Acta Chemica Scandinavica B 37 (1983) 555–566

Electrophilic Amidoalkylation of C–H Acidic Compounds with Cyclic *N*-Formylimmonium Precursors

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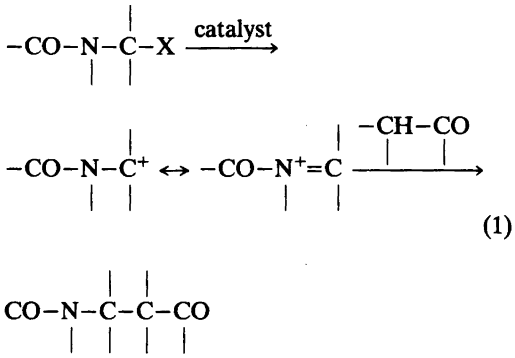
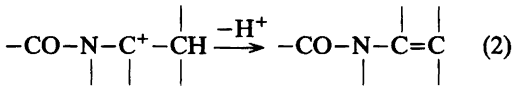
C–H acidic compounds, such as esters of malonic acid, substituted malonic acids, 2-oxocyclopentanecarboxylic acid and acetoacetic acid and in some cases monocarbonyl compounds, *e.g.* acetone and cyclopentanone, react with cyclic *N*-formyl-*N*-α-methoxyamines, easily prepared by the anodic methoxylation of cyclic *N*-formylamines, to form amidoalkylated products in fair to good yields. These compounds are convertible to a large variety of *N*-α-substituted heterocycles by well-established methods. As examples, the hydrolysis and decarboxylation of malonic and acetoacetic ester derivatives and the reaction between amidoalkylated malonic esters and urea to form barbituric acids are described.

The amidoalkylation of C–H acidic compounds is well documented.[1] The reaction has been carried out with various α-substituted amide derivatives, some of which are exemplified in eqn. (1). In the majority of cases the α-substituted amides have been acyclic, mainly because of the lack of expedient methods for the preparation of suitable α-substituted nitrogen heterocycles of the required type. By the introduction of the convenient, high-yield anodic α-methoxylation of cyclic amides a general method for the preparation of cyclic amidoalkylating agents was available. These reactions can be run on a large laboratory scale, the preparation of 10–20 mol samples being a matter of days.[2–5]





We have previously demonstrated the use of the α-methoxylated nitrogen heterocycles *1*–*6* as amidoalkylating agents toward aromatic compounds and dimethyl malonate.[6–8] The reaction proceeds *via* an α-nitrogen stabilized carbocation (eqn. (1)) which can also lose a proton to give an enamide (eqn. (2)). This frequently observed side-reaction does, however, not interfere in synthesis, since enamides usually are at least as reactive as amidoalkylating agents as the corresponding methoxy compounds. The enamides, which often can be used with some advantage over the α-methoxy derivatives, are easily prepared by elimination of methanol from α-methoxyamides.[9] An alternative route, isomerization of β,γ-unsaturated amides by

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0302-4369/83 $02.50

Table 1. Yields and conditions for reaction between α-methoxylated amides or enamides and malonic esters. Reactions were run at room temperature, unless otherwise stated.

α-Methoxylated amide or enamide [a]	R in $RCH(COOR')_2$ [b]	Ratio substrate/ ester/$AlCl_3$	Reaction period/h	Yield/ % [c]
1	H	1.0/1.0/1.4	20	70 [d]
2	H	1.0/1.0/1.4	20	73 [d]
3	H	1.0/1.0/1.4	20	73 [d]
5	H	1.0/1.1/1.4	19	48
6	H	1.0/1.1/1.4	2	62
1	CH_3	1.0/1.0/1.0	48	68
2 (E)	CH_3	1.0/2.0/1.4 [e]	120	38
3	CH_3	1.0/1.0/1.0	48	88
6	CH_3	1.0/1.0/1.0	17	38
1	C_4H_9	1.0/1.5/1.0 [e]	24	55
2	C_4H_9	1.0/1.0/1.4		0 [f]
1	C_6H_5	1.5/1.0/1.5 [e]	78+144 [g]	51
3	C_6H_5	2.0/1.0/2.0 [e]	216	24
1	$PhCH_2$	2.0/1.0/1.4 [e]	192	60
2 or 2(E)	$PhCH_2$			0 [f]

[a] An (E) after the compound No. indicates that the corresponding enamide was used. [b] R'=Et in all cases, except for R=H or $PhCH_2$. [c] Isolated yield of purified product. [d] See Ref. 7. [e] Successive addition of reagents in order to shift the equilibrium to the right; ratios refer to total amounts of reagents (see text and Experimental). [f] Product was detectable but the yield was too low for isolation to be meaningful. [g] The second period was run at reflux temperature in dichloromethane.

ruthenium or rhodium catalysts,[10] is far more laborious and applicable on a small scale only.

This paper is a full report on the amidoalkylation of C–H acidic compounds (malonates, acylacetic esters, monocarbonyl compounds) by *1–6*. A few conventional further conversions of the products thus prepared are exemplified. While this work was in progress, similar methods were described by Schmalzl [11] and Shono *et al.*[12] The latter group employed as the key step the anodic α-methoxylation of carbamates, the products of which can be used for amidoalkylation in much the same way as *N*-formyl compounds.

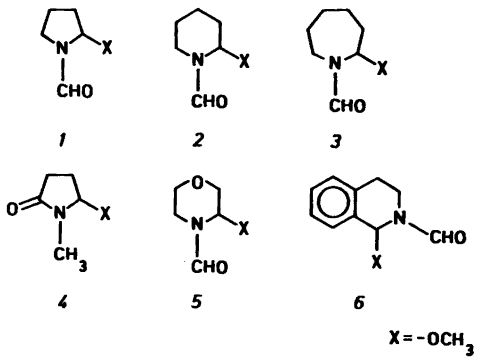
RESULTS

All amidoalkylations described here were carried out with anhydrous $AlCl_3$ as catalyst and dichloromethane as solvent. Other previously used catalysts, such as methanesulfonic acid or BF_3,[6,8] failed, mainly due to competition from the dimerization and polymerization of the enamide formed *via* eqn. (2).[8,11] $TiCl_4$ [12] was found to be a good alternative to $AlCl_3$ whereas $ZnCl_2$ gave inferior yields.

As in Friedel-Crafts acylation, stoicheiometric amounts or an excess of the catalyst must be employed due to the strong tendency of $AlCl_3$ to form complexes with Lewis donors, *i.e.*, with both starting materials and products of the amidoalkylation reaction, thus reducing its catalytic activity.[13,14] This effect was compensated for by keeping the catalyst/substrate ratio ≥1.4 in the appropriate cases. The C–H acidic reaction component was normally used in 10–100 % excess.

Amidoalkylation of malonic esters. Table 1 gives yields and reaction conditions for the amidoalkylation of malonic esters by *1–6*. In general, fair to good yields were obtained with unsubstituted or moderately hindered alkylmalonic esters, whereas more sterically hindered ones, such as diethyl cyclohexyl- or neopentylmalonate, failed to react.

The least reactive compound among *1–6* was *2*, presumably due to the known tendency of sp^2-hybridized atoms being more energetically favourable in a six-membered ring. This effect stabilizes the carbocation and/or the enamide, and thus the reactivity of the cation is low and/or the equilibrium becomes unfavourable for product formation. This situation could be slightly



improved by adding an excess of catalyst and malonic ester. By equilibrating pure diethyl (1-formyl-2-piperidyl)-methylpropanedioate with an equimolar amount of $AlCl_3$ in dichloromethane for 120 h, a value of the equilibrium constant $=1.5\ M^{-1}$ could be estimated. Reversibility has also been observed in the amidoalkylation of aromatics.[6]

In principle, *5* might eliminate methanol during the reaction to give an enamide with the possibility of reprotonation or coordination with the catalyst at two sites, *α* to nitrogen or oxygen. The product isolated was however only the 3-isomer, *i.e.* attack *α* to nitrogen was preferred. No reaction was observed when 5 was replaced by its enamide. The phenyl- and benzylmalonic esters might in principle be attacked at ring positions as well, but no such products were detected. The low yield in some of the reactions in Table 1 are due to competing polymerization reactions, especially with *1*, *3* and *6*. In contrast, the enamide from *2* turned out to be stable for several weeks in the presence of $AlCl_3$.

