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Decarboxylation Reactions. IX.[1] Reaction of Enamines with Trichloroacetic Anhydride

Toshiaki Morimoto and Minoru Sekiya

Shizuoka College of Pharmacy[2]

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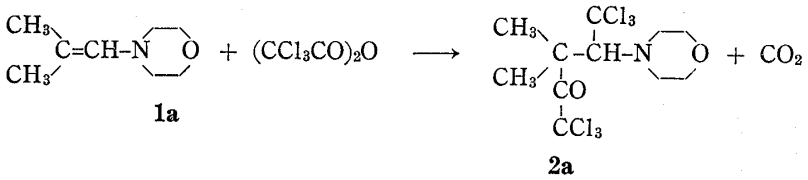
A reaction of β,β-dialkylenamines with trichloroacetic anhydride has been found to proceed with decarboxylation resulting in both β-trichloroacetylation and α-trichloromethylation. Mechanistically this reaction path involves an intermediate, β-trichloroacetylated iminium trichloroacetate, which suffers decarboxylation resulting in α-trichloromethylation. This course of the reaction was also stepwise processed by allowing to react with trichloroacetyl chloride, which was replaceable by *p*-nitrobenzoyl chloride, and succeedingly with trichloroacetate. The above reactions have provided a general method of synthesis of tertiary amines possessing both α-trichloromethyl and β-trichloroacetyl. Hydrolysis of these products is also described.

Keywords——enamines; decarboxylation reaction; acylation of enamines; iminium salts; trichloromethylation; hydrolysis of trichloroethylamines

β-Acylation of enamines, which possess β-hydrogen, with acyl chlorides or acid anhydrides is well known.[3] In the case of β,β-dialkylenamine, the reaction of 4-(2-methylpropenyl)morpholine (**1a**) with acyl chlorides has been reported to give the β-acylated iminium salts, hydrolysis of which gives β-diketones.[4] We wish to disclose here a unique reaction of β,β-dialkylenamines with trichloroacetic anhydride, which has been found to proceed with decarboxylation resulting in both β-trichloroacetylation and α-trichloromethylation. No paper has appeared describing such a reaction other than the reaction of enamines with trichloroacetic acid affording α-trichloromethylated products.[5] The present paper describes this reaction and, in addition, hydrolysis of the resulting products.

We first found that by allowing **1a** to react with trichloroacetic anhydride in tetrahydrofuran (THF) at room temperature, whereupon evolution of carbon dioxide was observed, 1,1,1,5,5,5-hexachloro-3,3-dimethyl-4-morpholino-2-pentanone (**2a**) was obtained in 62% yield. Its infrared (IR) and nuclear magnetic resonance (NMR) spectra are well interpreted to fit



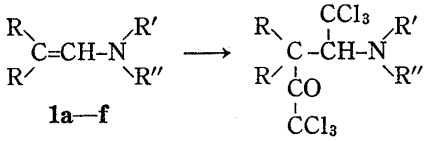
1a **2a**

Chart 1

the structure. When tetrahydrofuran was replaced by other solvents such as benzene, chloroform, and ethyl acetate, considerably lower yields, 40%, 25%, and 27%, respectively, were given.

1) Part VIII: K. Nanjo, K. Suzuki, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **26**, 848, (1978).
2) Location: *2-2-1, Oshika, Shizuoka, 422, Japan.*
3) G.H. Alt, "Enamines: Synthesis, Structure and Reactions," ed. by A.G. Cook, Marcel Dekker, New York and London, 1969, Chap. 4, pp. 135—152.
4) T. Inukai and R. Yoshizawa, *J. Org. Chem.*, **32**, 404 (1967).
5) A. Lukasiewicz and J. Lesinka, *Tetrahedron*, **24**, 7 (1968); G.H. Alt and A.J. Speziale, *J. Org. Chem.*, **31**, 1340 (1966).

