Reaction of Dimethyl Methylenesuccinate with Hydrazine

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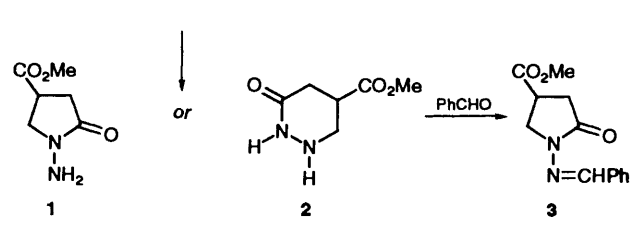
The addition of hydrazine to dimethyl methylenesuccinate gave a product whose structure could be either a 1-aminopyrrolidone **1** or a hexahydropyridazinone **2**. Chemical methods to establish the structure were contradictory. It gave a benzylidene derivative suggesting the former structure, but the *N*-benzoyl derivative of **1**, prepared by a different route, differed from that of the product suggesting the latter structure. X-Ray structural analysis established that the product is **2** while the benzylidene derivative was actually that of **1**, showing that rearrangement occurred when the product was heated with benzaldehyde.

Addition of hydrazines to α,β-unsaturated acids or esters is a general method for the synthesis of nitrogen-containing heterocycles.[1] The reaction of hydrazine with 4-methyl 2-methylenesuccinate was thought to give 1-amino-2-oxopyrrolidine-4-carboxylic acid,[2] a compound which could not be isolated and crystallized, but whose structure was deduced on the basis that it yielded a *p*-nitrobenzylidene derivative when heated with the corresponding aldehyde, the presence of a primary amino group thus being suggested.

On investigating the reaction of equimolar proportions of hydrazine and dimethyl methylenesuccinate in methanol or dioxane, we found that rapid addition occurred at room temperature (*ca.* 90% reaction in 20 min in methanol) to give a high yield of a compound which crystallized easily from ethyl acetate, had m.p. 115 °C, and the analysis for which corresponded to the molecular formula $C_6H_{10}N_2O_3$: this suggested that it was either the 1-aminopyrrolidone **1** or the hexahydropyridazinone **2**.



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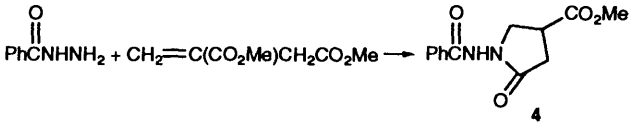
In trying to establish the structure, we tried different chemical methods but the evidence seemed to be contradictory. Thus, when heated with benzaldehyde at 130–140 °C it gave a benzylidene derivative, **3**, m.p. 187 °C, suggesting structure **1** which has a primary amino group. However, the product was benzoylated at room temperature to give a derivative, m.p. 92 °C which differed from **4**, the benzoyl derivative of **1** (m.p. 102 °C) which was prepared either by condensation of benzoylhydrazide with dimethyl methylenesuccinate or by condensation of benzoyl-



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hydrazide with methylenesuccinic acid in boiling water, followed by esterification of the resulting 1-benzamidooxopyrrolidinecarboxylic acid with $MeOH/H_2SO_4$. A noticeable difference in the NMR spectra of the two benzoyl derivatives is for the

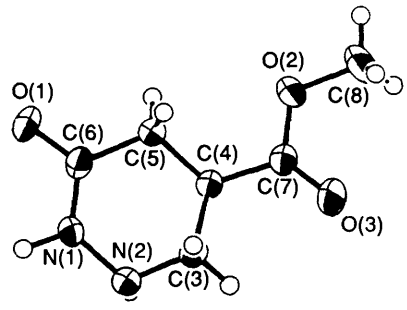

Fig. 1 X-Ray molecular structure of compound **2**

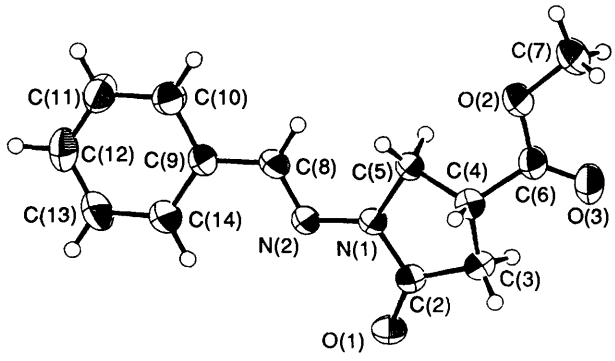

Fig. 2 X-Ray molecular structure of compound **3**

signal of the benzoyl groups. Whereas in the derivative of **2** it appears as a singlet because it is attached to a secondary amino group, in **4**, where it is attached to a primary amino group, it appears as a wide multiplet of the *o*, *m*, and *p*-hydrogens, the resonances for which differ significantly. In the mass spectra of the two products, a peak appears at 142 (which is M^+ – PhCONH) for the pyrrolidone derivative which is absent in that of the hexahydropyridazinone. These differences in the benzoyl derivatives suggested that the structure of the product with m.p. 115 °C might actually be **2**.