Amidoalkylation of acylacetic esters. Table 2 lists reaction conditions and yields for the amidoalkylation of a few acylacetic esters, including a cyclic one, ethyl 2-oxocyclopentanecarboxylate, by *1*, *3* and *6*. Good yields were obtained in most cases. Somewhat surprisingly, acetylacetone did not give any amidoalkylation product, neither by using $AlCl_3$ nor $TiCl_4$ or BF_3 as a catalyst.

Amidoalkylation of monocarbonyl compounds. Table 3 lists reaction conditions and yields for the amidoalkylation of monocarbonyl compounds by *6* and, in one case, *1* (*2* and *3* were also found to react with cyclopentanone but the products were not isolated due to poor yields). Compound *6* reacted with a number of monocarbonyl compounds, albeit in low to moderate yields. Other C–H acidic compounds (acetonitrile, nitromethane, ethyl phenylacetate, ethyl acetate and malononitrile) did not react with *6* under the conditions employed, 3,4-dihydroisoquinoline being the only detectable product.

Further conversions of amidoalkylated products. The amidoalkylated products obtained *via* the reactions of Tables 1–3 can be converted to a large number of other derivatives by conventional synthesis methodology. To exemplify, alkaline hydrolysis and subsequent decarboxylation of a few malonates (see Experimental) afforded the corresponding amino acids,[15] whereas reaction with urea in the classical manner [16] gave the corresponding barbituric acids (see Experimental).

Table 2. Yields and conditions for reaction between *α*-methoxylated amides and acylacetic esters. All reactions were run at room temperature.

α-Methoxylated amide	R and R′ in RCOCH(R′)COOMe	Ratio substrate–methylene compound–$AlCl_3$	Reaction period/h	Yield/ % [a]
1	CH_3,H	1.0:1.1:1.4	1	66
2	CH_3,H	1.0:1.1:1.4	2.5	71 [b]
3	CH_3,H	1.0:1.1:1.4	1.5	57
6	CH_3,H	1.0:1.1:1.4	1	58
2	Ph,H	1.0:1.0:1.0	2	58 [b]
1	$-(CH_2)_3-$ [c]	1.0:1.1:1.4	72	55
3	$-(CH_2)_3-$ [c]	1.0:1.1:1.4	48	45

[a] Isolated yield of purified product. [b] Mixture of two diastereomers. [c] A mixture of the methyl and ethyl ester was used.

Table 3 . Yields and conditions for reaction between α-methoxylated amides and monocarbonyl compounds. All reactions were run at room temperature.

α-Methoxylated amide	Carbonyl compound	Ratio substrate–carbonyl compound–$AlCl_3$	Reaction period/h	Yield/ % [a]
1	Cyclopentanone	1.0:2.0:1.0 [b]	168	37
6	Cyclopentanone	1.0:1.4:1.4	2	17
6	Cyclohexanone	1.0:1.4:1.4	17	33
6	Cycloheptanone	1.0:1.1:1.4	2	31
6	Acetone	1.0:1.0:1.4	2	70
6	3-Pentanone	1.0:2.0:1.4	2	42
6	Acetophenone	1.0:1.1:1.4	24	43
6	Phenylacetone	1.0:1.0:1.4	20	8 [c]
6	Acetaldehyde	1.0:1.4:1.4	1	11

[a] Isolated yield of purified product. [b] Successive addition of reagents in order to shift the equilibrium to the right; ratios refer to total amounts of reagents (see text and Experimental). [c] GLC analysis of the crude product mixture indicated a 70 % yield of four products (3:5:1.5:1); MS analysis showed that the major point of attack was the benzylic carbon.

The *N*-formyl compounds obtained from the amidoalkylation reactions reported here have not been described earlier. Among the malonic ester derivatives a few compounds with similar structure have been reported. Noteworthy are the preparations of 2-pyrrolidinylidene-, 2-piperidinylidene- and 2-azepinylidenemalonic esters. These compounds have been prepared by condensation of cyclic imino ethers or cyclic thioimino ethers with malonic ester,[17,18] condensation of thiolactams with bromomalonic esters,[19,20] and condensation of cyclic 2,2-diethoxyamines with malonic ester.[21–24] These and a few other methods have also been useful in the preparation of analogous derivatives from other carbonyl compounds, such as acetoacetic ester,[17,18,20,25–27] acetylacetone [17,25,27–29] and acetophenone.[25]

To our knowledge none of the heterocyclic systems *1–6*, substituted in the α-position with a barbituric acid moiety, has been reported. Among the *N*-formyl analogues of 2-acetonyl substituted compounds only 2-(2-oxopropyl)-1-piperidinecarboxaldehyde has been previously prepared for subsequent use in the preparation of myrtine.[30] However, some of the nonformylated analogues together with *N*-acetyl and *N*-methyl derivatives are well known alkaloids and have been thoroughly studied. This is also the case for the acetic acid derivatives described here.

Related work involving anodic acetoxylation and/or methoxylation of acylaminomalonic acid monoesters, *N*-acylprolines and *N*-acylpipecolic acids and their subsequent use as amidoalkylating agents has been carried out by Iwasaki *et al.*[31–33] Ben Ishai *et al.* have reported the amidoalkylation of β-dicarbonyl compounds with glyoxylic acid derivatives.[34] Amidoalkylation of malonic acid ester and acetoacetic acid ester with ω-alkoxylactams was the key step in the approach to pyrrolizidine alkaloids reported by Kraus and Neuenschwander.[35] A different approach to the subject of this paper has recently been made by Gugelchuk *et al.* in their preparation of vinylogous amides from *N*-alkyllactams.[36]

Concluding, the combination of fast and efficient anodic *N*-α methoxylation of cyclic amides and the subsequent use of the α-methoxyamides (or the corresponding enamides) as amidoalkylating agents toward enolizable carbonyl compounds offers a convenient approach to a large number of functionalized nitrogen heterocycles.

EXPERIMENTAL

In most cases reaction conditions and work-up methods were almost identical. In the case of significant deviations from the general procedure described below, these are detailed in connection with the actual reaction.

General procedure for amidoalkylation. The methoxylated amide or the corresponding ena-

mide, together with the carbonyl compound, usually in a slight excess, was dissolved in dichloromethane and added slowly to a stirred mixture of $AlCl_3$ in dichloromethane. As a general example 0.1 mol of the amide together with the carbonyl compound was dissolved in 20 ml of dichloromethane and added to 0.14 mol of $AlCl_3$ in 80 ml of dichloromethane. The course of reaction was checked by GLC analysis and, when necessary, additional catalyst and/or substrate were added.

After the appropriate time of reaction, water (same amount as the total volume of dichloromethane used as solvent) was added or the reaction mixture was poured into water. The organic layer was separated and the aqueous phase extracted with two more portions of dichloromethane. The combined dichloromethane solutions were washed with water, sodium hydrogen carbonate solution and finally with water. After drying over magnesium sulfate the solvent was removed by evaporation *in vacuo* and the product isolated by recrystallization or distillation at reduced pressure using a Claisen apparatus equipped with a Vigreux column.

The course of the reactions and the purity of the products were checked using a Hewlett-Packard HP-5830 gas chromatograph fitted with a 5 % OV 17 column (3 m×3 mm) or a Dexsil 300 column (0.5 m×3 mm). ^1H NMR spectra were recorded on a Jeol 100 MHz instrument with $CDCl_3$ as solvent and MS analyses were carried out on a Finnigan 4021 spectrometer at 70 eV using GLC inlet unless otherwise indicated.

In some cases unreacted starting material was removed by distillation using a "Kugelrohr" apparatus (Aldrich Co.).

The methoxylated amides [2,3] and the enamides [9] were prepared according to previously published methods whereas other chemicals where of commercial quality.

Dimethyl (4-formyl-3-morpholinyl)propanedioate. Compound *5* (0.1 mol) and dimethyl malonate in CH_2Cl_2 (20 ml) were added to $AlCl_3$ in CH_2Cl_2 (80 ml). The product was isolated by distillation at reduced pressure and later solidified. Yield 11.7 g (48 %), b.p. 159–165 °C/1.0–1.3 mmHg, m.p. 54–58 °C.