TABLE I. Reaction[a] of β,β-Dialkylenamines with Trichloroacetic Anhydride



1a—f **2a—f**

Substrate No.	R	$N\begin{matrix}R'\\R''\end{matrix}$	React. temp. (°C)	React. time (hr)	Yield (%)
1a	CH_3		r. t.	3	62
1b	CH_3		r. t.	2	47
1c	CH_3	$N(CH_3)_2$	r. t.	5	62
1d	CH_3	$N\begin{matrix}CH_3\\C_6H_5\end{matrix}$	68—72	5	46
1e	$-(CH_2)_5-$		r. t.	2.5	36
1f	$-(CH_2)_5-$		r. t.	2.5	20

a) Substrate: 0.03 mol; trichloroacetic anhydride: 0.03 mol; solvent: tetrahydrofuran, 40 ml.

The reaction was extensively examined by the use of a variety of β,β-dialkylenamines (**1b—f**). Results are summarized in Table I. Thus a general method of synthesis of a new class of the compounds (compound A), tertiary amines possessing both trichloromethyl and trichloroacetyl, has been provided.

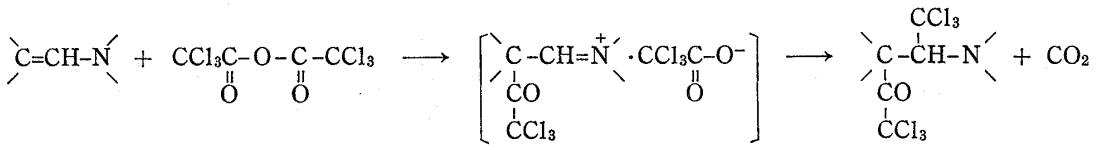
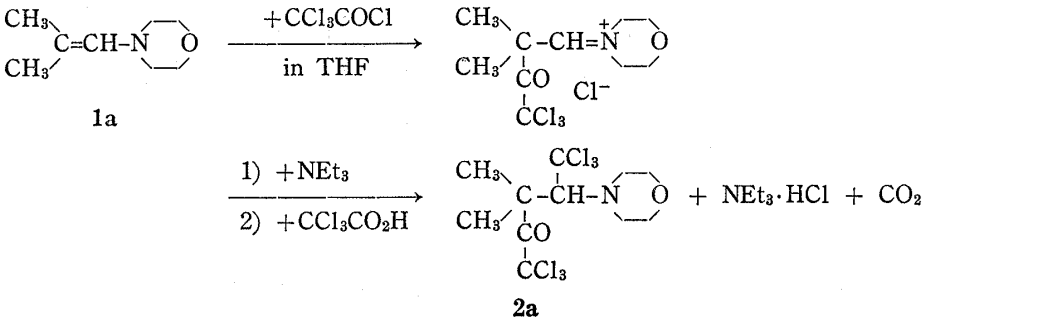
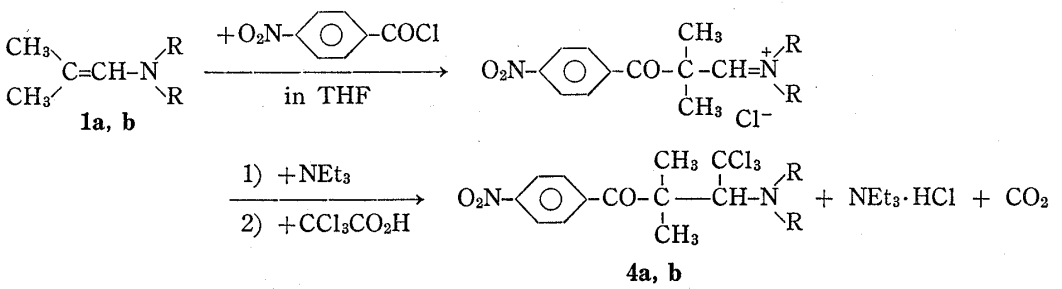


Chart 2



1a **2a**

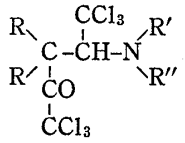


1a, b **4a, b**

a : $N\begin{matrix}R\\R\end{matrix}$ =  **b** : $N\begin{matrix}R\\R\end{matrix}$ =

