A New Synthesis of Substituted 2(1*H*)-Pyrazinones

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The hydrohalides of 2-*sec*-aminoalkanenitriles on treatment with oxalyl halides in *o*-dichlorobenzene at 80-100° give 3,5-dihalo-2(1*H*)-pyrazinones, of which the 3-halo substituent is easily replaced by nucleophiles. A reaction mechanism for the pyrazinone synthesis is proposed.

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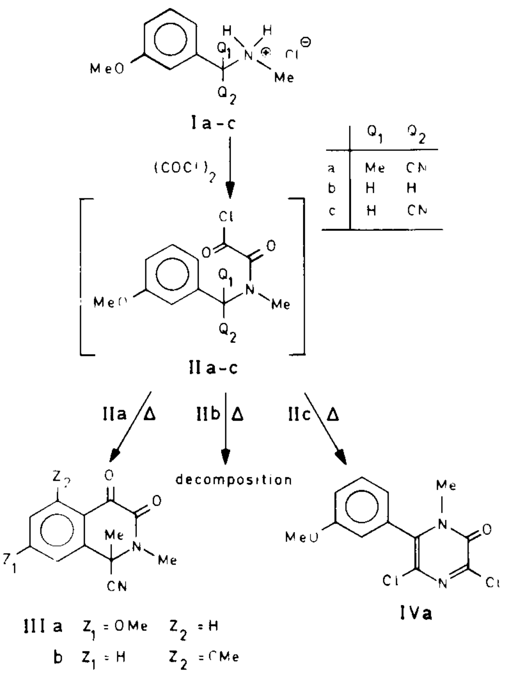
Reaction between oxalyl chloride and secondary benzamides leads to *N*-aroyloxamoyl chlorides, which may undergo cyclization to 1,3,4(2*H*)-isoquinolinetriones (2). In this context we have also investigated the possibilities of ring closure of some *N*-arylmethyloxamoyl chlorides (Scheme 1). On reaction with oxalyl chloride at 60° the ammonium salts Ia-c were transformed into the corresponding intermediates IIa-c, as shown spectroscopically. On further raising the temperature three divergent reaction pathways were followed. In case (a), the expected isoquinolinediones IIIa and IIIb were obtained; in case (b), only decomposition and tarry products were formed (2); in case (c), however, another type of product, identified as 3,5-dichloro-6-(3-methoxyphenyl)-1-methyl-2(1*H*)-pyrazinone (IVa), was isolated. This substitution pattern of the pyrazine skeleton appears to be unknown (3). This reaction is of interest not only for its mechanism but also because it can be used for the preparation of pyrazine derivatives some of which show antibacterial (3) or antileukemia (4) activity. In fact the 1-hydroxy-2-pyrazinone residue is found in natural antibiotics of the aspergillic acid type.

Scheme 1

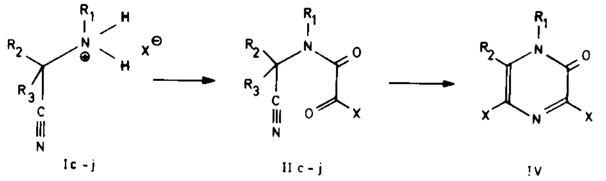


	Q1	Q2
a	Me	CN
b	H	H
c	H	CN

As indicated in Scheme 2, the reaction is not limited to salt Ic but can be extended to the readily accessible salts Id-h. As reactions of oxalyl halides with most free bases give symmetrical oxamides (5), the salts rather than the free amines must be used. Only in the case of less nucleophilic amines (*e.g.* I$_{\psi}$) can the free base be used.

All reactions were performed in *o*-dichlorobenzene (ODCB) in the presence of an excess of oxalyl chloride or bromide at 80-100°. After chromatographic purification and crystallization the desired pyrazinones IVa-g were isolated in good yield (43-67%).