MS *m/e* (% rel. int.): 245 (2, M), 217 (3), 186 (29, M–$COOCH_3$), 174 (5), 156 (6), 132 (8), 114 (100, M–$CH(COOCH_3)_2$), 100 (18), 86 (35, C_4H_8NO), 56 (37).

^1H NMR: δ 2.80–3.16 (1 H, t with further splitting, J 12.8 and 3.8 Hz), 3.24–4.42 (7 H, several m), 3.72 and 3.77 (6 H, 2 s). 8.01 and 8.07 (1 H, 2 s); the close shifts made a more accurate evaluation uncertain.

Dimethyl (2-formyl-1,2,3,4-tetrahydro-1-isoquinolinyl)propanedioate. Compound *6* (0.025 mol) and dimethyl malonate dissolved in CH_2Cl_2 (5 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (20 ml). After the usual work-up procedure the crude product was recrystallized from diethyl ether (5 ml). Yield 4.5 g (62 %), m.p. 76–79 °C.

MS *m/e* (% rel. int., direct inlet): 291 (3, M), 262 (10, M–CHO), 172 (5), 160 (100, M–$CH(COOCH_3)_2$), 132 (59, $C_9H_{10}N$), 130 (20), 117 (20), 115 (21), 105 (15), 77 (14).

^1H NMR: δ 2.95 (2 H, t, J 6.8 Hz), 3.22–3.52 (1 H, 2 t, J 6.8 Hz), 3.62, 3.64, 3.71 and 3.76 (6 H, 4 s), 3.92 and 3.94 (1 H, 2 d, J 10.2 and 7.4 Hz), 4.01–4.49 (1 H, 2 t, J 6.8 Hz), 5.39 and 6.14 (1 H, 2 d, J 10.2 and 7.4 Hz), 7.10–7.38 (4 H, m), 8.18 and 8.35 (1 H, 2 s).

Diethyl (1-formyl-2-pyrrolidinyl)methylpropanedioate. Compound *1* (0.2 mol) and diethyl methylmalonate were dissolved in CH_2Cl_2 (40 ml) and added to $AlCl_3$ in CH_2Cl_2 (160 ml). Yield 37.0 g (68 %), b.p. 165–167 °C/1.6 mmHg.

MS *m/e* (% rel. int.): 271 (2, M), 242 (3, M–CHO or M–CH_2CH_3), 226 (3, M–OCH_2CH_3), 152 (5), 98 (100, C_5H_8NO), 70 (58, C_4H_8N).

^1H NMR: δ 1.27 (6 H, t, J 7 Hz), 1,41 and 1.43 (3 H, 2 s), 1.70–2.47 (4 H, m), 2.92–4.04 (2 H, m), 4.18 and 4.19 (4 H, 2 q, J 7 Hz), 4.55–4.80 (1 H, m), 8.21 and 8.33 (1 H, 2 s).

Diethyl (1-formyl-2-piperidyl)methylpropanedioate. 3,4-Dihydro-1(2*H*)-pyridinecarboxaldehyde (0.2 mol) and diethyl methylmalonate were dissolved in CH_2Cl_2 (40 ml) and added to $AlCl_3$ in CH_2Cl_2 (160 ml). After 72 h GLC analysis showed the reaction to be incomplete and 0.08 mol of $AlCl_3$ was added. In order to improve the yield of product an additional 0.2 mol of the malonic ester was introduced and in 48 h most of the enamide was consumed. Work-up was performed as usual. Yield 21.8 g (38 %), b.p. 163–165 °C/0.9 mmHg.

MS *m/e* (% rel. int.): 285 (1, M), 256 (2, M–CHO or M–CH_2CH_3), 240 (2, M–OCH_2CH_3), 174 (3), 166 (3), 147 (4), 129 (17), 112 (100, $C_6H_{10}NO$), 102 (10), 84 (35, $C_5H_{10}N$), 80 (27) 74 (33).

^1H NMR: δ 1.16–1.38 (6 H, 4 t, J 7 Hz), 1.46 and 1.54 (3 H, 2 s), 1.30–2.30 approx. (6 H, m), 2.58–2.91 and 3.25–3.47 (2 H, m), 4.01–4.34 (4 H, 4 q, J 7 Hz), 4.25–4.50 and 5.05–5.20 (1 H, m), 8.10 and 8.13 (1 H, 2 s).

Diethyl (1-formyl-hexahydro-1H-azepin-2-yl)-methylpropanedioate. Compound *3* (0.1 mol) and diethyl methylmalonate in CH_2Cl_2 (20 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (80 ml). Yield 20.2 g (88 %), b.p. 163–170 °C/0.7–0.9 mmHg.

MS *m/e* (% rel. int.): 300 (1, M+1), 299 (1, M) 270 (2, M−CHO or M−CH_2CH_3), 254 (2, M−OCH_2CH_3), 180 (3) 152 (3), 126 (100, $C_7H_{12}NO$), 98 (25, $C_6H_{12}N$), 55 (28).

^{1}H NMR: δ 1.16−1.39 (6 H, 4 t, J 7.5 Hz), 1.44 and 1.46 (3 H, 2 s), 1.10−2.35 approx. (8 H, m), 2.55−2.87 and 3.09−4.4 and 4.75−5.01 (3 H, several coincident m), 4.04−4.33, (4 H, 4 q, J 7.5 Hz), 8.21 and 8.24 (1 H, 2 s).

Diethyl (2-formyl-1,2,3,4-tetrahydro-1-isoquinolinyl)methylpropanedioate. Compound *6* (0.025 mol) and diethyl methylmalonate in CH_2Cl_2 (10 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (20 ml). The crude product was recrystallized from ether (6 ml). Yield 3.16 g (38 %), m.p. 85−88 °C.

MS *m/e* (% rel. int.): 333 (very small, M), 304 (2, M−CH_2CH_3 or M−CHO), 214 (3), 197 (3), 186 (3), 174 (4), 160 (100, M−CCH_3 $(COOCH_2CH_3)_2$), 132 (30, $C_9H_{10}N$), 130 (30), 117 (10), 103 (15).

^{1}H NMR: δ 0.92, 1.18 and 1.26 (6 H, 3 t, J 6.9 Hz), 1.30 and 1.40 (3 H, 2 s, 2.76−2.99, 3.09−3.40 and 3.64−4.53 (4 H, m), 4.14 and 4.18 (4 H, 2 q, J 6.9 Hz), 5.77 and 6.33 (1 H, 2 s), 7.03−7.48 (4 H, m), 8.16 and 8.28 (1 H, 2 s).

Diethyl butyl(1-formyl-2-pyrrolidinyl)propanedioate. Compound *1* (0.1 mol) and diethyl butylmalonate (0.1 mol) in CH_2Cl_2 (20 ml) were added to $AlCl_3$ (0.1 mol) in CH_2Cl_2 (80 ml). After 24 h *1* was completely consumed while still large amounts of the malonic ester remained unreacted. Another portion of *1* (0.05 mol) was added and the reaction mixture was worked up as general after 72 h. Yield 17.3 g (55 %), b.p. 166−171 °C/0.8 mmHg.

MS *m/e* (% rel. int.): 313 (very small, M), 284 (2, M−CHO or M−CH_2CH_3), 268 (1, M−OCH_2CH_3), 194 (3), 98 (100, C_5H_8NO), 70 (38, C_4H_8N).

^{1}H NMR: δ 0.77−1.00 (3 H, t, J 7.5 Hz), 1.10−1.37 (6 H, 2 t, J 7.5 Hz), 1.0−1.4 approx. (4 H, m), 1.51−2.39 (6 H, m and multiple t, J 7.5 Hz), 2.82−4.05 (2 H, m), 4.10−4.35 (4 H, 3 t, J 7.5 Hz), 4.54 and 4.77 (1 H, 2 t, J 6.5 Hz), 8.22 and 8.44 (1 H, 2 s).