Chart 3

Table II. 3,3-Dialkyl-4-amino-1,1,1,5,5,5-hexachloro-2-pentanones (**2a—f**)



Compd. No.	R	N(R′)(R″)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	CH_3		90—91 (P)	$C_{11}H_{15}Cl_6NO_2$	32.54 (32.91	3.73 3.68	3.45 3.41)
2b	CH_3		79—80 (P)	$C_{12}H_{17}Cl_6NO$	35.67 (35.85	4.24 4.15	3.47 3.60)
2c	CH_3	$N(CH_3)_2$	104—105 (H)	$C_{19}H_{13}Cl_6NO$	29.70 (29.89	3.60 3.61	3.85 3.84)
2d	CH_3	$N\langle^{CH_3}_{C_6H_5}$	119—120 (H)	$C_{14}H_{15}Cl_6NO$	39.47 (39.70)	3.55 (3.57)	3.29 (3.32)
2e	$\{CH_2\}_5$		147.5—148.5 (I)	$C_{14}H_{19}Cl_6NO_2$	37.70 (37.84	4.29 4.33	3.14 3.15)
2f	$\{CH_2\}_5$		139—140 (I)	$C_{15}H_{21}Cl_6NO$	40.57 (40.48	4.77 4.64	3.15 3.20)

Compd. No.	IR ν_{max}^{KBr} cm^{-1} (C=O)	NMR δ ($CDCl_3$) $CH_3\rangle C\langle CH_3$ (3H, s)	$\rangle C\langle$ (3H, s)	$\rangle CH$ (1H, s)	Other H			
2a	1718	1.75	1.95	4.36	2.7—3.8	8H	m	$4\times CH_2$
2b	1716	1.77	1.97	4.40	1.1—1.9	6H	m	$3\times CH_2$
					2.8—3.6	4H	m	$N(CH_2)_2$
2c	1710	1.72	1.94	4.57	2.55	3H	s	NCH_3
					2.89	3H	s	NCH_3
2d	1725	1.60	2.15	6.00	3.25	3H	s	NCH_3
					6.7—7.4	5H	m	C_6H_5
2e	1710	—	—	4.58	1.0—2.1	6H	m	$3\times CH_2$
					2.1—3.5	8H	m	$N(CH_2)_2$, $2\times CH_2$
					3.65—3.85	4H	m	$(CH_2)_2O$
2f	1714	—	—	4.57	1.0—2.0	10H	m	$8\times CH_2$
					2.0—3.0	6H	m	
					3.0—3.6	4H	m	$N(CH_2)_2$

P=petr. ether; H=hexane; I=isopropyl ether.

When considered mechanism of the reaction, a path shown in Chart 2 may be plausible. The iminium salt formed by β-trichloroacetylation of enamine would be an initial intermediate as supposed in the reaction with acyl halides. As a model, a NMR spectrum of a cold deuterochloroform solution of **1a** and trichloroacetic anhydride in 1:1 molar proportion evidenced a formation of the iminium salt, of which methine proton signal (δ 8.78 ppm) exhibited a considerable shift to lower magnetic field, when compared with that of **1a** (δ 5.22—5.31 ppm), and other proton signals were sufficiently assigned. At the reaction temperature the iminium salt formed may undergo decarboxylation of its trichloroacetate ion moiety and successive nucleophilic attack of the resulting trichloromethyl anion at its iminium carbon.

This reaction is exclusive with the substrate, β,β-dialkylenamine. An experiment using 4-(1-cyclohexenyl)morpholine (**3**) as a β-hydrogen-possessing enamine encountered complication presumably arising from the reaction of trichloroacetic acid, initially formed with β-trichloroacetylated enamine, with the starting enamine in a similar way to that reported by

Lukasiewicz.[5]

In accordance with the reaction of **1a** with acyl chlorides reported previously,[4] reactions with trichloroacetyl chloride and *p*-nitrobenzoyl chloride furnished the corresponding *β*-acylated iminium chlorides. Taking account of the reaction path shown in Chart 2, allowing these iminium chlorides to react in trichloroacetic acid–triethylamine medium gave the same product **2a** and the product possessing *p*-nitrobenzoyl in place of trichloroacetyl. Thus, **1a** and **1b** gave the corresponding products, **4a** and **4b**, respectively (Chart 3).

