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THE REACTIONS OF UREAS WITH GLYOXYLIC ACID AND METHYL GLYOXYLATE

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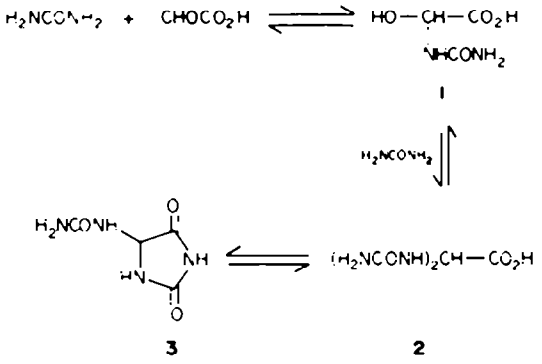
Abstract—The reactions of urea, methylurea and dimethylureas with glyoxylic acid and its methyl ester to give α-substituted hydantoic acid derivatives (**4**, **5**, **6**, **7**) and substituted allantoic acid derivatives (**8**) is discussed. The cyclization of the hydantoates and allantoates to 5-substituted hydantoins (**11**, **12**) is also described.

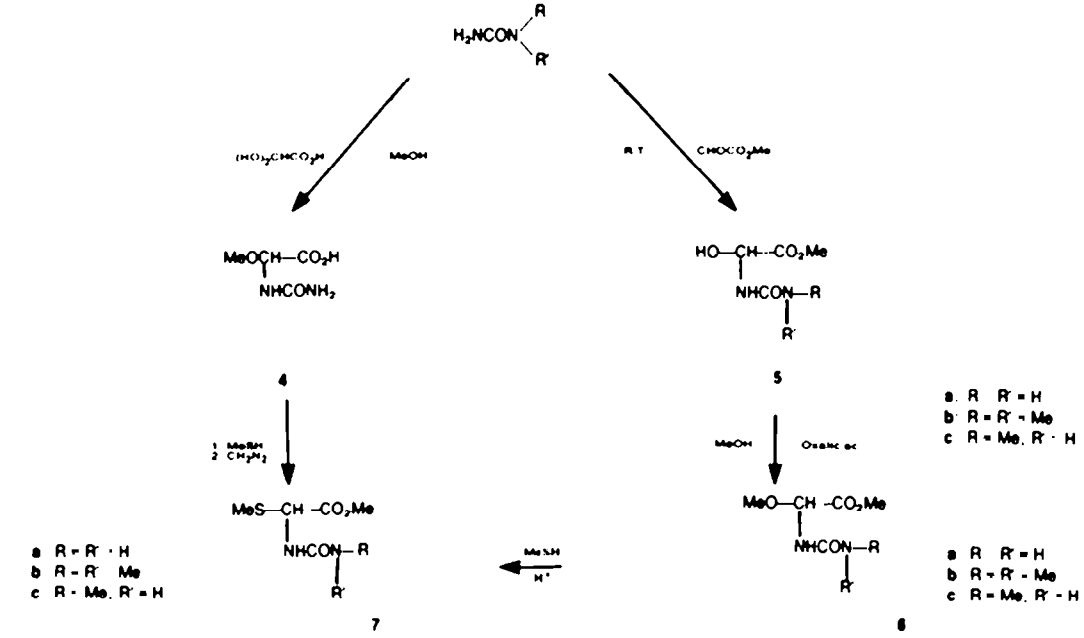
Although allantoin (**3**) formation from urea and glyoxylic acid was described as early as 1876,[1] relatively little is known about the reactions of ureas with glyoxylic acid or its esters:[2]



The reverse reaction (**3** → **1**) was shown to be part of the biological path by which uric acid is degraded to urea and glyoxylic acid.[3] Oxidative degradation of uric acid[4] and caffeine[5] led to the isolation of 5-hydroxyhydantoin and 5-hydroxy-1,3-dimethylhydantoin (**11b**). More recently the sodium salt of α-hydroxydantoic acid (**1**, glyoxylurea) was prepared under controlled pH reaction condition, the free acid (**1**) is unstable.[6]

In the present paper we describe the synthesis of relatively stable adducts of ureas and glyoxylic acid and discuss some of their chemical properties. Reacting glyoxylic acid monohydrate with urea in methanolic suspension in a 1:1 ratio at room temperature afforded the crystalline α-methoxyhydantoic acid (**4**). The free acid was esterified with diazomethane to give methyl α-methoxyhydantoate (**6a**) and was converted to the α-methylthiohydantoic acid on treatment with methyl mercaptan. The α-methoxyhydantoic acid (**4**) is a strong enough acid to authocatalyse its reaction with the mercaptan and the addition of an external acid catalyst was not essential. Attempts to obtain the N,N-dimethyl derivative of α-methoxyhydantoic acid by reacting N,N-dimethylurea with glyoxylic acid in methanol afforded a mixture of products.

α-Methoxyhydantoic acid (**4**) was found to be unstable in aqueous media, first the OMe group underwent hydrolysis and later more profound changes occurred. Even during the running of NMR spectra in D_2O solution

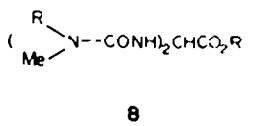


the OMe group changes to free methanol and the methine hydrogen of the hydantoic acid appeared as a singlet. After standing at room temperature for 1 hr the singlet of the methine group was converted to a more complex pattern indicating further changes in the molecule.

Reacting methyl glyoxylate (hemiacetale) with urea, monomethyl and N,N-dimethylurea at room temperature, afforded the corresponding methyl α-hydroxyhydantoates **5a**, **5b** and **5c**. Treatment with methanol in the presence of oxalic acid as catalyst converted the α-hydroxy methyl esters (**5**) to the corresponding methyl α-methoxy-hydantoates (**6**) in high yields. The methyl α-methoxy-hydantoate obtained by this procedure (**6a**) was identical with the methoxy ester prepared from **4** and diazomethane.

The conversion of methyl δ-methyl-α-hydroxy-hydantoate (**5c**) to the corresponding methoxy derivative (**6c**) is quite tricky because of the ease with which it cyclizes to the corresponding 5-hydroxy (**11a**) or 5-methoxyhydantoin (**12a**). The cyclization is catalyzed by both base and acid. The ease of cyclization of the adduct of monomethylurea to hydantoins is further supported by the fact that monomethyl urea and N,N'-dimethylurea when treated with only one equivalent of glyoxylic acid at room temperature afforded directly the 5-hydroxy- and 5-methoxy-hydantoins (**11** and **12**). Both the hydroxy esters (**5**) and the methoxy esters (**6**) were converted to the methyl esters of α-methylthiohydantoates (**7**) on treatment with methyl mercaptan in methylene chloride solutions and in the presence of catalytic amounts of oxalic acid.