Diethyl (1-formyl-2-pyrrolidinyl)phenylpropanedioate. Compound *1* (0.1 mol) and diethyl phenylmalonate (0.1 mol) in CH_2Cl_2 (20 ml) were added to a mixture of $AlCl_3$ (0.1 mol). After 78 h at room temperature most of *1* was consumed while substantial amounts of diethyl malonate still remained. Compound *1* (0.05 mol) was added and the mixture was refluxed for 72 h. GLC analyses showed a slight increase in the ratio of product/unreacted malonic ester and an additional 0.05 mol of $AlCl_3$ was introduced. The reaction mixture equilibrated within 72 h at reflux temperature and was then worked up as general. The crude product was dissolved in ether (20 ml) and chilled. The solid product was filtered off and washed with ether (yield 39 %) and the remaining ether solutions were concentrated. The resulting oil was heated at reduced pressure (160 °C/1 mmHg), in order to remove most of the remaining starting materials, and the residue was recrystallized from ethanol. Yield 17.2 g (51 %), m.p. 77−80 °C.

MS *m/e* (% rel. int.): 333 (very small, M), 236 (3, M−C_5H_7NO), 190 (4), 164 (4), 163 (4), 136 (4), 135 (4), 118 (7), 98 (100, C_5H_8NO), 91 (8), 77 (7), 70 (43, C_4H_8N), 68 (18).

^{1}H NMR: δ 1.23 and 1.26 (6 H, 2 t, J 7 Hz), 1.95−2.89 (4 H, m), 3.41−3.47 and 4.09−4.43 (2 H, m), 4.23, 4.26 and 4.28 (4 H, 3 q, J 7 Hz), 4.90−5.05 (1 H, dd, J 4.5 and 7.2 Hz), 7.28−7.38 (5 H, m), 8.22 and 8.36 (1 H, 2 s).

Diethyl (1-formyl-hexahydro-1H-azepin-2-yl)-phenylpropanedioate. Compound *3* (0.1 mol) and diethyl phenylmalonate (0.1 mol) dissolved in CH_2Cl_2 (20 ml) were added to $AlCl_3$ (0.1 mol) in CH_2Cl_2 (80 ml). GLC analyses showed the equilibrium to be in favour of the starting materials and successive additions of *3* and catalyst were made with periodic checking of the composition of the reaction mixture. Totally 0.1 mol of *3* and $AlCl_3$ were added during 216 h before work-up. The residue after evaporation of the solvent was purified by removing most of the unreacted starting materials by distillation at reduced pressure (135 °C/0.8 mmHg). The crude product was dissolved in ether (25 ml) and temporarily chilled to −78 °C to promote crystallization. The crystals were filtered off and washed with ether and from the concentrated mother liquors additional product was retained by repeated crystallization from ether. Yield 8.7 g (24 %), m.p. 72−78 °C.

MS *m/e* (% rel. int., direct inlet): 361 (very small, M), 316 (1, M−OCH_2CH_3), 236 (2, M−$C_7H_{11}NO$), 190 (3), 127 (8), 126 (100, $C_7H_{12}NO$), 105 (4), 98 (14, $C_6H_{12}N$), 55 (13).

^{1}H NMR: δ 1.10−2.42 (8 H, m), 1.22 and 1.24 (6 H, 2 t, J 7 Hz), 3.34−3.83 and 4.09−4.36 (2 H, m), 4.23 and 4.24 (4 H, 2 q, J 7 Hz), 4.40−4.61 (1 H, dd, J 5.7 and 11.7 Hz), 7.28−7.56 (5 H, m), 8.33 (1 H, 2 s).

Diethyl (1-formyl-2-pyrrolidinyl)phenylmethylpropanedioate. Compound *1* (0.1 mol) and diethyl benzylmalonate (0.1 mol) in CH_2Cl_2 (20 ml) were added to a mixture of $AlCl_3$ (0.1 mol) in CH_2Cl_2 (80 ml). Substantial amounts of starting materials were still present after 48 h and another portion of *1* (0.05 mol) was introduced. A slightly increased yield was observed after another 48 h

and was further improved by subsequent additions of catalyst (0.04 mol) and *1* (0.05 mol). After a total reaction period of 192 h most of the starting materials were consumed and the mixture was worked up as general. The product solidified after removal of the starting materials on a Kugelrohr apparatus at reduced pressure and was recrystallized from ethyl acetate (15 ml). Yield 19.0 g (60 %), m.p. 101–103 °C. MS *m/e* (% rel. int., direct inlet): 319 (1, M), 290 (1, M–CHO), 221 (3, M–C_5H_8NO), 99 (79), 98 (100, C_5H_8NO), 91 (19), 77 (6), 70 (71, C_4H_8N).

^{1}H NMR: δ 1.66–1.94 (2 H, q, *J* 7 Hz), 2.02–2.35 (2 H, m), 2.84–3.2 and 3.7–4.02 approx. shifts due to complex signal pattern (2 H, several t, *J* 7 Hz), 3.24, (1 H, d, *J* 9 Hz), 3.47 (1 H, d, *J* 9 Hz), 3.57 (3 H, s), 3.68 (3 H, s), 4.51 and 4.85 (1 H, 2 t, *J* 6 and 7 Hz resp.), 7.00–7.32 (5 H, m), 8.31 and 8.71 (1 H, s).

Methyl 2-(1-formyl-2-pyrrolidinyl)-3-oxobutanoate. Compound *1* (0.2 mol) together with methyl acetoacetate in CH_2Cl_2 (40 ml) was added to $AlCl_3$ in CH_2Cl_2 (160 ml). Yield 28.3 g (66 %), b.p. 155–161 °C/1.1–1.5 mmHg.

MS *m/e* (% rel. int.): 213 (1, M), 184 (3, M–CHO), 170 (23, M–$COCH_3$), 138 (30), 110 (29), 98 (76, C_5H_8NO), 70 (100, C_4H_8N).

^{1}H NMR: δ 1.57–2.45 (4 H, m), 2.24 and 2.26 (3 H, 2 s), 3.09–3.95 and 4.27–4.76 (4 H, m and multiple d *J* 9 Hz), 3.72–3.76 (3 H, 4 s), 8.26 (1 H, 2 s).

Methyl 2-(1-formyl-2-piperidyl)-3-oxobutanoate. Compound *2* (0.2 mol) and methyl acetoacetate dissolved in CH_2Cl_2 (40 ml) were added to $AlCl_3$ in CH_2Cl_2 (160 ml). Yield 32.2 g (71 %), b.p. 154–161 °C/1.0–1.4 mmHg.

MS *m/e* (% rel. int.): 227 (2, M), 212 (2, M–CH_3), 198 (3, M–CHO), 184 (6, M–$COOH_3$), 152 (13), 124 (13), 112 (100, $C_6H_{10}NO$), 84 (62, $C_5H_{10}N$).

^{1}H NMR: δ 1.23–1.89 (6 H, m), 2.16, 2.20, 2.23 and 2.26 (3 H, 4 s), 3.06–4.55 and 5.13–5.43 (4 H, m), 3.65, 3.70, 3.72 and 3.76 (3 H, 4 s), 7.94, 7.96, 8.04 and 8.06 (1 H, 4 s).

Methyl 2-(1-formyl-hexahydro-1H-azepin-2-yl)-3-oxobutanate. Compound *3* (0.2 mol) and methyl acetoacetate in CH_2Cl_2 (40 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (160 ml). The crude oil was dissolved in ether (50 ml) and the solid product was filtered off and washed with ether. Additional product was recovered from the concentrated mother liquor by repeated treatment with ether. Yield 27.6 g (57 %), m.p. 87–91 °C.

MS *m/e* (% rel. int., direct inlet): 241 (3, M), 226 (1, M–CH_3), 212 (1, M–CHO), 198 (8, M–$COCH_3$), 166 (16), 138 (14), 126 (100, $C_7H_{12}NO$), 98 (34, $C_6H_{12}N$).

^{1}H NMR: δ 1.05–2.77 (9 H, several m), 2.19 and 2.22 (3 H, 2 s), 3.65–4.39 (3 H, m), 3.74 and 3.82 (3 H, 2 s), 8.07 and 8.11 (1 H, 2 s).