Conclusive confirmation of the structure was obtained from X-ray single-crystal analyses of both this product and its benzylidene derivative **3** (Figs. 1 and 2), which showed that the product is actually **2**, and compound **3** the benzylidene derivative of 1-aminopyrrolidone. This clearly shows that there is a thermal rearrangement of a hexahydropyridazinone to 1-aminopyrrolidone.

Some rearrangements involving 1-aminopyrrolidines[3] or pyrrolidones[4] to 1,4,5,6-tetrahydropyradizine or pyridazinones

were found to occur under oxidizing conditions. Pyridazinones may undergo ring contraction to pyrroles or pyrazoles, the process being induced either by an acid or base.[5]

The thermal rearrangement of the hexahydropyridazinone to 1-aminopyrrolidone might occur through an internal nucleophilic attack of the secondary amino nitrogen on the carbonyl of the amide.

To find out the temperature range required for the rearrangement to occur, we studied the reaction of benzaldehyde with the hexahydropyridazinone at lower temperatures and found that at 60 °C the reaction already occurred, but the yield was very low (10% after 12 h).

The reaction of **2** with other aromatic aldehydes, such as *p*-chlorobenzaldehyde and piperonal also occurred easily yielding the corresponding arylidene derivatives of 1-aminopyrrolidone. Isocyanates, such as phenyl and *p*-chlorophenyl reacted with **2** at room temperature yielding the corresponding *N*-ureido derivatives of **2**. Likewise, 2,4-dichlorophenoxyacetyl chloride gave with **2**, the corresponding *N*-acyl derivative.

Experimental

M.p.s were taken on a Fisher-Johns apparatus and are uncorrected. NMR spectra ($CDCl_3$ solutions) were recorded on a Bruker WH-200 spectrometer. TLC was carried out on E. Merck Kieselgel 60 F254 using ethyl acetate as developing solvent.

Reaction of Hydrazine with Dimethyl Methylenesuccinate.—Hydrazine hydrate (2.06 g, 41.2 mmol) was added dropwise to a solution of dimethyl methylenesuccinate (6.5 g, 41.1 mmol) in methanol (25 cm^3) and left 4 h at room temperature. The mixture was evaporated under reduced pressure and the residue recrystallized from ethyl acetate to give *methyl 6-oxohexahydropyridazine-4-carboxylate* **2** (5.2 g, 80%), m.p. 115 °C (Found: C, 45.4; H, 6.2; N, 17.5. $C_6H_{10}N_2O_3$ requires C, 45.6; H, 6.3; N, 17.7%); TLC, R_f 0.12; δ_H 3.8 (3 H, s, OCH_3), 3.2 (2 H, dd, NCH_2), 3.0 (1 H, m, CH), 2.7 (2 H, dd, $COCH_2$), 4.3 (1 H, s, NH) and 7.9 (1 H, s, NH) (the last 2 peaks disappeared on addition of D_2O).

Reaction of Compound **2** *with Benzaldehyde.*—A mixture of benzaldehyde (4.2 g, 39.4 mmol) and **2** (3.0 g, 19 mmol) was heated in an oil-bath at 130–140 °C for 1 h, cooled, triturated with ethanol (15 cm^3) and collected to give *methyl 1-benzylidenamino-5-oxopyrrolide-3-carboxylate* **3** (3.3 g, 70%), m.p. 187 °C (Found: C, 63.5; H, 5.7; N, 11.1. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); TLC, R_f 0.75; δ_H 8.0 (1 H, s, CH=N), 7.4–7.8 (5 H, m, Ph), 4.1 (2 H, d, N-CH_2), 3.8 (3 H, s, OCH_3), 3.4 (1 H, m, CH) and 2.9 (2 H, dd, $COCH_2$).