Condensing glyoxylic acid with two equivalents of methylurea in aqueous solution or with two equivalents of N,N-dimethylurea in acetone solution gave the allantoic acid derivatives (**8a**, **8c**) in 65 and 67% yield. The acids were esterified with diazomethane to give the corresponding methyl esters (**8b**, **8d**).



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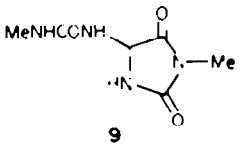
a: R = R' = H
b: R = H, R' = Me
c: R = Me, R' = H
d: R = R' = Me



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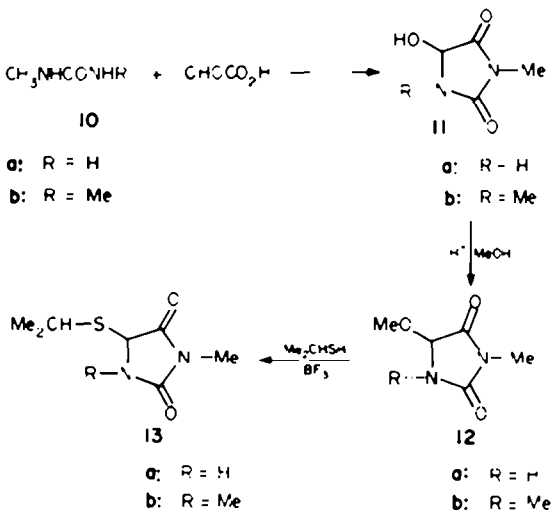
The same bisadduct esters (**8b**, **8d**) were also prepared from methyl glyoxylate and two equivalents of methyl and N,N-dimethylurea in the presence of an acid catalyst.

As mentioned above methylurea reacted with glyoxylic acid in methanol solution at room temperature to give directly the 3-methyl-5-methoxyhydantoin (**12a**) in 52% yield. The isomeric 1-methyl-5-methoxyhydantoin was obtained in only small quantities (3%). N,N'-Dimethylurea afforded on reacting with glyoxylic acid in acetone solution 5-hydroxy-1,3-dimethylhydantoin (**11b**) which was converted in methanol and in the presence of boron trifluoride to the 5-methoxyhydantoin (**12b**). If the reaction of the dimethylurea and glyoxylic acid was carried out in methanol a mixture of the hydroxy-hydantoin (**11b**) and the methoxyhydantoin (**12b**) was obtained in a 3:1 ratio (NMR).

Both the hydroxy- and methoxy-hydantoins (**11**, **12**) were converted to the 5-isopropyl-thiohydantoins (**13**) on treatment with isopropyl mercaptan in methylene chloride



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a: R = H
b: R = Me

11

a: R = H
b: R = Me

13

a: R = H
b: R = Me

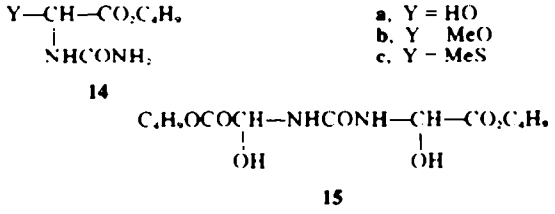
12

a: R = H
b: R = Me

solution and in the presence of boron trifluoride. The thioalkylation of the hydantoins did not take place if only oxalic acid was used as a catalyst.

Methyl 2-methoxy-5-methylhydantoate (**6c**) cyclized very readily to the 5-methoxy-3-methylhydantoin (**12a**). Thus treatment of the methoxy ester with catalytic amount of $KHCO_3$ in methanol gave the cyclic hydantoin in 61% yield. The methoxydantoin was also obtained on treatment of **6c** with boron trifluoride in methanol solution. A similar sensitivity to cyclization was also observed in the case of methyl 5,5'-dimethylallantoate (**8b**) which cyclized on treatment with $KHCO_3$ to the corresponding dimethylallantoin **9**.

In addition to methyl glyoxylate we also used butyl glyoxylate in the condensation with urea and obtained the corresponding butyl esters **14**:



14

a, Y = HO
b, Y = MeO
c, Y = MeS

15

If the ratio of urea to butylglyoxylate was changed to 1:2 a different type of a bisadduct was obtained (**15**). We intend to use the urea glyoxylic acid adducts in our amidoalkylation studies.

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were recorded on Perkin-Elmer 237-spectrophotometer; NMR spectra were obtained on Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS.

α-Methoxyhydantoic acid (**4a**). Glyoxylic acid (23.5 g, 0.25 mol) and urea (16.5 g, 0.275 mol) were mixed in MeOH (125 ml). After 20 min a clear soln was obtained and after 1 hr precipitation of the product began. The reaction was left with stirring at room temp. overnight, filtered, washed with a small volume of MeOH and dried in high vacuum; 25 g, 65%, m.p. 184° (dec) with swelling IR (KBr): 3415, 3320, 1725, 1635, 1565 cm^{-1}; NMR (DMSO-d_6): δ 7.00 (d, 1, NH, J = 9 c/s); 5.93 (broad s, 2, NH_2); 5.16 (d, 1, CH, J = 9 c/s); 3.23 (s, 3, OCH_3); (D_2O) 5.44 (s, 1, CH); 3.30 (s, 3, OCH_3). (Found: C, 32.05; H, 5.31; N, 19.06. $C_4H_8N_2O_4$ requires: C, 32.43; H, 5.44; N, 18.91%).

Methyl α-hydroxyhydantoate (**5a**). Freshly prepared methyl glyoxylate methoxyhemiacetal (26 g, 0.217 mol) and urea (13.65 g, 0.228 mol) were dissolved in acetone (120 ml) and stirred for 48 hr. The partially precipitated product was filtered off (15.5 g, 48.5%). The mother liquid was concentrated, the residue was triturated twice with ether and then with acetone yielding another crop of the compound (8.4 g, 26.3%), m.p. 108–111° (dec). IR (KBr): 3445, 3340 sh, 3280, 3200 sh, 1740, 1645, 1590, 1545 cm $^{-1}$. NMR (DMSO-d_6) δ: 6.88 (d, 1, NH, J = 9 c/s); 6.40 (d, 1, OH, J = 6.6 c/s); 5.85 (s, 2, NH_2); 5.43 (q, 1, CH, J = 9 and 6.6 c/s); 3.68 (s, 3, OCH_3). (Found: C, 32.52; H, 5.40; N, 18.87. $C_4H_6N_2O_4$ requires: C, 32.43; H, 5.44; N, 18.91%).