Methyl 2-(2-formyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-3-oxobutanoate. Compound *6* (0.05 mol) and methyl acetoacetate in CH_2Cl_2 (10 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (40 ml). The pure product was obtained by recrystallization from ether (10 ml). Yield 8.0 g (58 %), m.p. 93–102 °C; the product decomposed at GLC analysis.

MS *m/e* (% rel. int., direct inlet). 275 (4, M), 246 (4, M–CHO), 243 (7), 232 (3, M–$COCH_3$), 204 (4), 200 (7), 172 (11), 160 (100, M–$CH_3COCHCOCH_3$), 132 (68, $C_9H_{10}N$), 117 (23), 115 (20), 105 (20), 77 (23).

^{1}H NMR: δ 2.22 and 2.30 (3 H, 2 s), 2.94 (2 H, t, *J* 6.5 Hz), 3.15–3.47 (1 H, multiplet, *J* 6.5 Hz), 3.59 and 3.61, (3 H, 2 s), 3.59–4.35 (2 H, m and 2 d corresponding to approx. 1 H and centered at 3.86 and 4.16, *J* 9 and 9.5 Hz), 5.47 and 6.22 (1 H, 2 d, *J* 9.5 and 9 Hz), 7.01–7.37 (4 H, m), 8.12 and 8.32 (1 H, 2 s).

2-(2-Oxocyclopentyl)-1-pyrrolidinecarboxaldehyde. Compound *1* (0.1 mol) together with cyclopentanone (0.1 mol) dissolved in CH_2Cl_2 (20 ml) was added to $AlCl_3$ (0.1 mol) in CH_2Cl_2 (80 ml). After 48 h GLC analysis showed substantial amounts of unreacted starting materials and 0.1 mol of cyclopentanone was added. The reaction mixture, still containing some unreacted amide, was worked up after totally 168 h. The diastereomers were detected at GLC analysis in a ratio of 1:6.5. Yield 6.8 g (37 %), b.p. 134–150 °C/0.6–1.0 mmHg.

MS *m/e* (% rel. int.): 181 (3, M); 151 (3), 136 (3), 125 (3), 110 (3), 98 (100, C_5H_8NO), 70 (97, C_4H_8N).

^{1}H NMR: δ 1.51–2.69 (10 H, approx., m), 2.79 (1 H approx., t, *J* 6.8 Hz), 3.05–3.83 (3 H approx., m), 4.07–4.49 (1 H approx., m), 8.11, 8.24 and 8.31 (1 H, 3 s).

3,4-Dihydro-1-(2-oxocyclopentyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.05 mol) and cyclopentanone in CH_2Cl_2 (10 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (40 ml). Yield 2.12 g (17 %), m.p. 81–83 °C.

MS *m/e* (% rel. int.): 243 (3, M), 212 (7), 160 (100, M–C_5H_7O), 132 (39, $C_9H_{10}N$), 117 (13), 105 (10), 77 (13).

^{1}H NMR: δ 1.19–3.30 and 4.28–4.55 (9 H, m), 2.91 and 3.67 (2 H, 2 t, *J* 6 Hz), 5.24 and 5.81 (1 H, 2 d, *J* 3.3 and 4.1 Hz), 6.84–7.37 (4 H, m), 8.21 and 8,42 (1 H, 2 s).

3,4-Dihydro-1-(2-oxocyclohexyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.025 mol) and cyclohexanone in CH_2Cl_2 (5 ml) were added to $AlCl_3$ in CH_2Cl_2 (20 ml). The crude

product was dissolved in ether and the slowly crystallizing product was filtered off and washed with ether. The mother liquors were concentrated and chromatographed on silica gel with CH_2Cl_2 as eluent in order to remove polymeric material. The eluate was concentrated and additional product was recovered by repeated treatment with ether. Yield 2.10 g (33 %), m.p. 102–104 °C.

MS *m/e* (% rel. int.): 257 (4, M), 228 (5, M–CHO), 185 (5), 160 (100, M–C_6H_9O), 132 (42, $C_9H_{10}N$), 117 (14), 105 (11), 77 (12).

^{1}H NMR: δ 1.32–2.20 approx. (6 H, m), 2.20–2.60 (2 H, m), 2.60–3.80 and 4.10–4.44 (7 H, m), 5.30 and 6.00 (1 H, 2 d, *J* 7 and 9 Hz), 7.00–7.37 (4 H, m), 8.17 and 8.30 (1 H, 2 s).

3,4-Dihydro-1-(2-oxocycloheptyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.05 mol) and cycloheptanone dissolved in CH_2Cl_2 (10 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (40 ml). The crude oil was dissolved in ether (10 ml) and the solid product was filtered off and washed with ether. Additional product was obtained by repeated crystallization of the concentrated mother liquors from ether. Yield 4.2 g (31 %), m.p. 108–111 °C.

MS *m/e* (% rel. int.): 271 (3, M), 242 (4, M–CHO), 161 (12), 160 (100, M–$C_7H_{11}O$), 132 (41, $C_9H_{10}N$), 117 (15), 105 (11), 77 (11), 55 (15).

^{1}H NMR: δ 1.05–2.01 (8 H, m), 2.32–2.56 (2 H, m), 2.80–3.30, 3.40–3.81 and 4.18–4.54 (5 H, m), 5.13 and 5.73 (1 H, 2 d, *J* 8.2 and 8 Hz), 6.95–7.22 (4 H, m), 8.23 (1 H, s).

Ethyl 1-(1-formyl-2-pyrrolidinyl)-2-oxocyclopentanecarboxylate. Compound *1* (0.1 mol) and ethyl 2-oxocyclopentanecarboxylate (the commercially purchased ethyl ester later turned out to contain substantial amounts of the methyl ester. This was also reflected in the composition of the isolated product) dissolved in CH_2Cl_2 (20 ml) was added to a mixture of $AlCl_3$ in CH_2Cl_2 (80 ml). Yield 13.9 g (55 %), b.p. 162–166 °C/0.6–0.8 mmHg.

MS *m/e* (% rel. int.), M=ethyl ester, M′=methyl ester: 253 (3, M), 239 (2, M′), 224 (3, M–CHO or M=CH_2CH_3 or M′–CH_3), 210 (3, M′–CHO), 180 (5, M and M′–COOR), 152 (9, M and M′–(COOR and CHO)), 98 (100, C_5H_8NO), 70 (79, C_4H_8N). MS of the two diastereomers were almost identical.

^{1}H NMR; as mentioned above the product was a mixture of methyl and ethyl ester in the ratio 1:1.4: δ 1.13–1.37 (2 H, approx., 2 t, *J* 7 Hz), 1.52–2.76 (10 H, m), 2.92–4.40 (2 H, m) 3.73 and 3.79 (1 H, approx., 2 s), 4.08–4.33 (1.2 H approx., 2 q, *J* 7 Hz), 4.43–4.88 (1 H, m), 8.11, 8.23, 8.28 and 8.32 (1 H, 4 s).

Ethyl 1(1-formyl-hexahydro-1H-azepin-2-yl)-2-oxocyclopentanecarboxylate. Compound *3* (0.1 mol) and ethyl 2-oxocyclopentanecarboxylate (a mixture of methyl and ethyl ester as in the preceding experiment) dissolved in CH_2Cl_2 (20 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 80 ml). Yield 12.6 g (45 %), b.p. 187–190 °C/1.3 mmHg; after distillation a minor portion of the product slowly crystallized, m.p. 119–122 °C.

MS *m/e* (% rel. int.), 281 (2, M, ethyl ester), 267 (1, M, methyl ester), 253 (1), 236 (1), 197 (4), 180 (3, M–(CHO+COOR)), 126 (45, $C_7H_{12}NO$), 125 (33), 110 (33), 98 (10, $C_6H_{12}N$), 96 (32), 82 (43), 68 (80), 55 (100).

^{1}H NMR; δ 0.97–2.97 (14 H, m), 1.11–1.37 (2 H approx., 2 t, *J* 7 Hz), 3.12–4.75 (3 H. m), 3.70 and 3.72 (1 H, 2 s), 4.07–4.37 (1.3 H approx., 2 q, *J* 7 Hz), 8.01, 8.07, 8.17 and 8.23 (1 H, 4 s).