Lukasiewicz previously reported the hydrolysis of the compound of CCl_3–$\dot{C}$–N< leading to Cl–$\dot{C}$–CON< .[5] Hydrolysis of the compound A gave a new class of amides, CCl_3CO–$\dot{C}$–$\dot{C}$Cl-CON<, as exemplified by the following two experiments (Chart 4).

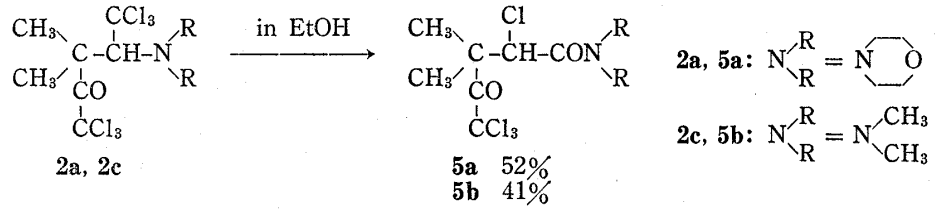


Chart 4

In addition, two examples of hydrolysis of *p*-nitrobenzoyl derivatives (**4a, b**) are shown in Chart 5. The IR and NMR spectra of the products are well interpreted to fit the structures.

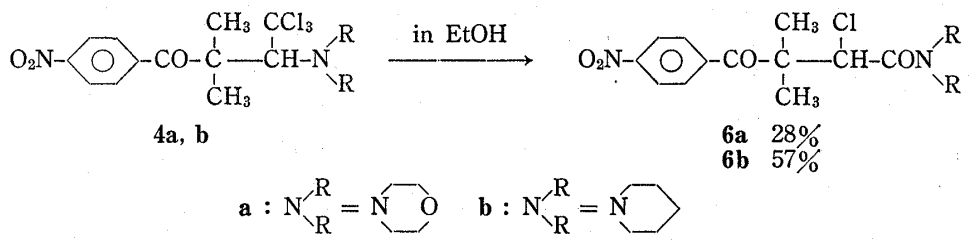


Chart 5

Experimental

All boiling and melting points are uncorrected. IR spectra were measured on a Hitachi EPI-G2 spectrophotometer. NMR spectra were measured by a Hitachi R-24 spectrometer and all chemical shifts are given in ppm downfield from TMS. The following abbreviations are used: s=singlet, d=doublet, m=multiplet, br=broad.

General Procedure for the Reaction of *β,β*-Dialkylenamines with Trichloroacetic Anhydride——The following *β,β*-dialkylenamines were prepared according to the previously reported method: 4-(2-methylpropenyl)morpholine (**1a**), bp 76—78° (27 mmHg) [lit.[6] bp 56—57° (11 mmHg)]; 1-(2-methylpropenyl)-piperidine (**1b**), bp 95—96° (75 mmHg) [lit.[6] bp 52° (14 mmHg)]; N,N,2-trimethylpropenylamine (**1c**), bp 87—88° (lit.[7] bp 87—88°); N,2-dimethylpropenylaniline (**1d**), bp 82—83° (0.85 mmHg) [lit.[7] bp 50—53° (0.1 mmHg)], 4-(cyclohexylidenemethyl)morpholine (**1e**), bp 123—125° (17 mmHg) [lit.[8] bp 105—107° (6 mmHg)]; 1-(cyclohexylidenemethyl)piperidine (**1f**), bp 117—119 (20 mmHg) [lit.[9] bp 75—88° (1.5—3.0 mmHg)].