Methyl α-methoxyhydantoate (**6a**). Compound **5a** (579 mg, 3.9 mmol) and anhyd oxalic acid (36 mg, 0.4 mmol) were dissolved in MeOH (15 ml) and left overnight. EtOAc (15 ml) was added and the mixture was neutralized with anhyd $NaHCO_3$, filtered and concentrated. The residue was triturated twice with EtOAc yielding 375 mg, 60% of product m.p. 113–115°. IR (KBr): 3420, 3340 sh, 3280, 1740, 1665, 1600, 1550 cm $^{-1}$. NMR (DMSO-d_6) δ: 7.13 (d, 1, NH, J = 9 c/s); 5.95 (broad s, 2, NH_2); 5.25 (d, 1, CH, J = 9 c/s); 3.70 (s, 3, OCH_3); 3.25 (s, 3, OCH_3); (D_2O) δ: 5.45 (s, 1, CH); 3.95 (s, 3, OCH_3); 3.55 (s, 3, OCH_3). (Found: C, 36.77; H, 6.09; N, 17.50; $C_5H_{10}N_2O_4$ requires: C, 37.03; H, 6.22; N, 17.28%).

The same ester (**6a**) was also prepared when **4** (500 mg) was dissolved in MeOH (100 ml), filtered from the small amount of undissolved solid and treated with freshly prepared etheral soln of diazomethane. After 3 hr the contents were filtered and concentrated. The residue was triturated with EtOAc yielding 480 mg, 87% of **5a**, m.p. 113–115°.

Methyl-α-methylthiohydantoate (**7a**). Methyl-α-methoxyhydantoate (330 mg) and anhyd oxalic acid (160 mg) was treated with CH_2Cl_2 soln, saturated with methyl mercaptan (50 ml) for 72 hr at room temp. The solvent was removed, EtOAc (30 ml) was added and a few drops of MeOH until all solids were dissolved. The soln was washed with 10% $NaHCO_3$, dried over Na_2SO_4 and evaporated. The residue was triturated with ether yielding **7a** 302 mg, 84%, m.p. 159°. IR (KBr): 3430, 3290, 3210 sh, 1725, 1655, 1595 cm $^{-1}$. NMR (DMSO-d_6) δ: 7.00 (d, 1, NH_2); 6.90 (s, 2, NH_2); 5.30 (d, 1, CH), 4.70 (s, 3, OCH_3); 2.18 (s, 3, SCH_3). (Found: C, 34.10; H, 5.73; N, 15.40; S, 18.17. $C_5H_{10}N_2O_3S$ requires: C, 33.71; H, 5.66; N, 15.73; S, 17.96%).

The same compound was prepared in two steps when **4** (725 mg) was treated with the mixture of MeOH (25 ml) and methylene chloride soln saturated with methyl mercaptan (25 ml). The mixture was stirred for 72 hr, then the solvent was evaporated and the residue was triturated with absolute ether yielding 706 mg, 87.5%, m.p. 138° (dec). IR (KBr): 3450, 3370, 3320 sh, 3230 sh, 1690, 1640, 1525 cm $^{-1}$. NMR (DMSO-d_6) δ: 6.95 (d, 1, NH); 5.98 (s, 2, NH_2); 5.26 (d, 1, CH); 2.13 (s, 3, SCH_3). (D_2O) δ: 5.20 (s, 1, CH); 2.06 (s, 3, SCH_3). The acid (140 mg) was suspended in MeOH (50 ml) and treated with freshly prepared diazomethane etheral soln. After standing overnight the soln was filtered, evaporated and the residue was triturated with ether yielding **7a** 77 mg, m.p. 159°.

δ',δ'-Dimethylallantoic acid (**8c**). A soln of glyoxylic acid monohydrate (4.6 g, 0.05 mol) and monomethylurea (dry; 7.4 g, 0.1 mol) in 40 ml water was stirred at room temp. for 24 hr. After a short time the product precipitated from an initially clear yellowish soln. It was collected by filtration, washed and dried over P_2O_5 to afford 6.5 g (64%) crude, m.p. 116°. Upon drying in high vacuum (0.2 mm Hg) the m.p. was raised to 132–133°. IR (KBr): 3480, 3450, 2950, 2905, 2500 (sh), 1710, 1600, 1500, 1410, 1330, 1240, 1200, 1090 cm $^{-1}$. NMR (DMSO-d_6) δ: 6.8 (*d*, J = 8 cps, 2H); 6.17 (*q*, J = 4 c/s, 2H); 5.34 (*t*, J = 8 c/s, 1H); 2.57 (*d*, J = 4 c/s, 6H), with the addition of D_2O to the sample the triplet changes into a singlet and the doublet of Me to a wide singlet, in the presence of base one sees only two singlets one for Me and one for CH; MS (HR): no molecular peak or any other significant peak can be detected. (Found: C, 35.14; H, 5.98; N, 27.47. $C_6H_{12}N_2O_4$ requires: C, 35.29; H, 5.92; N, 27.44%).

Methyl δ,δ'-Dimethylallantoate (**8d**). A suspension of methyl glyoxylate monoacetal (1.2 g; 0.01 ml), monomethylurea (1.48 g, 0.02 m) and BF_3–OEt_2 (0.11 ml; 0.001 mol) in 40 ml EtOAc was stirred at ambient temp. 24 hr. Even before complete soln occurred, the product started to precipitate as an amorphous solid. It was collected by filtration and amounted to 1.5 g (69%) crude, m.p. 201–203°. Purification by trituration in ether yielded 1.4 g (64%) pure product, m.p. 209–210°; IR (KBr): 3340, 3150, 2960, 2930, 2880, 1740, 1600, 1430, 1360, 1330, 1215, 1090, 1040, 1000, 970, 770 cm $^{-1}$; NMR (DMSO-d_6) δ: 6.68 (d, J = 8 c/s, 2H); 5.99 (m, J = 4 c/s, 2H); 5.25 (t, J = 8 c/s, 1H); 3.48 (s, 3H); 2.4 (d, J = 4 c/s, 6H); MS (HR): (*m/e*-MeOH) 186.0750 for $C_6H_{10}N_2O_4$ Calc. 186.0753. (Found: C, 38.48; H, 6.42; N, 25.91. $C_7H_{14}N_2O_4$ requires: C, 38.53; H, 6.47; N, 25.68%).

Alternatively the bis-adduct ester can be obtained from the bis-adduct acid with diazomethane. When a methanolic soln of the latter (0.644 g, 0.00315 mol) was treated with an ethereal soln of CH_2N_2, after 3 hr the color faded and a white ppt formed was collected, it amounted to 0.231 g (34%) m.p. 220° and was identified by its spectral data as the ester. From the filtrate was obtained the main product, 5-methylureido-3-methyl hydantoin.