Benzoylation of Compound **2**.—A solution of benzoyl chloride (4.5 g, 32 mmol) in dry methylene dichloride (10 cm^3) was added dropwise to a stirred mixture of **2** (5.0 g, 31.6 mmol) and triethylamine (8 ml, 57.5 mmol) in methylene dichloride (20 cm^3) at 0 °C. The reaction mixture was stirred for 1 h in the cold followed by 3 h at room temperature and then filtered to remove the precipitated triethylamine hydrochloride. After evaporation of the filtrate under reduced pressure, the residue was crystallized from a small volume of ethanol (stored 2 h in the cold) to give *methyl 1-benzoyl-6-oxopyridazine-4-carboxylate* which was collected and dried at 50 °C (4.9 g, 59%), m.p. 92 °C (Found: C, 59.2; H, 5.3; N, 10.6. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.3, N, 10.7%); TLC, R_f 0.34; δ_H 7.5 (5 H, s, Ph), 4.1 (2 H, d, N-CH_2), 3.7 (3 H, s, OCH_3), 3.1 (1 H, m, CH), 2.8 (2 H, m, $COCH_2$), 8.9 (1 H, bs, NH); *m/z* 262 (M^+, 7), 231 (M^+ − OMe, 2), 105 (PhCO, 100), 77 (Ph, 28), 59 (CO_2Me, 1).

Methyl 1-Benzamido-5-oxopyrrolidine-3-carboxylate **4**.—(*a*) Benzoylhydrazide (2.0 g, 14.7 mmol) and dimethyl methylenesuccinate (2.3 g, 14.5 mmol) were mixed and heated neat in an oil-bath at 120 °C for 40 h. The product was recrystallized from aqueous ethanol. Compound **4** crystallized with 1 mol equiv. of water of hydration which it lost at 40 °C under reduced pressure; yield 1.5 g (40%), m.p. 102 °C (Found: C, 59.2; H, 5.2; N, 10.8. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.3; N, 10.7%); TLC, R_f 0.4; δ_H 7.4–7.9 (5 H, m, Ph), 4.1 (2 H, m, N-CH_2), 3.9 (3 H, s, OCH_3), 3.6 (1 H, m, CH), 3.0 (2 H, d, $COCH_2$); *m/z* 262 (M^+, 1.5), 231 (M^+ − OMe, 2), 142 (M^+ − PhCONH, 5), 121 ($PhCONH_2$, 15) 119 (PhCON, 1), 105 (PhCO, 100) and 77 (Ph, 25).

(*b*) Benzoylhydrazide (5.2 g, 38.2 mmol) and methylenesuccinic acid (5 g, 38.4 mmol) were added to water (20 cm^3) and the mixture boiled for 3 h. It was then cooled and filtered to give *1-benzamido-5-oxopyrrolidine-3-carboxylic acid* (7.9 g, 83%), m.p. 242 °C (Found: C, 58.3; H, 4.6; N, 11.1. $C_{12}H_{12}N_2O_4$ requires C, 58.1; H, 4.8; N, 11.3%); TLC, R_f 0.08; δ_H 7.5–7.8 (5 H, m, Ph), 4.1 (2 H, d, NCH_2), 3.6 (1 H, m, CH) and 3.1 (2 H, d, CH_2CO). This acid (2 g, 8.1 mmol) was dissolved in absolute methanol (10 cm^3) to which sulfuric acid (0.3 cm^3) was added, and the mixture heated under reflux for 10 h. Evaporation of the mixture under reduced pressure gave a residue which was recrystallized from aqueous ethanol to yield compound **4** (1.0 g, 47%), m.p. and mixed m.p. with the product obtained in the previous procedure, 102 °C, after drying at 40 °C under reduced pressure.

Methyl 1-(2,4-Dichlorophenoxyacetyl)-6-oxohexahydropyridazine-4-carboxylate.—Thionyl chloride (1.2 cm^3, 19.6 mmol) was added dropwise to a stirred solution of 2,4-dichlorophenoxyacetic acid (3.3 g, 15 mmol) in dichloromethane (30 cm^3) and DMF (5 cm^3) at 0 °C. The reaction mixture was stirred for 1 h and then added dropwise to a solution of **2** (2.37 g, 15 mmol) and triethylamine (5 cm^3, 33 mmol) in dichloromethane (15 cm^3). The reaction mixture was left for 5 h, and the product which crystallized out was collected and washed with water and ethanol (3.7 g, 68%), m.p. 175 °C (Found: C, 46.8; H, 3.9; N, 7.7. $C_{14}H_{14}Cl_2N_2O_5$ requires C, 46.5; H, 3.9; N, 7.7%); TLC, R_f 0.67; δ_H 7.4 (1 H, s, ArH), 7.3 (1 H, d, ArH), 6.9 (1 H, d, ArH), 4.9 (2 H, s, OCH_2), 4.3 (2 H, m, NCH_2), 3.8 (3 H, s, OMe), 3; (1 H, m, CH) and 3.1 (2 H, m, CHCO).