Scheme 2

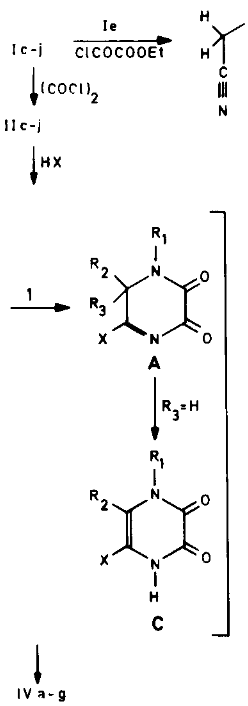


salt I	R_1	R_2	R_3	X	pyrazinone IV	yield %
c	Me	m-MeOC_6H_4	H	Cl	a	44
d	Me	Et	H	Cl	b	43
e	Me	H	H	Cl	c	55
f	Me	H	H	Br	d	49
g	$C_6H_5CH_2$	H	H	Cl	e	67
h	c-C_6H_{11}	H	H	Cl	f	62
i (free amine)	C_6H_5	H	H	Cl	g	56
j	$C_6H_5(CH_2)_2$	—$(CH_2)_5$—		Cl	—	—

With regard to the mechanism it can be assumed that acylation of the amine function and formation of oxamoyl halides IIc-j, occurs in the first step (6). The nmr spectra of evaporated samples from the reaction mixture at 60° are comparable with spectra of IIa and IIb (2); moreover reaction of Ie with ethyl chlorooxoacetate gave a stable product, identified as ethyl *N*-cyanomethyl-*N*-methyloxamate (V). The intermediate oxamoyl halides IIc-i can be converted into A by acid catalyzed intramolecular acylation of the nitrile function (path 1). Tautomerization to the cyclic intermediate C, followed by introduction of a second halogen atom by treatment with excess oxalyl halide, may explain the formation of 3,5-dihalo-2(1*H*)-pyrazinones IVa-g. In any event, IVc is formed on treatment of 5-chloro-1,4-dihydro-1-methyl-2,3-pyrazinedione IVa -obtained by hydrolysis of IVc - with oxalyl chloride in ODCB at 80°.

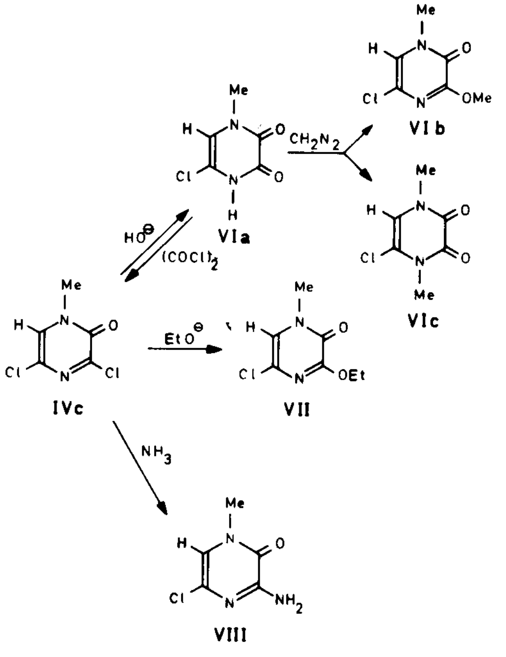
However, the following facts favour a mechanism involving the addition of HX to the nitrile function and tautomerization to an enamine before cyclization (path 2). Such a mechanism has been proposed by Simmchen for the ring closure of *o*-cyanomethylbenzoylchloride to 3-chloro-1(2*H*)-isoquinoline (6). Tautomerization to the enamine structure is impossible with Ia as starting material. If the alternative path 1 prevails one would expect the formation of a (1*H*,6*H*)-pyrazinedione of type A. This is not the case at 70-100° and at higher temperature (170°) isoquinoline diones IIIa and IIIb are formed. The presence of only 3 aromatic protons in both IIIa and IIIb - as shown by their nmr spectra - proves that ring closure occurs on the aromatic nucleus. The signals at 4.0 ppm (OMe) and 3.4 ppm (NMe) also appear in the nmr spectra of the corresponding isoquinolinetriones (2). Finally the molecular ion (M^+ 244 found for both products) would be expected for the proposed structure. The fact that IIj could not be converted into a (1*H*,6*H*)-pyrazinedione of type A (R_2,R_3 = cyclohexyl) but remained unchanged on heating, also favours a mechanism *via* an intermediate of type B when R_2 or R_3 = H.