Methyl α-hydroxy-δ-methylhydantoate (**5c**). A soln of methyl glyoxylate hemiacetal (9.0 g, 0.075 mole) and monomethylurea (5.55 g, 0.075 mol) in 110 ml EtOAc was stirred at room temp. for 48 hr. The initial suspension became clear after a few hr, and then suddenly the product started to precipitate out of the soln (it can also occur before complete soln is obtained). The solid was collected by filtration and dried (high vacuum), it amounted to 9.703 (80.2%) white crystalline crude, m.p. 112–114°, the m.p. is not very constant for different reactions although each time it is quite sharp and it ranges from 98–99° to 103–105° till 112–114°; IR (KBr): 3420, 3320, 3259, 3100, 2960, 2925, 2860, 2780, 1730, 1680, 1600, 1500, 1440, 1420, 1340 cm $^{-1}$; NMR (DMSO-d_6) δ: 6.8 (d, J = 9 c/s, 1H); 6.34 (d, J = 6.5 c/s, 1H); 6.09 (m, 1H); 5.49, 5.39 (d of d, J = 9 c/s, J = 6.5 c/s, 1H); 3.72 (s, 3H); 2.6 (d, J = 4 c/s, 3H); MS (HR): (*m/e*-H_2O) 144.0524 for $C_5H_8N_2O_4$ Calc. 144.0534. (Found: C, 37.10; H, 6.21; N, 17.41. $C_5H_{10}N_2O_4$ requires: C, 37.03; H, 6.22; N, 17.28%).

Methyl α-methoxy-δ-methylhydantoate (**6c**). Methyl α-hydroxy-N-methylhydantoate (1.638 g, 0.01 mol) prepared as described was dissolved in abs MeOH (20 ml) and combined with oxalic acid (0.090 g, 0.001 mol). The reaction was allowed to proceed at room temp. with stirring, 24 hr, before it was carefully neutralized with solid $KHCO_3$ so as not to get near basic pH (at which ring closure to the hydantoin was shown to occur). After neutralization time of 25 min, the mixture was filtered from insoluble solids, concentrated *in vacuo* at an external temp. of 30–35° and the residual white solid dissolved in EtOAc (200 ml). The organic soln was dried over $MgSO_4$, filtered and evaporated to dryness to yield 1.569 g (89.2%) crude product m.p. 93–94°. For analysis the product was triturated under ether and the m.p. raised to 96.5–97.5°; IR ($CHCl_3$): 3430, 2995, 2955, 2840, 1750, 1675, 1550, 1525, 1440, 1350, 1200 (wide), 1085, 1020 cm $^{-1}$; NMR ($CDCl_3$) δ: 6.46 (d, J = 9 c/s, 1H); 5.64 (q, J = 4.5 c/s, 1H); 5.5 (d, J = 9 c/s, 1H), 3.84 (s, 3H); 3.47 (s, 3H); 2.82 (d, J = 4.5 c/s, 3H); MS (HR): (*m/e*-CH_3) 161.0567 for $C_5H_9N_2O_4$ Calc. 161.0527, also (*m/e*-OCH_3) 145.0584 for $C_5H_9N_2O_3$ Calc. 145.0603. (Found: C, 41.16; H, 6.92; N, 15.96. $C_6H_{12}N_2O_4$ requires: C, 40.90; H, 6.87; N, 15.90%).

Methyl α-methylthio-δ-methylhydantoate (**7c**). A soln of methyl α-methoxy-N-methylhydantoate (1.76 g, 0.01 mol) in CH_2Cl_2 (20 ml) was treated with oxalic acid (0.090 g, 0.001 mol) anhyd and methyl mercaptan in CH_2Cl_2 soln (8 eq.). The soln was stirred at room temp. 48 hr, before the solvent was removed *in vacuo* with external heating. The solid residue was dissolved in EtOAc 200 ml, neutralized with solid $KHCO_3$ and dried over $MgSO_4$. The organic soln was filtered from all solids and evaporated to dryness. The crude was triturated under ether, collected, it amounted to 1.395 g (72.6%), m.p. 109.5–111°. For analysis the product was recrystallized from EtOAc, m.p. 112–113°; IR ($CHCl_3$): 3450, 3410, 3000, 2960, 2920, 2850, 1740, 1680, 1550, 1520, 1440, 1335, 1185 cm $^{-1}$; NMR ($CDCl_3$) δ: 6.21 (d, J = 8 c/s, 1H); 5.50 (d, J = 8 c/s, 1H); 5.63 (m, 1H); 3.82 (s, 3H); 2.83 (d, J = 4.5 c/s, 3H); 2.18 (s, 3H); MS (HR): *m/e* 192.0565 for $C_6H_{12}N_2O_3S$ Calc. 192.0568. (Found: C, 37.76; H, 6.29; N, 14.44; S, 16.77. $C_6H_{12}N_2O_3S$ requires: C, 37.50; H, 6.29; N, 14.58; S, 16.65%).

Alternatively, when a suspension of methyl α-hydroxy N-methylhydantoate (1.62 g, 0.01 mol) is taken under the exact

conditions described and the reaction is allowed to proceed 7 days, the same workup afforded 0.631 g (33%) product (together with a second crop 48.1%) which was identical in all respects with the above compound, m.p. 108.5–110°, MS (HR): *m/e* 192.0574 for $C_8H_{12}N_2O_3S$ Calc. 192.0568.

5-Iso-propylthio-3-methylhydantoin (**13a**). A soln of 5-methoxy-3-methylhydantoin (1.45 g, 0.01 mol) in chloroform (40 ml) together with isopropyl mercaptan (1.8 ml, 0.02 mol) and BF_3 ethereate (0.13 ml, 0.001 mol) was subjected to reflux during 48 hr. The solvent was removed *in vacuo* and the resulting solid dissolved in EtOAc. The soln was neutralized with solid $KHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow viscous oil which under ether yielded 0.982 g (52%) crystalline product, m.p. 81–83° together with a second crop 0.245 g, m.p. 67–78°, the yield raised to 65%. For analysis the compound was recrystallized from CH_2Cl_2: hexane, m.p. 85.5–86.5°, IR ($CHCl_3$): 3440, 2960, 1790, 1725, 1460, 1400, 1310, 1200 cm^{-1}; NMR ($CDCl_3$) δ: 6.98 (sh, 1H, NH); 5.09 (q, J = 0.5 c/s, 1H, CH); 3.15 (m (7 peaks), J = 6.5 c/s, 1H, CH–S); 3.07 (s, 3H, OCH_3); 1.33 (d, J = 6.5 c/s, 6H $(CH_3)_2CH$); MS (HR): *m/e* 188.0622 for $C_7H_{12}N_2O_2S$ Calc. 188.0619. (Found: C, 44.54; H, 6.50; N, 15.09; S, 17.12. $C_7H_{12}N_2O_2S$ requires: C, 44.68; H, 6.43; N, 14.88; S, 17.005%).