Methyl 6-Oxo-1-(N-phenylureido)hexahydropyridazine-4-carboxylate.—Phenyl isocyanate (2.6 g, 22 mmol) was added to a solution of **2** (3.0 g, 19 mmol) in carbon tetrachloride (50 cm^3) at room temperature and left for 3 h. The precipitated product was collected and washed with ethanol (3.7 g, 70%); m.p. 197 °C (Found: C, 56.6; H, 5.2; N, 15.3. $C_{13}H_{15}N_3O_4$ requires C, 56.3; H, 5.4; N, 15.2%); TLC, R_f 0.59; δ_H 7.9 (1 H, s, NH), 7.3 (5 H, s, Ph), 7.2 (1 H, br s, NH), 4.1 (2 H, m, CH_2N), 3.7 (3 H, s, OMe), 3.3 (1 H, m, CH) and 2.8 (2 H, m, CH_2CO).

Methyl 1-(N-p-Chlorophenylureido)-6-oxohexahydropyridazine-4-carboxylate.—*p*-Chlorophenyl isocyanate (2.9 g, 18.9 mmol) in chloroform (10 cm^3) was added to a solution of **2** (2.0 g, 12.6 mmol) in chloroform (20 cm^3) at room temperature. The mixture was stirred for 1 h after which the precipitated product was filtered off and washed with ethanol (3 g, 76%); m.p. 245 °C (Found: C, 50.1; H, 4.3; N, 13.4. $C_{13}H_{15}ClN_3O_4$ requires C, 50.2; H, 4.5; N, 13.3%); TLC, R_f 0.7; δ_H 7.9 (1 H, br s, NH),

Table 1 Crystallographic data

	2	3
Formula	$C_6H_{10}N_2O_3$	$C_{13}H_{14}N_2O_3$
M	158.1	246.1
Space group	$P2_1/c$	P_1
a/Å	12.748(1)	7.522(1)
b/Å	6.096(1)	13.218(1)
c/Å	9.549(1)	6.448(1)
α/°	—	97.35(1)
β/°	98.14(1)	102.68(1)
γ/°	—	98.54(1)
V/Å^3	734.6(4)	609.9(3)
Z	4	2
D_c/g cm^{-3}	1.43	1.34
μ(Cu-Kα)/cm^{-1}	9.38	7.59
Number of unique reflections	1056	1795
Number of reflections with $[I \geq 3\sigma(I)]$	1008	1666
R	0.054	0.043
R_w	0.082	0.078

Table 2 Selected bond lengths (Å) and angles (°) for compound **2**

O(1)–C(6)	1.241(2)	N(2)–N(1)–C(6)	126.6(1)
O(2)–C(7)	1.322(2)	N(2)–N(1)–H(1)	116.60
O(2)–C(8)	1.445(2)	C(6)–N(1)–H(1)	116.82
O(3)–C(7)	1.192(2)	N(1)–N(2)–C(3)	111.5(1)
N(1)–N(2)	1.421(2)	N(1)–N(2)–H(2)	107.11
N(1)–C(6)	1.333(2)	N(2)–C(3)–C(4)	112.0(1)
N(1)–H(1)	0.966	C(3)–C(4)–C(5)	108.6(1)
N(2)–C(3)	1.453(2)	C(3)–C(4)–C(7)	111.1(1)
N(2)–H(2)	0.824	C(4)–C(5)–C(6)	114.8(1)
C(3)–C(4)	1.531(2)	O(1)–C(6)–N(1)	120.7(1)
C(4)–C(7)	1.501(2)	N(1)–C(6)–C(5)	119.0(1)

7.25–7.3 (4 H, d, ArH), 4.2 (2 H, d, NCH_2), 3.8 (3 H, s, OMe), 3.4 (1 H, m, CH) and 2.9 (2 H, m, CH_2CO).

Methyl 1-p-*Chlorobenzylideneamino*-2-*oxopyrrolidine*-4-*carboxylate*.—A mixture of *p*-chlorobenzaldehyde (1.3 g, 9.5 mmol) and **2** (1 g, 6.3 mmol) was heated in an oil-bath at 140 °C for 3 h after which it was cooled, triturated with ethanol and the product collected (1.4 g, 80%); m.p. 192 °C (Found: C, 55.5; H, 4.6; N, 10.2. $C_{13}H_{13}ClN_2O_3$ requires C, 55.6; H, 4.6; N, 10.0%); TLC, R_f 0.64; δ_H 7.9 (1 H, s, CH=N), 7.7 (2 H, d, ArH), 7.4 (2 H, d, ArH), 4.1 (2 H, d, NCH_2), 3.8 (3 H, s, OMe), 3.5 (1 H, m, CH) and 3.1 (2 H, d, CH_2CO).