Ethyl α-benzoyl-1-formyl-2-piperidineacetate. Compound *2* (0.1 mol) and ethyl benzoylacetate were dissolved in CH_2Cl_2 (20 ml) and added to a mixture of $AlCl_3$ in CH_2Cl_2 (80 ml). Since the crude oil, after evaporation of the solvent, resisted all attempts to achieve crystallization the residual starting materials were removed by distillation on a Kugelrohr apparatus at 0.1–0.2 mmHg. According to GLC analysis the resulting light brown oil was 100 % pure. Attempts to distill the product resulted in decomposition. Yield 17.6 g (58 %).

MS *m/e* (% rel. int., direct inlet): 304 (1, M+1), 303 (2, M), 285 (2), 274 (2, M–CHO or M–CH_2CH_3), 258 (2), 257 (2), 230 (7, M–$COOCH_2CH_3$), 212 (4), 202 (7), 152 (11), 124 (8), 112 (100, $C_6H_{10}NO$), 111 (60), 105 (58, COC_6H_5), 84 (61, $C_5H_{10}N$), 77 (61, C_6H_5), 56 (40).

^{1}H NMR: δ0.96–1.30 (3 H, 3 t, *J* 7 Hz), 1.30–3.42 (7 H approx., m), 3.81–5.20 (3 H, m and multiple d at 4.58–4.79 and 5.01–5.20, *J* 11 Hz), 3.90–4.29 (2 H, 3 q, *J* 7 Hz), 7.29–7.65 (3 H, m), 7.93–8.12 (2 H, t with additional splitting, *J* 7 and 2 Hz). 8.02 and 8.11 (1 H, 2 s).

3,4-Dihydro-1-(2-oxopropyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.025 mol) was dissolved in acetone and $AlCl_3$ was added in portions. After 2 h reaction was complete and excess acetone was removed by evaporation *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 ml) and after addition of water (25 ml) work-up was performed as usual. The solid product was recrystallized from ethyl acetate. Yield 3.8 g (70 %), m.p. 106–107.5 °C.

MS *m/e* (% rel. int.): 217 (36, M), 188 (56, M–CHO), 174 (20, M–$COOH_3$), 160 (100, M–CH_2COCH_3), 146 (24), 132 (85, $C_9H_{10}N$), 130 (22), 117 (24), 115 (18), 105 (17).

^{1}H NMR; δ 2.13 and 2.22 (3 H, 2 s), 2.65–3.34, 3.56–3.74 and 4.32–4.60 (6 H, m),

5.17–5.34 and 5.76–5.93 (1 H, 2 dd, *J* 3.6 and 9.5 and 5.9 and 8.2), 7.02–7.37 (4 H, m), 8.11 and 8.29 (1 H, 2 s).

3,4-Dihydro-1-(3-oxo-2-pentyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.025 mol) and 3-pentanone in CH_2Cl_2 (5 ml) were added to a mixture of $AlCl_3$ in CH_2Cl_2 (20 ml). Ether (5 ml) was added to the crude oil and the product precipitated. The crystals were filtered off and washed with ether. From the concentrated mother liquors additional product was recovered by repeated crystallization from ether. Yield 2.56 g (42 %), m.p. 74–79 °C.

MS *m/e* (% rel. int.): 245 (1, M), 216 (3, M–CHO), 160 (100, M–C_5H_9O), 132 (39, $C_9H_{10}N$), 130 (32).

^{1}H NMR: δ 0.80–1.20 (6 H, multiple d and t, *J* 7 Hz), 1.68–2.62 (2 H, 4 q, *J* 7 Hz), 2.82–4.45 (5 H, several m), 4.81, 5.62 and 5.78 (1 H, 3 d, *J* 9.5, 7 and 8 Hz), 6.84–7.38 (4 H, m), 8.13, 8.18 and 8.26 (1 H, 3 s).

3,4-Dihydro-1-(2-oxo-2-phenylethyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.05 mol) and acetophenone in CH_2Cl_2 (10 ml) were added to $AlCl_3$ in CH_2Cl_2 (40 ml). The product was purified by recrystallization from ethanol (6 ml). Yield 6.0 g (43 %), m.p. 104–107 °C.

MS *m/e* (% rel.int.): 279 (4, M), 251 (7), 250 (20, M–CHO), 207 (3), 174 (13, M–COC_6H_5), 160 (100, M–$CH_2COC_6H_5$), 132 (72, C_9H_{10}), 130 (33), 117 (31), 105 (71), 91 (17), 77 (82).

^{1}H NMR: δ 2.73–3.92 and 4.31–4.60 (6 H, m), 5.37–5.54 and 5.88–6.04 (1 H, dd and t, *J* 3 and 9.6 and 6.3 Hz), 7.03–7.31 (4 H, m), 7.31–7.67 (3 H, m), 7.82–8.08 (2 H, m), 8.10 and 8.42 (1 H, 2 s).

3,4-Dihydro-1-(2-oxo-1-phenylpropyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.05 mol) and phenylacetone in CH_2Cl_2 (10 ml) were added to $AlCl_3$ in CH_2Cl_2 (40 ml). GLC analysis indicated the presence of four products in the proportions 3:5:1.5:1 in a total yield of 70 %. Phenylacetone was still present while the methoxy compound was completely consumed. The two minor products gave mass spectra in agreement with formation of the 1-(3-phenyl-2-oxopropyl)- and 1-(2-oxopropylphenyl) derivatives, respectively. The identical mass spectra of the two major products only gave clear evidence for the presence of the *N*-formyltetrahydroisoquinoline moiety, whereas heavier fragments were of low intensity. From these results we conclude that alkylation takes place preferably at the benzylic carbon, giving a mixture of diastereomers. The less satisfactory mass spectrum might be explained by a strong tendency of the molecular ion to fragment into an *N*-formyltetrahydroisoquinoline cation and a relatively stable benzyl radical. The ^{1}H NMR spectrum, displaying 2+2 doublets (due to the hindered rotation around the CO–N bond) with identical coupling constants, and with chemical shifts in agreement with expectations, indicated alkylation at the benzylic carbon.

The crude oil was dissolved in ethyl acetate. However, only minor amounts of the main products (probably only one of the diastereomers) were collected at recrystallization and considerable amounts were retained in the mother liquors. No additional product could be isolated by repeated recrystallization from various solvents. Proper isolation may probably be accomplished by preparative GLC. Yield 1.18 g (8 %), m.p. 175–176 °C.

MS *m/e* (% rel. int.); the spectra of the diastereomers proved to be identical: The spectra showed numerous peaks of low intensity between 264 (0.5, M–CHO) and 160. No molecular ion was recorded. 160 (100, M–$C_6H_5CHCOCH_3$), 132 (44, $C_9H_{10}N$), 117 (16), 105 (13), 91 (8), 77 (12).

^{1}H NMR: δ 1.95 and 1.97 (3 H, 2 s), 2.80–3.15, 3.30–3.47 and 3.87–4.08 (4 H, m), 4.18 and 4.12 (1 H, 2 d, *J* 9.5 Hz), 4.49 and 6.47 (1 H, 2 d, *J* 9.5 Hz), 7.11–7.42 (9 H, m), 7.72 and 7.91 (1 H, 2 s).

3,4-Dihydro-1-(2-oxoethyl)-2(1H)-isoquinolinecarboxaldehyde. Compound *6* (0.05 mol) and acetaldehyde in CH_2Cl_2 (25 ml) were added to a stirred mixture of $AlCl_3$ in CH_2Cl_2 (25 ml).

The crude oil, after evaporation of the solvent, was dissolved in ethyl acetate (6 ml) and the solution was chilled. The solid product was filtered off and washed with ethyl acetate. Yield 1.15 g (11 %), m.p. 84–86 °C.

MS *m/e* (% rel. int., direct inlet): 203 (18, M), 186 (6, M–OH), 174 (17, M–CHO), 160 (94, M–CH_2CHO), 132 (100, $C_9H_{10}N$), 117 (43), 105 (34), 91 (18), 77 (41).

