*H*)-trione (V) on the basis of mixed melting point determination and comparison of IR spectra.

2-Methyl-4-(*N'*-methylureido)isoquinoline-1,3(2*H*,4*H*)-dione (VIIa)——A mixture of II (2.0 g) and Pd-C in THF (50 ml) was stirred under hydrogen in the usual manner. After the absorption of hydrogen had ceased, methylisocyanate (0.86 g) was added to the hydrogenated mixture and stirring was continued for 6 h under nitrogen at room temperature. The reaction mixture became clear, and was then filtered to remove the catalyst. The filtrate was concentrated to give VIIa. Recrystallization from MeOH–C_6H_6 (1: 1) gave colorless needles of mp 240—241°C. Yield, 1.92 g (79%). IR ν_{max}^{Nujol} cm^{-1}: 3310—3380 (2 NH), 1720, 1650, 1630 (3 C=O). PMR (DMSO-d_6) δ: 2.56 (3H, d, J=4 Hz, changed to s by D_2O treatment, $CONHC\underline{H}_3$), 3.2 (3H, s, NCH_3), 5.4 (1H, d, J=8 Hz, exchang. >CH–N<u>H</u>–), 6.2 (1H, q, J=4 Hz, exchang. $CON\underline{H}CH_3$), 7.1 (1H, d, J=8 Hz, changed to s. by D_2O treatment, >C<u>H</u>–NH–), 7.4—8.0 (4H, m). MS *m/e*: 247 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_3O_3$: C, 58.30; H, 5.26; N, 17.00. Found: C, 58.40; H, 5.27; N, 17.08.

A small amount of product IV was obtained from the mother liquor after the separation of VIIa.

2-Methyl-4-(*N'*-phenylureido)isoquinoline-1,3(2*H*,4*H*)-dione (VIIb)——This compound was obtained from the hydrogenated mixture of II in the manner described for the preparation of VIIa except for the use of phenylisocyanate instead of methylsiocyanate. Yield, 2.40 g (79%). Colorless needles, mp 220—221°C (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3375—3500 (NH), 1710, 1660, 1620 (3 C=O). PMR (DMSO-d_6) δ: 3.2 (3H, s, NCH_3), 5.6 (1H, d, J=8 Hz, changed to s by D_2O treatment, >C<u>H</u>–NH–), 6.8—8.2 (10H, m, >CH–N<u>H</u>– and Ar–H), 9.0 (1H, s, exchang. CONH–). MS *m/e*: 309 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.83; H, 4.73; N, 13.57.

A small amount of product IV was obtained from the filtrate after the separation of VIIb.

2-Methyl-4-(methylcarbamoylimino)isoquinoline-1,3(2*H*,4*H*)-dione (VIIIa)——A mixture of VIIa (0.5 g) and Pd-C (10%, 0.2 g) in THF (20 ml) was stirred at 40°C for 3 h. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residual product was recrystallized from MeOH to give pale yellow needles of mp 219—220°C. Yield, 0.3 g (60%). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1710, 1660, 1640 (3 C=O). PMR (DMSO-d_6) δ: 2.7 (3H, d, J=4 Hz, changed to s by D_2O treatment, $-NHC\underline{H}_3$), 3.2 (3H, s, NCH_3), 7.05 (1H, q, J=4 Hz, exchang. $-N\underline{H}CH_3$), 7.7—8.2 (4H, m, Ar–H). MS *m/e*: 245 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_3O_3$: C, 58.78; H, 4.49; N, 17.49. Found: C, 58.53; H, 4.37; N, 17.30.

2-Methyl-4-(phenylcarbamoylimino)isoquinoline-1,3(2*H*,4*H*)-dione (VIIIb)——This compound was obtained from VIIb in the manner described for the preparation of VIIIa. Pale yellow needles, mp 189—191°C (MeOH). Yield, 0.43 g (89%). IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1710, 1675, 1650 (3 C=O). PMR (DMSO-d_6) δ: 3.3 (3H, s, NCH_3), 6.8—8.3 (9H, m, Ar–H), 9.5 (1H, s, ecxhang. CONH–). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.46; H, 4.57; N, 13.24.

1,2'-Dimethylspiro[imidazolidine-4,1'-isoindoline]-2,3',5-trione (XIIa)——Triethylamine (0.1 ml) was added to a solution of VIIIa (0.1 g) in EtOH (20 ml), and the mixture was refluxed for 30 min. After removal of EtOH, the resulting solid was recrystallized from MeOH to give colorless needles, mp 272°C. Yield, 0.08 g (80%). IR ν_{max}^{Nujol} cm^{-1}: 3275 (NH), 1790, 1720, 1670 (3 C=O). PMR (DMSO-d_6) δ: 2.87 (3H, s, NCH_3), 3.1 (3H, s, NCH_3), 7.6—7.8 (4H, m, Ar–H), 9.1 (1H, s, exchang. NH). MS *m/e*: 245 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.48; N, 17.14. Found: C, 58.71; H, 4.40; N, 17.19.

Ethyl 2-Methyl-1-(*N'*-methylureido)-3-oxo-isoindoline-1-carboxylate (XIc)——This compound was obtained from VIIIa by carrying out the reaction in the manner described for the preparation of XIIa, but only for 5 min. Yield, 83%. Colorless needles, mp 176°C (Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3400 (2 NH), 1790, 1720, 1640 (3 C=O). PMR ($CDCl_3$) δ: 1.2 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.95 (3H, d, J=5 Hz, changed to s. in D_2O, $NHC\underline{H}_3$), 3.1 (3H, s, NCH_3), 3.5 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.1 (1H, q, dull, exchang. with D_2O, $N\underline{H}CH_3$), 7.14—7.22 (4H, m, Ar–H), 7.75 (1H, s, exchang. NH). CMR ($CDCl_3$) δ: 14.16 (q, CH_3), 24.41 (q, NCH_3), 26.75 (q, NCH_3), 59.40 (t, $-CH_2-$), 89.71 (s, quaternary C), 154.42, 171.14, 171.72 (each s, 3 C=O). MS *m/e*: 291 (M^+).

The product (XIc) was easily changed into XIIa by refluxing it in MeOH with a trace of Et_3N.

2'-Methyl-1-phenylspiro[imidazolidine-4,1'-isoindoline]-2,3',5-trione (XIIb)——This compound was obtained from VIIIb in the manner described for the preparation of XIIa. Yield, 86%. Colorless needles, mp 249—251°C. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1790, 1730, 1690 (3 C=O). PMR ($CDCl_3$) δ: 3.0 (3H, s, NCH_3), 6.2 (1H, s, exchang. NH), 7.4—7.8 (9H, m, Ar–H). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.11; H, 4.08; N, 13.55.

References and Notes

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