Methyl 1-(3,4-*Methylenedioxybenzylideneamino*)-2-*oxopyrrolidine*-4-*carboxylate*.—A mixture of piperonal (1.4 g, 9.4 mmol) and **2** (1 g, 6.3 mmol) was heated in an oil-bath at 140 °C for 3 h after which the product was triturated with ethanol and collected (1.2 g, 65%); m.p. 245 °C (Found: C, 58.1; H, 4.8; N, 9.8. $C_{14}H_{14}N_2O_5$ requires C, 57.9; H, 4.8; N, 9.7%); TLC, R_f 0.75; δ_H 7.8 (1 H, s, CH=N), 7.4 (1 H, s, ArH), 7.2 (1 H, d, ArH), 6.9 (1 H, d, ArH), 6.1 (2 H, s, OCH_2O), 4.2 (2 H, m, NCH_2), 3.8 (3 H, s, OMe), 3.6 (1 H, m, CH) and 3.1 (2 H, m, CH_2CO).

X-Ray Crystal Structure Analyses.—*Data for compounds* **2** and **3** were measured on an Enraf–Nonius CAD-4 automatic diffractometer. Cu-Kα (λ = 1.541 78 Å) radiation with graphite crystal monochromator in the incident beam was used. The standard CAD-4 centring, indexing, and data collection programs were used. The unit cell dimensions were obtained by a least-squares fit of 24 centred reflections in the range of $23 \leq \theta \leq 28°$ for **2** and $24 \leq \theta \leq 30°$ for **3**.

Intensity data were collected using the ω-2θ technique to a maximum 2θ of 120°. The scan width, $\Delta\omega$, for each reflection was 0.80 + 0.15 tan θ. An aperture with a height of 4 mm and a variable width, calculated as (2.0 + 0.5 tan θ) mm, was located 173 mm from the crystal. Reflections were first measured with a scan of 8.24° min^{-1}. The rate of the final scan was calculated from the preliminary scan results so that the ratio $I/\sigma(I)$ would be at least 40 and the maximum scan time would not exceed 60 s. If, in a preliminary scan, $I/\sigma(I) < 2$, this measurement was used as the datum. Scan rates varied from 1.26 to 8.24° min^{-1}. Of the 96 steps in the scan, the first and the last 16 steps were considered to be background. During data collection the intensities of three standard reflections were monitored after every hour of X-ray exposure. No decay was observed. In addition, three orientation standards were checked after 100 reflections to check the effects of crystal movement. If the standard deviation of the h, k and l values of any orientation reflection exceeded 0.06, a new orientation matrix was calculated on the basis of the recentring of the 24 reference reflections.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[6] After several cycles of refinements the positions of the hydrogen atoms bonded to carbon atoms were calculated, while the positions of the hydrogen atoms bonded to nitrogen (in compound **2**) were found in the Fourier difference map and all added to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.3 e Å^{-3} scattered about the unit cell without a significant feature. Selected bond lengths and angles for compound **2** are given in Table 2 and for **3** are given in Table 3.

The discrepancy indices, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{\frac{1}{2}}$ are presented with other pertinent crystallographic data in Table 1.*

Table 3 Selected bond lengths (Å) and angles (°) for compound **3**

O(1)–C(2)	1.218(2)	N(2)–N(1)–C(2)	119.6(1)
N(1)–N(2)	1.369(2)	N(2)–N(1)–C(5)	126.4(1)
N(1)–C(2)	1.371(2)	C(2)–N(1)–C(5)	114.1(1)
N(1)–C(5)	1.457(2)	N(1)–N(2)–C(8)	117.3(1)
N(2)–C(8)	1.281(2)	O(1)–C(2)–N(1)	124.6(1)
C(8)–C(9)	1.462(2)	N(1)–C(2)–C(3)	107.5(1)
C(9)–C(10)	1.389(3)	C(2)–C(3)–C(4)	103.8(1)
C(9)–C(14)	1.400(2)	N(1)–C(5)–C(4)	101.7(1)
C(10)–C(11)	1.388(3)	N(2)–C(8)–C(9)	119.8(1)
C(13)–C(14)	1.372(3)	C(8)–C(9)–C(10)	119.1(2)
		C(8)–C(9)–C(14)	122.1(2)
		C(10)–C(9)–C(14)	118.8(2)

* Tables of positional and thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. For details of the scheme, see 'Instructions for Authors (1993),' *J. Chem. Soc., Perkin Trans. 1*, 1993, issue 1.

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Paper 3/01828H
Received 30*th March* 1993
Accepted 7*th May* 1993