5-Methoxy-3-methylhydantoin (**12a**). A soln of glyoxylic acid monohydrate (9.2 g, 0.1 mol), and monomethylurea (3.7 g, 0.05 mol) in MeOH (25 ml), was stirred at ambient temp. for 48 hr. The clear yellowish mixture thus obtained was concentrated *in vacuo*, care being taken not to overheat the soln. The crude oil was taken up in EtOAc, dried over $MgSO_4$ and the solvent evaporated to dryness. The resulting crude was purified on a neutral deactivated alumina column chromotography (250 g, 25 ml MeOH) and the product eluted with methylene chloride. Trituration under hexane of the pure fractions yielded 48.5% pure hydantoin,[4] m.p. 68.5–70°; IR ($CHCl_3$): 3440, 2940, 2840, 1800, 1735, 1465, 1400, 1360, 1320, 1080 cm^{-1}; NMR ($CDCl_3$) δ: 7.15 (sh, 1H); 5.2 (d, J = 1 c/s, 1H); 3.45 (s, 3H); 3.04 (s, 3H); MS (HR): (*m/e* + H) 145.0577 for $C_5H_9N_2O_3$ Calc. 145.0613 or (*m/e*-H^+) 143.0434 for $C_5H_7N_2O_3$ Calc. 143.0436. (Found: C, 41.75; H, 5.72; N, 19.41. $C_5H_8N_2O_3$ requires: C, 41.66; H, 5.59; N, 19.44%).

In an attempt to increase the yield of the 5-methoxy-3-methylhydantoin by trapping the side product, probably the 5-hydroxy derivative formed as well in the reaction, 5 equivalents of thionyl chloride were added to the methanolic reaction mixture and the latter allowed to proceed 24 hr more. The usual workup afforded 1.5 g (83.5%) crude which according to NMR contained at the most 70% product. Purification on a column, as described, yielded 45.1% white solid from hexane trituration (or 53.6% as an oil). The last fraction afforded 6.8% of the isomeric 5-methoxy-1-methyl hydantoin whose identification was proved by conversion with diazomethane to the known 5-methoxy-1,3-dimethyl-hydantoin.

Proof for the isolation of 5-methoxy-1-methylhydantoin as a minor side product in the preparation of 5-methoxy-3-methyl hydantoin. When 5-methoxy-3-methylhydantoin was purified on column chromatography, toward the end of the elution together with the product a small amount (3.4%) of the isomeric hydantoin 5-methoxy-1-methylhydantoin was observed as an equal component in several fractions. The formation of the latter can be explained by ring closure of a different adduct, the one in which N–Me is attached to the CH–. Since during the study we have prepared 5-methoxy-1,3-dimethylhydantoin and we have also shown that 5-methoxy-3-methylhydantoin cannot be converted to the former under the action of diazomethane we thought that the N^1-imidic nitrogen of the isomeric hydantoin, if present, would indeed be converted to the N^1-Me derivative. When the fractions containing the equal mixture of 5-methoxy-1(3)hydantoins were subjected to diazomethane treatment, a new mixture with unchanged 5-methoxy-3-methylhydantoin NMR ($CDCl_3$) δ: 7.2 (sh, 1H); 5.18 (d, J = 3 c/s, 1H); 3.47 (s, 3H); 3.05 (s, 3H) and 5-methoxy-1,3-dimethylhydantoin NMR ($CDCl_3$) δ: 4.95 (s, 1H); 3.37 (s, 3H); 3.02 (s, 3H); 2.92 (s, 3H), still in equal ratio was obtained and identified. Extraction with petrol-ether afforded pure 5-methoxy-1,3-dimethylhydantoin.

The chemical stability of methyl α-methoxy-δ-methylhydantoate (**6c**)

(A) A sample of methyl α-methoxy-δ-methylhydantoate (0.88 g, 0.05 mol) dissolved in 10 ml MeOH was treated with a catalytic amount of $KHCO_3$ (a few mg of solid) and then allowed to react for 1 hr at rt, whereupon it was filtered, washed with MeOH and concentrated *in vacuo* keeping the external bath temp. under 40°. The crude thus obtained was dissolved in EtOAc, dried ($MgSO_4$) and again evaporated to dryness, its NMR spectrum indicated the absence of any starting material and the presence of 5-methoxy-3-methylhydantoin, in $CDCl_3$, δ: 7.20 (sh, 1H); 5.24 (d, J = 1 c/s, 1H); 3.43 (s, 3H); 3.07 (s, 3H), which upon trituration in pet. ether yielded 61% powdered solid, m.p. 73–74°.

The important conclusion from this experiment, is that the monoadduct in weak basic conditions is totally converted into the ring closed hydantoin. The various amounts of hydantoin obtained together with the expected monoadduct during its preparation is now explained and clearly can be minimized when neutralization is done with extreme care.

(B) A soln of methyl α-methoxyhydantoate (0.622 g, 0.00352 mol) in 8 ml MeOH was treated with BF_3–OEt_2 (0.40 ml) and allowed to react 24 hr at room temp. The mixture was evaporated to dryness under reduced pressure and the resulting crude oil analyzed by its NMR spectrum, ($CDCl_3$) δ: 5.54 (sh, 1H); 5.24 (wide s, 1H); 3.49 (s, 3H); 3.05 (s, 3H), it showed the total conversion of starting material to the ring closed product 5-methoxy-3-methylhydantoin. The crude oil was taken up in EtOAc, neutralized with $KHCO_3$ (solid), dried ($MgSO_4$) and concentrated *in vacuo*, to afford after trituration in ether 0.253 g, (50%), pure hydantoin: NMR ($CDCl_3$) δ: 7.06 (sh, 1H); 5.19 (d, J = 1 c/s, 1H); 3.48 (s, 3H); 3.05 (s, 3H).

Preparation of 5-(3-methylureido)hydantoin (**9**)

(A) A suspension of methyl bis-(δ-monomethylureido)acetate (0.545 g, 0.0025 mol) in 10 ml MeOH was treated with a catalytic amount of $KHCO_3$ (solid, few mg), so as to afford a weak basic pH 7–8, and stirred at rt overnight. The suspended solid was collected by filtration, well dried, it amounted to 0.368 g (79.1%), product, m.p. 224°, NMR (DMSO-d_6) δ: 8.27 (wide s, 1H); 6.96 (d, J = 8 c/s, 1H); 6.16 (m, J = 4 c/s, 1H); 5.34 (d, J = 8 c/s, 1H); 2.85 (s, 3H); 2.4 (d, J = 4 c/s, 3H) identified as the ring closure compound 5-(N-methylureido)-3-methyl hydantoin. No indication for the presence of hydantoin in soln was observed.

Again the important conclusion from this experiment, is that the bis-adduct behaves as the monoadduct under similar conditions, although solubility character of both starting material and product are quite different and dictate an heterogeneous reaction.