A solution of trichloroacetic anhydride (9.3 g, 0.03 mol) in THF (10 ml) was added dropwise to a stirred solution of each of enamines **1a—f** (0.03 mol) in THF (30 ml) with cooling in an ice bath. The mixture was warmed in a stream of dry N_2 at the temperature effecting considerable evolution of CO_2. After subsidence

6) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).
7) K.C. Brannock and R.D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).
8) D.E. Heitmeier, J.T. Hortenstine, Jr., and A.P. Gray, *J. Org. Chem.*, **36**, 1449 (1971).
9) K.C. Brannock, A. Bell, R.D. Burpitt, and C.A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

of the CO_2 evolution the solvent was removed by evaporation. The resulting residue was triturated with a small amount of petr. ether with cooling to afford crystals which were collected by filtration and recrystallized from an appropriate solvent. In this way the corresponding 3,3-dialkyl-4-amino-1,1,1,5,5,5-hexachloro-2-pentanones (**2a**—**f**) were obtained as shown in Table I. Physical and analytical data of **2a**—**f** are listed in Table II.

A solution of **1a** and trichloroacetic anhydride in a 1:1 molar proportion dissolved in $CDCl_3$ was submitted to NMR spectral measurement. The observed spectrum was suggestive of a formation of the adduct intermediate, β-trichloroacetylated iminium trichloroacetate, as recorded in comparison with that of **1a** in the following; Iminium salt: δ 1.89 (6H, s, $2\times CH_3$), 3.88 (8H, br.s, $4\times CH_2$), 8.78 (1H, s, $\geqslant$CH). **1a**: δ: 1.60 (3H, s, CH_3), 1.66 (3H, s, CH_3), 2.49—2.65 (4H, m, $N(CH_2)_2$), 3.60—3.76 (4H, m, $(CH_2)_2O$), 5.22—5.31 (1H, m, =CH).

Reaction of 4-(1-Cyclohexenyl)morpholine (3) with Trichloroacetic Anhydride——A solution of trichloroacetic anhydride (6.2 g, 0.02 mol) in THF (10 ml) was added dropwise to a stirred solution of **3** (3.3 g, 0.02 mol) and triethylamine (2.0 g, 0.02 mol) in THF (20 ml) with cooling in an ice bath. After standing overnight, the reaction mixture was concentrated under reduced pressure. The residue was extracted with ether and the ethereal extract was shaken with 10% HCl (20 ml) overnight. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent left a pasty solid which was filtered and recrystallized from petr. ether to give 0.7 g (14%) of 2-trichloroacetylcyclohexanone as plates, mp 94—95°. IR ν_{max}^{KBr} cm^{-1}: 1750 (CCl_3 C=O), 1708 (C=O). *Anal.* Calcd. for $C_8H_9Cl_3O_2$: C, 39.01; H, 3.65. Found: C, 39.58; H, 3.77.

1,1,1,5,5,5-Hexachloro-3,3-dimethyl-4-morpholino-2-pentanone (2a)——Trichloroacetyl chloride (3.6 g, 0.02 mol) was added dropwise to a stirred solution of **1a** (2.8 g, 0.02 mol) in THF (20 ml) with cooling in an ice bath, whereupon a precipitate was deposited. Then triethylamine (2.0 g, 0.02 mol) and a solution of trichloroacetic acid (3.3 g, 0.02 mol) in THF (10 ml) were added dropwise to the mixture with occasional shaking. The reaction mixture was warmed at 30—35° for 3 hr in a stream of N_2 so as to effect considerable evolution of CO_2. After filtration of the deposited triethylamine hydrochloride, the filtrate was concentrated under reduced pressure. The residue was triturated with cold petr. ether and 5.0 g (62%) of raw **2a** was obtained by filtration. Recrystallization from isopropyl ether gave needles, mp 90—91°, undepressed on admixture with **2a** obtained above. Its IR spectrum was identical with that of **2a**.