^{1}H NMR: δ 2.61–3.88 and 4.29–4.58 (6 H, m), 5.19–5.38 and 5.81–5.99 (1 H, 2 dd, *J* 3.8, 8.7, 6.0 and 8.0 Hz), 6.96–7.26 (4 H, m), 8.14 and 8.34 (1 H, 2 s), 9.73–9.82 (1 H, m).

Preparation of barbituric acid derivatives. Sodium (1 eq.) was dissolved in the appropriate alcohol to give a 1 M solution and the amidoalkylated malonic ester was added (1 eq.). Urea (1 eq., dried *in vacuo* at 110 °C) was added and the mixture refluxed for 2–24 h. The time of reaction was roughly estimated from the rate of precipitation of the product. Finally the reaction mixture was chilled (0 °C) and the solid product was filtered off and washed with alcohol. The sodium barbiturate was converted to the acid by dissolving it in water and adding a slight excess of hydrochloric acid. The product precipitated and

was filtered off and washed with water. Only the acid was subjected to MS and NMR analyses.

5-(1-Formyl-2-piperidyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione. The reaction was carried out with 0.02 mol of each reactant and was worked up after 17 h at reflux temperature. Yield 4.63 g (89 %), m.p. (partial decomposition) 240–250 °C. Some of the sodium salt (2 g) was treated with diluted hydrochloric acid and the acid could be collected. Yield 1.04 g (57 %), m.p. 162–165 °C.

MS *m/e* (% rel. int., direct inlet): 239 (small, M), 222 (6, M–OH), 204 (16), 193 (4), 150 (6), 129 (6), 128 (100, $C_4H_4N_2O_3$), 112 (7, $C_6H_{10}NO$), 111 (24, C_6H_9NO), 85 (29, $C_5H_{11}N$), 82 (19), 68 (7), 69 (9), 70 (8).

^{1}H NMR (DMSO-d_6 as solvent): δ 1.08–2.25 (5 H, m), 2.57–3.17 (1 H, m), 3.24–3.52 (1 H, m), 3.65 and 3.68 (1 H, 2 d, J 8.5 and 10 Hz), 3.91–4.57 (2 H, m), 7.91 and 7.93 (1 H, 2 s), 10.95, 11.07. 11.10 and 11.16 (2 H, 4 s).

5-(1-Formyl-hexahydro-1H-azepin-2-yl)-2,4,6-(1H,3H,5H)-pyrimidinetrione. Starting from 0.01 mol of each reactant the resulting mixture was refluxed for 5 h before subsequent isolation of the product. Yield 1.24 g (45 %), m.p. 230–235 °C. 1 g of the sodium salt was dissolved in water (20 ml) and the solution was acidified. Yield 0.70 g (76 %), m.p. 124–127 °C.

MS *m/e* (% rel. int., direct inlet): The spectra showed a large number of peaks between 128 and 251, all of low intensity (less than 5 %). The peak of the molecular ion (253) was absent. 128 (82, $C_4H_4N_2O_3$), 112 (17), 98 (32, $C_6H_{12}N$), 85 (59), 70 (57), 69 (68), 58 (100), 55 (100), 45 (100).

^{1}H NMR (DMSO-d_6 as solvent): δ 0.90–2.26 (8 H, m), 2.44–4.62 (3 H approx., m), 3.49 (br. s, presumably originating from water), 3.61 (1 H approx., d J 3.5 Hz), 7.85 and 8.16 (1 H, 2 s), 11.13, 11.16. 11.29 and 11.32 (2 H, 4 s).

5-(2-Formyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-2,4,6-(1H,3H,5H-pyrimidinetrione. The reaction was carried out by refluxing a mixture of 0.015 mol of each reactant for 24 h. Yield 4.40 (95 %), m.p. >325 °C. 0.5 g of the sodium barbiturate was dissolved in water (20 ml at 100 °C) and the solution was acidified. Yield 0.25 g (54 %), m.p. (simultaneous decomposition) 145–195 °C.

MS *m/e* (% rel. int., direct inlet): 287 (3, M), 258 (12, M–CHO), 242 (7), 172 (7), 160 (68, M–$C_4H_3N_2O_3$), 132 (68, $C_9H_{10}N$), 131 (68), 130 (100, C_9H_8N), 128 (53, $C_4H_4N_2O_3$), 117 (31), 115 (41), 103 (53), 85 (28), 77 (73).

^{1}H NMR (DMSO-d_6): δ 2.62–2.98 (2 H, m), 3.60–3.88 (1 H, m), 4.00–4.66 and 4.51–5.93 (3 H, m), 6.92–7.28 (4 H, m), 8.15, (1 H, apparently br s), 10.59–11.57 (2 H, 2 very br s).

5-(1-Formyl-2-pyrrolidinyl)-5-methyl-2,4,6-(1H)-pyrimidinetrione. The reaction mixture –0.05 mol of each reactant – was refluxed for 2 h before work-up. The solid product proved to be hygroscopic. Yield 8.5 g (65 %). The sodium salt was dissolved in water (20 ml) and the acid precipitated as the solution was acidified. Yield 4.1 g (53 %), m.p. (involving slight decomposition) 235–237 °C. MS *m/e* (% rel. int., direct inlet): 239 (5, M), 210 (18, M–CHO), 142 (3, $C_5H_6N_2O_3$), 124 (7), 98 (100, C_5H_8NO), 97 (22), 70 (96, C_4H_8N), 68 (32). ^{1}H NMR (DMSO-d_6 as solvent: δ 1.35 and 1.38 (3 H, 2 s), 1.51–2.26 (4 H, m), 2.79–3.79 (4 H, m), 3.32 (br s, presumably due to water), 4.13–4.46 (1 H, m), 7.95 and 8.10 (1 H, 2 s), 11.05, 11.08, 11.32 and 11.40 (2 H, 4 s).

2-Piperidineacetic acid hydrochloride. Dimethyl 1-formyl-2-piperidylmalonate (0.05 mol) was dissolved in sodium hydroxide solution (100 ml, 2.5 M) and the mixture refluxed for 20 h. The solution was cooled off and acidified with a slight excess of hydroxhloric acid. The solvent was removed by evaporation *in vacuo* and the residual solid was dried and decarboxylated at 100 °C at 1 mmHg. Anhydrous ethanol (100 ml) was added and the sodium chloride was filtered off and washed several times with anhydrous ethanol. The alcohol was removed by evaporation *in vacuo* and the product was collected as an oil. The product solidified after addition of ethanol and was, after cooling (9 °C), sucked off and washed with ethanol. Yield 5.22 g (58 %), m.p. 181–185 °C (reported 185 °C). MS *m/e* (% rel. int., direct inlet): 144 (2, M–Cl), 143 (5, M–HCl), 85 (7), 84 (100, $C_5H_{10}N$), 82 (9), 60 (10), 56 (17), 55 (11). ^{1}H NMR (DMSO-d_6 as solvent): δ 1.26–2.05 (6 H, m), 2.42–3.48 (5 H, m), 8.8–10.4 (2–3 H, very br s).

1-Formyl-hexahydro-α-phenyl-1H-azepine-2-acetic acid. Diethyl (1-formyl-hexahydro-1*H*-azepin-2-yl)phenylpropanedioate (0.0084 mol) was added to sodium hydroxide solution (35 ml, 1 M) and ethanol (20 ml) was added. Most of the starting material was dissolved and the mixture was stirred for 24 h at room temperature. As considerable amount of the starting material still remained unreacted (undissolved) the reaction mixture was refluxed for 1 h and a homogeneous solution was obtained. The solution was made acidic with hydrochloric acid and evaporated *in vacuo* at 100 °C. This procedure has earlier been observed to bring about decarboxylation of similar compounds. The residual dry solid was washed several times with anhydrous ethanol and the solution was filtered and evaporated *in vacuo*. The product was recrystallized from ethanol (10 ml). According to MS and NMR analyses,

the formyl group was still present in the isolated product despite exposure to high temperature under hydrolytic conditions. Yield 0.81 g (37 %), m.p. 214–215 °C.

MS *m/e* (% rel. int., direct inlet): 262 (1, M+1); the spectrum showed several peaks of low intensity between 262 and 126, 127 (9), 126 (100, $C_7H_{12}NO$), 98 (20, $C_6H_{12}N$), 91 (9), 77 (7).