(B) A suspension of methyl bis-(δ-monomethylureido)acetate (0.545 g, 0.0025 mol) in 10 ml MeOH was treated with BF_3–OEt_2 (0.03 ml) and the reaction allowed to proceed overnight at rt. The white solid was filtered off, washed with MeOH and triturated in abs ether to afford 0.251 g (46.1%) white solid, m.p. 218°, which according to its NMR spectrum (DMSO-d_6) δ: 6.88 (d, J = 8 c/s, 2H); 6.16 (q, J = 4 c/s, 2H); 5.4 (t, J = 8 c/s, 1H); 3.65 (s, 3H); 2.57 (d, J = 4 c/s, 6H), was identified as starting material. No other products could be detected to be present, nor isolated. The important conclusion of the experiment is the fact that under acidic solution, there is no parallel behavior of the bis-adduct and monoadduct as in basic conditions. Moreover, the bis-adduct itself has different susceptibility to basic and acidic media.

(C) A suspension of bis-adduct derived from glyoxylic acid and monomethylurea (1.02 g, 0.005 mol) in 10 ml MeOH was treated with H_2SO_4 (96%, 0.01 ml) and stirred at ambient temp. 48 hr. The insoluble white solid was collected by filtration and amounted to 0.245 g (26.4%) of product, m.p. 217–222° identified by its spectral data. The compound was recrystallized from MeOH, m.p. 230.5° (sharp); IR (KBr): 3395, 3320, 3295, 2970, 2950, 2800, 1775, 1735, 1710, 1670, 1550, 1485, 1465, 1400, 1360, 1310, 1265, 1105, 1085 cm^{-1}; NMR (DMSO-d_6) δ: 8.3 (s (wide), 1H); 6.9 (d, J = 8 c/s, 1H); 6.14 (q, J = 5 c/s, 1H); 5.3 (d of d, J = 8 c/s, J = 1 c/s, 1H); 2.82 (s, 3H); 2.55 (d, J = 5 c/s, 3H); MS (HR): *m/e* 186.0754 for $C_6H_{10}N_4O_3$ Calc. 186.0753. (Found: C, 38.59; H, 5.32; N, 30.14. $C_6H_{10}N_4O_3$ requires: C, 38.71; H, 5.41; N, 30.10%).

1,3-Dimethyl-5-hydroxyhydantoin (**11b**). A soln of glyoxylic acid monohydrate (4.6 g, 0.05 mol) and sym-dimethylurea (4.4 g, 0.05 mol) in acetone (50 ml) was refluxed during 4 hr. The mixture was allowed to reach room temp., then filtered and concentrated *in vacuo* to afford a yellowish oil. The crude was dissolved in EtOAc and the pH (slightly acidic) of the soln was adjusted with solid $KHCO_3$, the soln was dried, $MgSO_4$, and evaporated to dryness. The crude oily product was triturated under ether and solidified slowly (24 hr), the white solid was collected, it amounted to 4.84 g (67%) product m.p. 58.5–60°. For analysis the compound was triturated under ether and well dried (0.2 mm Hg), m.p.: 63.5–65°; IR ($CHCl_3$): 1785, 1725, 1485, 1465, 1450, 1060 cm^{-1}; NMR ($CDCl_3$) δ: 5.49 (sh, 1H); 5.16 (s, 1H); 3.00 (s, wide, 6H); NMR (DMSO-d_6) δ: 7.04 (d, J = 9 c/s, 1H); 5.13 (d, J = 9 c/s, 1H); 2.95 (s, 3H); 2.92 (s, 3H), decoupling experiment by irradiation of the 7.04 d converted the 5.13 doublet into a singlet and *vice versa*; MS (HR): *m/e* 144.0539 for $C_5H_8N_2O_3$ Calc. 144.0535. (Found: C, 41.82; H, 5.61; N, 19.50. $C_5H_8N_2O_3$ requires: C, 41.66; H, 5.59; N, 19.44%).

1,3-Dimethyl-5-methoxyhydantoin (**12b**). A soln of 5-hydroxy-1,3-dimethyl-hydantoin (0.277 g, 0.00157 mol) in 5 ml MeOH and a catalytic amount of H_2SO_4 (2 drops, 96%) was subjected to reflux overnight. The acidic soln was neutralized with solid $KHCO_3$, filtered from solids and concentrated *in vacuo*, care being taken not to overheat the sample. The residue was dissolved in EtOAc, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The crude 0.202 g (81.2%) crystallized only in the freezer, but at room temp. it melted into an oil, it was pure enough, however, to be used as such. For analysis, it was recrystallized from pet. ether in the freezer, m.p. oil at rt; IR ($CHCl_3$): no NH, 2940, 2840, 1770, 1750 cm^{-1}; NMR ($CDCl_3$) δ: 5.00 (s, 1H); 3.37 (s, 3H); 3.03 (s, 3H); 2.99 (s, 3H). MS (HR): *m/e* 158.0676 for $C_6H_{10}N_2O_3$ Calc. 158.0691. (Found: C, 45.29; H, 6.29; N, 17.58. $C_6H_{10}N_2O_3$ requires: C, 45.56; H, 6.37; N, 17.71%).

It is interesting to note that upon treatment in MeOH with BF_3–OEt_2 overnight at room temp. there was no conversion to the methoxy derivative. Also H_2SO_4 (96%) in MeOH overnight at room temp. gave only 20% product. However, an ethereal soln of diazomethane added to a MeOH solution of the hydroxy derivative was as effective as the above procedure in obtaining the methoxy compound.

1,3-Dimethyl-5-isopropylthiohydantoin (**13b**). A sample of 1,3-dimethyl-5-methoxyhydantoin (0.819 g, 0.00518 mol) was dissolved in benzene (20 ml, AnalaR) together with isopropyl mercaptan (0.9 ml) and boron BF_3–OEt_2 (0.07 ml), and the resulting cloudy soln was refluxed 48 hr. After removing the solvent *in vacuo*, the obtained oil was dissolved in EtOAc (100 ml), extracted with $NaHCO_3$ aq. (10 ml, 1 M), with water (10 ml) and dried over $MgSO_4$. The organic solvent was evaporated to dryness to afford 0.546 g (52.1%) crude product obtained as an oil. NMR ($CDCl_3$) δ: 4.86 (s, 1H, CH); 3.8 (s, 3H, CH_3NCO); 3.05 (s, 3H, CH_3–$N\begin{matrix}CO\\CO\end{matrix}$) together with another H of $SCH(CH_3)_2$; 1.33 (d, J = 7 c/s, 6H, $(CH_3)_2CHS$–)[†] MS (HR): *m/e* 202.0780 for $C_8H_{14}N_2O_2S$ Calc. 202.0776; IR ($CHCl_3$): no NH, 2965, 2930, 2870, 1775, 1730 cm^{-1}.

For analysis the oil was eluted through a fluorisil column chromatography with CH_2Cl_2. (Found: C, 47.63; H, 6.93; N, 13.49; S, 15.6. $C_8H_{14}N_2O_2S$ requires: C, 47.52; H, 6.98; N, 13.86; S, 15.825%).