4,4,4-Trichloro-2,2-dimethyl-3-morpholino-4′-nitrobutyrophenone (4a)——A solution of *p*-nitrobenzoyl chloride (3.7 g, 0.02 mol) in THF (10 ml) was added dropwise to a stirred solution of **1a** (2.8 g, 0.02 mol) in THF (30 ml) with cooling. After the addition, the mixture was stirred at room temperature for 2 hr, during which time a precipitate was deposited. To the stirred suspension was added dropwise triethylamine (2.0 g, 0.02 mol) and a solution of trichloroacetic acid (3.3 g, 0.02 mol) in THF (10 ml). The reaction mixture was warmed at 44—46° for 2.5 hr in a stream of N_2. After cooling the deposited triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure. The residue was triturated with cold hexane and 7.0 g (85%) of raw **4a** was obtained by filtration. Recrystallization from benzene–isopropyl ether gave pale yellow prisms, mp 128.5—129.5°. IR ν_{max}^{KBr} cm^{-1}: 1666 (C=O). NMR ($CDCl_3$) δ: 1.52 (3H, s, CH_3), 1.69 (3H, s, CH_3), 3.0—3.8 (8H, m, $4\times CH_2$), 4.68 (1H, s, $\geqslant$CH), 7.76 (2H, d, $J=9$ Hz, $H_{2',6'}$), 8.29 (2H, d, $J=9$ Hz, $H_{3',5'}$). *Anal.* Calcd. for $C_{16}H_{19}Cl_3N_2O_4$: C, 46.91; H, 4.67; N, 6.84. Found: C, 47.16; H, 4.60; N, 6.91.

4,4,4-Trichloro-2,2-dimethyl-4′-nitro-3-piperidinobutyrophenone (4b)——The reaction was carried out with **1b** (2.8 g, 0.02 mol), *p*-nitrobenzoyl chloride (3.7 g, 0.02 mol), triethylamine (2.0 g, 0.02 mol), and trichloroacetic acid (3.3 g, 0.02 mol) in THF in the same manner as described above. After reacting at 32—33° for 3 hr, the precipitated triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure. The crystalline residue was triturated with hexane and 6.9 g (85%) of raw **4b** was obtained by filtration. Recrystallization from benzene–isopropyl ether gave yellow prisms, mp 132—133°. IR ν_{max}^{KBr} cm^{-1}: 1688 (C=O). NMR ($CDCl_3$) δ: 1.48 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.2—1.8 (6H, m, $3\times CH_2$), 2.7—3.6 (4H, m, $2\times CH_2$), 4.62 (1H, s, $\geqslant$CH), 7.69 (2H, d, $J=9$ Hz, $H_{2',6'}$), 8.21 (2H, d, $J=9$ Hz, $H_{3',5'}$). *Anal.* Calcd. for $C_{17}H_{21}Cl_3N_2O_3$: C, 50.08; H, 5.19; N, 6.87. Found: C, 50.16; H, 5.13; N, 6.86.

4-(2,5,5,5-Tetrachloro-3,3-dimethyl-4-oxovaleryl)morpholine (5a)——A solution of **2a** (4.0 g) in 99% EtOH (40 ml) was heated under reflux for 24 hr. The solvent was removed by evaporation and the residual oil was fractionally distilled under reduced pressure to give 1.8 g (52%) of **5a** as a solid distillate, bp 195—200° (0.35 mmHg). Colorless needles, mp 74—75°, were obtained by recrystallization from petr. ether. IR ν_{max}^{KBr} cm^{-1}: 1722 (C=O), 1641 (N–C=O). NMR ($CDCl_3$) δ: 1.60 (3H, s, CH_3), 1.91 (3H, s, CH_3), 3.68 (8H, br.s, $4\times CH_2$), 4.95 (1H, s, $\geqslant$CH). *Anal.* Calcd. for $C_{11}H_{15}Cl_4NO_3$: C, 37.63; H, 4.31; N, 3.99. Found: C, 37.67; H, 4.27; N, 3.95.