^{1}H NMR δ 0.97–1.91 (6 H, m), 2.20–2.90 (2 H, m), 3.06–3.26 and 3.39–4.21 (3 H, m), 3.68 and 3.81 (1 H, 2 d, *J* 10.5 Hz), 7.19–7.32 (5 H, m), 7.41 and 7.79 (1 H, 2 s).

α-Phenyl-2-pyrrolidinylacetic acid hydrochloride. Diethyl (1-formyl-2-pyrrolidinyl)phenylmalonate (0.02 mol) was added to sodium hydroxide solution (40 ml, 2.5 M) and the mixture was heated. The starting material was found to be sparingly soluble in sodium hydroxide solution even at reflux temperature and after 30 min, without any indication of reaction, ethanol (5 ml) was added. After 15 min a homogeneous solution was obtained and reflux was continued for 12 h. The reaction mixture was allowed to cool down and was acidified with hydrochloric acid, causing evolution of CO_2. The acidic solution was refluxed for a few min to assure complete decarboxylation and filtered, in order to remove a small amount of precipitates, before evaporation of the solvent. In order to obtain a dry product anhydrous ethanol (50 ml) was added to the residual solid and then evaporated *in vacuo*. The procedure was repeated twice.

Finally anhydrous ethanol was added to the dry product and the sodium chloride was filtered off and washed with ethanol. The alcohol was evaporated *in vacuo* and the solid product was recrystallized from ethanol (5 ml). Yield 2.82 g (58 %), m.p. (simultaneous decomposition) ≥214 °C (reported 223 °C (decomposition). MS *m/e* (% rel. int., direct inlet): No molecular ion was observed; small peaks between 224 and 136, 136 (6, $C_6H_5-CH_2-COOH$), 91 (33), 77 (6), 70 (100, C_4H_8N).

^{1}H NMR (DMSO-d_6 as solvent): δ 1.35–2.43 (4 H m), 2.92–3.34 (2 H, m), 3.78–4.30 (2 H, m and d (centered at 4.20), *J* 11 Hz), 8.9–9.2 and 9.3–9.8 (2 H approx., 2 very br s).

(1-Formyl-2-piperidyl)propanedioic acid. Dimethyl (1-formyl-2-piperidyl)-malonate (0.03 mol) was dissolved in sodium hydroxide solution (50 ml, 2.5 M) and allowed to stand for 20 h at room temperature. The solution was acidified with hydrochloric acid and the solvent was removed by evaporation *in vacuo*. Dry acetone was added to the residue and subsequently removed by evaporation *in vacuo*. The procedure was repeated twice and the mixture of product and NaCl was dried for several h at 1 mmHg. The product was dissolved in acetone and the solution was filtered. After evaporation of the solvent the product crystallized after being dissolved in 8 ml of acetone. During the work-up care was taken not to exceed 60 °C. Yield 5.0 g (78 %), .p. (involving simultaneous decarboxylation) >140 °C.

^{1}H NMR (DMSO-d_6 as solvent): δ 0.98–1.83 (6 H, m), 2.62 and 3.14 (1 H, 2 t, *J* 12 Hz), 3.36–4.34 and 4.84–5.05 (2 H, m), 3.83 and 3.93 (1 H, 2 d, *J* 11 Hz), 8.07 and 8.11 (1 H, 2 s), the carboxylic acid protons were scarcely discernible as a broad signal at δ 10–14.

1-Formyl-2-piperidineacetic acid. (1-Formyl-2-piperidyl)propanedioic acid (0.0139 mol) was kept at 140–150 °C for 4 h. Acetone (2 ml) was added and the solution was chilled. The solid product was filtered off and washed with acetone. Yield 1.25 g (53 %), m.p. 89–94 °C.

MS *m/e* (% rel. int., direct inlet): 171 (13, M), 142 (24, M–CHO), 125 (7), 112 (100, $C_6H_{10}NO$), 97 (13), 84 (82, $C_5H_{10}N$), 56 (75).

^{1}H NMR (DMSO-d_6 as solvent): δ 1.02–1.77 (6 H, m), 2.24–3.25 (3 H, several coincident dd, *J* 9 and 15 Hz, and m), 3.34–3.60, 3.88–4.22 and 4.60–4.85 (2 H, m), 7.93 and 7.98 (1 H, 2 s).

2-(2-Oxopropyl)-1-piperidinecarboxaldehyde. Methyl 2-(1-formyl-2-piperidyl)-3-oxobutanoate (0.056 mol) was dissolved in sodium hydroxide solution (110 ml, 1 M) and was allowed to react for 24 h at room temperature. The solution was acidified with hydrochloric acid and evaporated *in vacuo* at 100 °C. Evolution of carbon dioxide was observed during the acidification. Several portions of anhydrous ethanol were added and the sodium chloride was filtered off. The solvent was removed by evaporation *in vacuo* and the residual oil was distilled at reduced pressure. The isolated product was found to be contaminated by 10 % of 1-formyl-2-piperidineacetic acid ethyl ester. Yield (including the by-product) 3.53 g (37 %), b.p. 140–143 °C/1.2–1.6 mmHg.

MS *m/e* (% rel. int.): 169 (17, M), 152 (17), 140 (22, M–CHO), 126 (70, M–$COCH_3$), 112 (87, $C_6H_{10}NO$), 98 (36), 84 (100, $C_5H_{10}N$), 56 (98), and (carboxylic acid ester): 199 (4, M), 170 (25, M–CHO or M–C_2H_5), 154 (7, M–OC_2H_5), 126 (7, M–$COOC_2H_5$), 125 (10), 122 (100, $C_6H_{10}NO$), 84 (88, $C_5H_{10}N$), 56 (49).

^{1}H NMR: δ 1.40–1.85 (6 H, m), 2.16 and 2.19 (3 H, 2 s), 2.51–4.37 and 4.86–5.11 (3 H, several coincident m), 2.70 and 2.90 (2 H, 2 d, *J* 8 Hz), 8.09 and 8.43 (1 H, 2 s). The main part of the spectrum was poorly resolved.

Hexahydro-2-(2-oxopropyl)-1H-azepine-1-carboxaldehyde. 2-(1-Formyl-hexahydro-1*H*-azepin-2-yl)-3-oxobutanoate (0.047 mol) was dissolved in sodium hydroxide solution (110 ml, 1 M) and

allowed to stand for 120 h at room temperature before acidification with hydrochloric acid. During the addition of hydrochloric acid evolution of carbon dioxide was observed. The solution was evaporated *in vacuo* at 100 °C and the residue was washed several times with anhydrous ethanol. The ethanol solutions were filtered and the solvent was removed by evaporation *in vacuo*. The resulting oil was distilled at reduced pressure. According to MS and NMR analyses the isolated product was contaminated by 10 % of 1-formyl-hexahydro-1*H*-azepine-2-acetic acid ethyl ester. Yield (including the by-product) 5.96 g (69 %), b.p. 140–143 °C/0.8–1.2 mmHg.

MS *m/e* (% rel. int.): 183 (7, M+1), 183 (12, M), 166 (5), 154 (17, M−CHO), 140 (72, M−$COCH_3$), 126 (87, M−CH_2COCH_3), 112 (41), 98 (72, $C_6H_{12}N$), 70 (40), 56 (100), and (carboxylic acid ester): 213 (4, M), 184 (21, M−CHO or M−CH_2CH_3), 168 (7, M−OCH_2CH_3), 140 (10, M−$COOCH_2CH_3$), 126 (100, M−$CH_2COOCH_2CH_3$), 112 (12), 98 (57, $C_6H_{12}N$), 70 (18), 56 (42), 55 (43).

^{1}H NMR: δ 1.07–2.89 (8 H, m), 2.11 and 2.15 (3 H, 2 s), 2.53–2.74 (2 H, m), 3.03–3.65, 3.83–4.24 and 4.34–4.64 (3 H, m), 8.08 (1 H, s).

Acknowledgements. This work was supported by grants from the Swedish Natural Science Research Council and from the Royal Physiographic Society in Lund.

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Received November 13, 1982.