The reaction was repeated with bicarbonate or water extraction to yield 85% crude oily product.

δ,δ,δ',δ'-Tetramethylallantoate (**8c**). A suspension of glyoxylic acid monohydrate (9.66 g, 0.105 mol), dimethylurea (unsym) (17.6 g, 0.2 mol) and naphthalenesulfonic acid (1.13 g) in 75 ml acetone (dist. over K_2CO_3) was stirred at room temp. (24 hr). The dimethylurea slowly went into soln but soon the bisadduct acid precipitated out. The solid was collected, it yielded 16.4 g (70.6%) crude acid, m.p. 146–147°; IR (KBr): 3455, 3335, 2940, 2550, 1740, 1640, 1600, 1525, 1395, 1345, 1290, 1245, 1225, 1200, 1150, 1000, 960, 910, 780, 765 cm^{-1}; NMR (DMSO-d_6) δ: 6.82 (d, J = 7 c/s, 2H); 5.46 (t, J = 8 c/s, 1H); 2.84 (s, 12H); MS (HR): (*m/e*-CO_2) 188.1252 for $C_7H_{16}N_4O_2$ Calc. 188.1273; (Found: C, 41.53; H, 6.90; N, 24.34. $C_8H_{16}N_4O_4$ requires: C, 41.37; H, 6.94; N, 24.13%).

Methyl δ,δ,δ',δ'-tetramethyl allantoate (**8d**). A soln of methyl-glyoxylate monoacetal (1.2 g, 0.01 mol) and dimethylurea (1.76 g, 0.02 mol) together with BF_3–OEt_2 (0.125 ml, 0.001 mol) in 50 ml benzene was subjected to reflux (oil bath) during 3 hr. The soln was decanted and evaporated to dryness to afford an oil which triturated with several portions of ether yielded a crystalline product which amounted to 20 g (81.4%), m.p. 155°. For analysis the product was recrystallized from EtOAc m.p. 150.5–151.5°, IR ($CHCl_3$): 3440, 2950, 1745, 1650, 1600, 1510, 1380, 1310 cm^{-1}; NMR ($CDCl_3$) δ: 6.38 (d, J = 7 c/s, 1H); 5.51 (t, J = 7 c/s, 1H); 3.82 (s, 3H); 2.93 (s, 12H); MS (HR): *m/e* 246, 1337 for $C_9H_{18}N_4O_4$ Calc. 246.1327; (Found: C, 44.06; H, 7.36; N, 23.09. $C_9H_{18}N_4O_4$ requires: C, 43.89; H, 7.37; N, 22.75%). The crude oil obtained from the reaction can be purified as well on a deactivated (5%) neutral alumina column chromatography. The bisadduct ester is accompanied by methyl α-methoxy monoadduct which is easily removed with ether. The yields thus obtained are 64.8% bisadduct, m.p. 155° and 12.4% monoadduct ester m.p. 68–71°.

Alternatively the bisadduct ester can be prepared by diazomethane esterification of the acid. A methanolic soln of bisadduct 1.2 g treated with CH_2N_2, filtered and concentrated *in vacuo* afforded, after trituration in ether, a yellowish solid 1.2 g (94.6%) m.p. 143.5–148.5°, with the similar physical data as above.

Methyl α-hydroxy-δ,δ-dimethylhydantoate (**5b**). A suspension of methyl glyoxylate monoacetal (12 g, 0.1 mol) and dimethylurea (4.4 g, 0.05 mol) in 75 ml EtOAc was stirred at room temp. for 72 hr. After a few hours the mixture cleared up, almost completely, it was filtered and concentrated *in vacuo* to yield a clear oil which upon trituration under ether afforded a nice white crystalline solid which collected, amounted to 7.26 g, (83.6%) product, m.p.: 88–91°. For analysis the compound was triturated in ether and the m.p. was raised to 94–95°, IR (KBr): 3440, 3300, 3190, 2930, 2810, 2700, 1750, 1620, 1510, 1380, 1285, 1215, 1195, 1070, 1005, 955, 905 cm^{-1}; NMR ($CDCl_3$) δ: 6.0 (d, 1H); 5.59 (d, J = 7.5 c/s, 1H); 5.25 (sh, 1H); 3.82 (s, 3H), 2.94 (s, 6H); (DMSO-d_6) δ: 6.98 (d, J = 8 c/s, 1H); 5.84 (sh, 1H); 5.2 (d, J = 8 c/s, 1H), 3.5 (s, 3H); 2.67 (s, 6H); MS (HR): *m/e* 176.0769 For $C_6H_{12}N_2O_4$ Calc. 176.0796. (Found: C, 41.19; H, 6.92; N, 15.74. $C_6H_{12}N_2O_4$ requires: C, 40.90; H, 6.87; N, 15.90%).

Methyl α-methoxy-δ,δ-dimethylhydantoate (**6b**). A soln of methyl α-hydroxy-δ,δ-dimethylhydantoate (0.88 g, 0.005 mol) in 10 ml MeOH abs. was combined with oxalic acid (0.045 g, 0.0005 mol) and the reaction was allowed to proceed at room temp., with stirring 24 hr. The acidic soln was neutralized with solid $KHCO_3$ (care to the basicity of the soln is not as important as in the mono-substituted hydantoate, since the ring closure to hydantoin shown to occur under these conditions is impossible), filtered from insoluble solid and carefully, without external heating, evaporated to dryness. The crude residue was dispersed in EtOAc, dried over $MgSO_4$ and again concentrated *in vacuo* carefully because the lability of the product. The crude was triturated under pet. ether to afford a well dispersed solid, which was collected to yield 0.687 g (72.5%) m.p. 71°, product. Further purification raised the m.p. 74–75.5°; IR ($CHCl_3$): 3445, 3050, 2980, 2930, 2835, 1745, 1655, 1645, 1520, 1440, 1385, 1320 cm^{-1}; NMR ($CDCl_3$) δ: 5.78 (d, J = 9 c/s, 1H); 5.5 (d, J = 9 c/s, 1H); 3.82 (s, 3H); 3.48 (s, 3H); 2.98 (s, 6H); MS (HR): *m/e* 190.0943 for $C_7H_{14}N_2O_4$ Calc. 190.0953. (Found: C, 44.40; H, 7.41; N, 14.82. $C_7H_{14}N_2O_4$ requires: C, 44.20; H, 7.42; N, 14.73%).

The monoadduct can be obtained alternatively from the corresponding bisadduct acid.