N,N-Dimethyl-2,5,5,5-tetrachloro-3,3-dimethyl-4-oxovaleramide (5b)——A solution of 1,1,1,5,5,5-hexachloro-3,3-dimethyl-4-dimethylamino-2-pentanone (**2c**) (2.0 g) in 99% EtOH (20 ml) was heated under reflux for 8 hr. After filtration of an unidentified precipitate on cool, raw crystals of **5b** were obtained by concentration of the filtrate under reduced pressure. Recrystallization from petr. ether gave colorless needles (0.7 g, 41%), mp 80—81°. IR ν_{max}^{KBr} cm^{-1}: 1728 (C=O), 1646 (N–C=O). NMR ($CDCl_3$) δ: 1.71 (3H, s, CH_3), 1.91 (3H, s, CH_3), 2.93 and 3.18 (3H and 3H, s and s, $N(CH_3)_2$), 5.97 (1H, s, $\geqslant$CH). *Anal.* Calcd. for $C_9H_{13}Cl_4NO_2$: C, 34.98; H, 4.27; N, 4.53. Found: C, 34.97; H, 4.12; N, 4.50.

4-[2-Chloro-3,3-dimethyl-4-(4′-nitrophenyl)-4-oxobutyryl]morpholine (6a)——A solution of **4a** (2.0 g) in 99% EtOH (30 ml) was heated under reflux for 4 hr. The solvent was removed by evaporation and isopropyl ether was added to the residue. Insoluble morpholine hydrochloride was filtered off. Removal of the solvent gave an oily residue in which crystals deposited on cooling. The crystals of **6a** (0.4 g, 23%) collected by filtration were recrystallized from ether to give colorless prisms, mp 117.5—118.5°. IR ν_{max}^{KBr} cm^{-1}: 1687 (C=O), 1640 (N–C=O). NMR ($CDCl_3$) δ: 1.45 (3H, s, CH_3), 1.55 (3H, s, CH_3), 3.67 (8H, br.s, $4\times CH_2$), 5.02 (1H, s, $\geqslant$CH), 7.68 (2H, d, $J=9$ Hz, $H_{2',6'}$), 8.23 (2H, d, $J=9$ Hz, $H_{3',5'}$). *Anal.* Calcd. for $C_{16}H_{19}ClN_2O_5$: C, 54.16; H, 5.40; N, 7.90. Found: C, 54.20; H, 5.32; N, 7.95. The filtrate was submitted to column chromatography on silica gel using benzene and benzene–AcOEt (4: 1) as eluents. From the eluates *p*-nitroisobutyrophenone (0.33 g) and additional **6a** (0.08 g, 5%) were obtained.

4-[2-Chloro-3,3-dimethyl-4-(4′-nitrophenyl)-4-oxobutyryl]piperidine (6b)——A solution of **4b** (2.0 g) in 99% EtOH (30 ml) was heated under reflux for 3 hr. The solvent was removed by evaporation and isopropyl ether was added to the residue. Insoluble piperidine hydrochloride was filtered off and the filtrate was allowed to stand in a refrigerator. Precipitated crystals were collected by filtration and recrystallized from hexane to give 0.83 g of **6b** as colorless needles, mp 100—101°. IR ν_{max}^{KBr} cm^{-1}: 1693 (C=O), 1638 (N–C=O). NMR ($CDCl_3$) δ: 1.45 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.4—1.8 (6H, m, $3\times CH_2$), 3.4—3.7 (4H, m, $N(CH_2)_2$), 5.08 (1H, s, $\geqslant$CH), 7.73 (2H, d, $J=8$ Hz, $H_{2',6'}$), 8.23 (2H, d, $J=8$ Hz, $H_{3',5'}$). *Anal.* Calcd. for $C_{17}H_{21}ClN_2O_4$: C, 57.87; H, 6.00; N, 7.94. Found: C, 58.00; H, 5.97; N, 7.97. After removal of the solvent the oily residue was chromatographed over a silica gel column eluting benzene and benzene–AcOEt (1: 4) to give additional crystals of **6b** (0.16 g). Total yield of **6b** was 0.99 g (57%).

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