A soln of bisadduct acid (9.28 g, 0.04 mol) prepared as described previously, in 80 ml abs MeOH and 1 ml H_2SO_4 (merk 96%) was refluxed 48 hr. When the temp. reached the rt, the soln was neutralized with solid $KHCO_3$, filtered from solids and concentrated *in vacuo*. A rough purification was affected on a deactivated neutral alumina column (420 g, 21 ml MeOH). With pet. ether:benzene (1:1) as eluent 4.216 g (55.5%) pure product was obtained. It was followed by 1.334 g (13.2% product) product

[†]When the d at 1.33 was irradiated the m hidden under MeN at 3.05 δ disappeared and turned into a singlet.

contaminated with 15–33% bisadduct ester (benzene as eluent), 0.102 g (1.02%) pure bisadduct ester and 0.381 g (3.9%) contaminated bisadduct. Additional purification on a fluorisil column (200 g) using CH_2Cl_2 as eluent yielded only 2.803 (37%) pure product m.p. 74–75.5° with identical physical data as described above. It was preceded by 0.101 g (1.43%) methyl α-methoxy-N-methoxycarbonylglycinate.

Methyl α-methylthio-δ,δ-dimethylhydantoate (**7b**). A soln of methyl α-methoxy-δ,δ-dimethyldantoate (1.98 g, 0.01 mol) in 40 ml CH_2Cl_2 (EtOH free) was combined with methyl mercaptan (8 eq) in CH_2Cl_2, and oxalic acid (0.090 g, 0.001 mol) to afford an almost homogeneous mixture. After 48 hr at ambient temp., the solvent was removed *in vacuo* without applying any external heating, and the residual yellowish oil was dissolved in EtOAc. The acidic soln was neutralized with solid $KHCO_3$ (heterogeneous), dried over $MgSO_4$, filtered and concentrated *in vacuo*, the crude according to the NMR spectrum proved to be a mixture of starting material (45.2%) and product (54.8%). No attempts were made to separate it, and as such the mixture was subjected to the exact initial conditions. After 5 days it was worked up again as described to yield 1.905 g (92.4%) crude product, oil. IR ($CHCl_3$): 3400, 2950, 2910, 2885, 1740, 1665, 1510–1500, 1435, 1370, 1300, 1160 cm^{-1}; NMR ($CDCl_3$) δ: 5.58 (d, wide, 1H); 5.5 (s, wide, 1H); 3.83 (s, 3H); 2.98 (s, 6H); 2.21 (s, 3H); MS (HR): *m/e*: 206.0751 for $C_7H_{14}N_2O_3S$ Calc. 206.0724. For analysis, it can be recrystallized from pet. ether–ether at lower temperature, m.p. 38°. (Found: C, 40.67; H, 6.88; N, 13.72; S, 15.73. $C_7H_{14}N_2O_3$ requires: C, 40.77; H, 6.84; N, 13.59; S, 15.52%).

Butyl α-hydroxyhydantoate (**14a**). Butyl ester **4b** was prepared in 63% yield according to the previous method using butylglyoxalate† and urea in 10% excess m.p. 113° (recrystallized from water). IR (KBr): 3440, 3300, 2960, 1735, 1640, 1550 cm^{-1}. NMR (DMSO-d_6) δ: 6.82 (d, 1, NH, J = 9 c/s); 6.34 (d, 1, OH, J = 6.6 c/s); 5.78 (s, 2, NH_2); 5.40 (9, 1, CH, J = 9 and 6.6 c/s); 4.09 (t, 2, OCH_2); 0.7–1.9 (m, 7 $(CH_2)_2CH_3$); (Found: C, 44.32; H, 7.42; N, 14.70. $C_7H_{14}N_2O_4$ requires: C, 44.20; H, 7.42; N, 14.73%).

Bisadduct **15**. Urea (3 g, 0.05 mol) and *n*-butyl glyoxalate (14.3 g, 0.11 mol) were dissolved in acetone (150 ml) and stirred for 72 hr. The ppt was filtered off and triturated with a new portion of acetone (30 ml) yielding 7.4 g, 46%. Another crop of the compound was obtained after the mother liquid was concentrated and the residue was triturated three times with ether–pet. ether to remove the excess of butyl glyoxalate (4.1 g, 25%); m.p. 143° (recrystallized from EtOAc). IR (KBr): 1740, 1650, 1580 cm^{-1}. NMR (DMSO-d_6) δ: 7.18 (d, 1, NH); 5.38 (d, 1, CH); 5.1 (broad, 1, OH); 4.12 (t, 2, OCH_2); 0.6–1.8 (m, 7, $(CH_2)_2CH_3$). (Found: C, 48.80; H, 7.58; N, 8.70. $C_{11}H_{24}N_2O_7$ requires: C, 48.74; H, 7.55; N, 8.75%).

Butyl α-methoxyhydantoate (**14b**). Compound **4b** (8.8 g, 0.046 mol) was dissolved in MeOH (60 ml) containing anhyd oxalic acid (900 mg, 0.01 mol). The mixture was left overnight at room temp. and evaporated. The residue was dissolved in EtOAc, washed with 10% $NaHCO_3$, dried over Na_2SO_4, concentrated, triturated with ether and crystallized from EtOAc–hexane, 7.48 g, 78%, m.p. 94–95°. IR ($CHCl_3$): 3510, 3420, 1740, 1690 cm^{-1}. NMR (DMSO-d_6) δ: 7.1 (d, 1, NH); 5.95 (broad s, 2, NH_2), 5.26 (d, 1, CH); 4.18 (t, 2, OCH_2); 3.25 (s, 3, OCH_3); 0.7–1.9 (m, 7, $(CH_2)_2CH_3$). (Found: C, 47.26; H, 7.54; N, 13.64. $C_8H_{14}N_2O_4$ requires: C, 47.05; H, 7.90; N, 13.72%).

Butyl α-methylthiohydantoate (**14c**). Butyl α-hydroxyhydantoate (380 mg, 2 mmol) and anhyd oxalic acid (90 mg, 1 mmol) were suspended in CH_2Cl_2 soln saturated with methyl mercaptan (20 ml) and stirred for 72 hr at room temp. The solvent was removed, the residue dissolved in EtOAc, washed with 10% $NaHCO_3$, dried over Na_2SO_4, evaporated and triturated with ether yielding **5b** (quantitative), m.p. 85° (recrystallized from EtOAc–hexane). IR ($CHCl_3$): 3500, 3410, 3360, 1725, 1680, 1595 cm^{-1}. NMR (DMSO-d_6) δ: 6.94 (d, 1, HN); 5.84 (broad s, 2, NH_2); 4.15 (t, 2, OCH_2); 2.08 (s, 3, SCH_3); 0.7–1.9 (m, 7, $(CH_2)_2CH_3$). (Found: C, 43.44; N, 7.22; N, 12.08; S, 13.94. $C_8H_{16}N_2O_3S$ requires: C, 43.63; H, 7.32; N, 12.72; S, 14.53%).

The ester **14c** was also prepared under the same reaction conditions using **14b** as a starting material.

†*Org. Synthesis Coll.* Vol. 4, 124 (1963).

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