Scheme 3



As can be expected, the use of different halides in one reaction leads to mixtures. Reaction of Ie and oxalyl bromide affords almost exclusively the 3,5-dibromo derivative IVd. However, according to ^{13}C nmr and mass spectral data, the reaction of If with oxalyl chloride leads to IVc and substantial amounts of unisolated 3-chloro-5-bromopyrazinone. The pyrazinone structure proposed for IVa-g has been confirmed by spectroscopic measurements and by chemical transformations. The ^{13}C nmr spectrum of model compound IVc is comparable with the published spectrum of 2-(1H)-pyrazinone (7); C−2 absorbs as a multiplet at 152.4 ppm, C−3 and C−5 appear as singlets at 146.5 and 123.6 ppm respectively and two quartets centered around 128.5 ppm correspond to C−6. The coupling constant with the adjacent proton H−6 is 189 Hz, indicating the presence of a vinylic carbon (8), and the long-range coupling with the *N*-methyl protons is approximately 4 Hz. The ^{13}C nmr spectra of the other 3,5-dichloropyrazinones show the same basic features. Replacement of chlorine by bromine (IVd) causes upfield shifts for C−3 (δ = 140.0 ppm) and C−5 (δ = 110.7 ppm) and a small downfield shift for C−6 (δ = 131.7 ppm). From their mass spectra it is clear that the chloropyrazinones IVa-c,e-g contain two chlorine atoms. The relative abundances of the M^+, $M+2^+$ and $M+4^+$ ions are: 9:6:1. In IVd, containing two bromine atoms, this relation is 1:2:1. The presence of a vinylic proton in IVc-g is revealed in ^1H nmr by a singlet at 7.3 ± 0.1 ppm. In the ^1H nmr spectra of IVb-d the *N*-methyl protons absorb at around 3.7 ppm, but in IVa the *m*-methoxyphenyl group is responsible for an upfield shift of 0.3 ppm. The infrared absorptions at 1660-1675 cm^{-1} are due to the conjugated six-membered lactam ring and to the imine bond. In agreement with this structure we have observed that substitution reactions at C−3 are possible, as shown for pyrazinone IVc (Scheme 4).

Scheme 4



On addition of potassium hydroxide to IVc in aqueous dioxane, it is transformed immediately into the very polar pyrazinedione VIa, which on treatment with diazomethane leads to 58% *O*-methylated product VIb and 42% *N*-methylated product VIc. Comparison with the

3-ethoxy derivative VII, prepared by the action of potassium ethoxide on IVc, allows unequivocal distinction between these two structures. The blue fluorescence, the polarity on silica gel and the δ-value of the vinylic proton in ^{1}H nmr are almost identical in VIb and VII; the 4-*N*-methyl derivative VIc is much more polar and has a markedly different ^{1}H nmr spectrum. The vinylic proton absorbs at higher field (6.4 ppm instead of 6.9 ppm) and the 4-*N*-methyl protons absorb at 3.5 ppm as compared with 4.0 ppm for the 3-*O*-methyl protons of VIb. The 3-amino derivative VIII has been prepared by reaction of IVc with ethanolic ammonia at room temperature; this compound could be easily purified because of its low solubility in common solvents. In contrast with VIa, where the lactam tautomer predominates, the amidine tautomer with an exocyclic amino group is preferred in VIII. We can conclude that a number of 5-halo-2(1*H*)-pyrazinones may be prepared by a short and efficient route. On treatment of an appropriate 2-aminoalkanenitrile hydrohalide with an oxalyl halide the corresponding 3,5-dihalopyrazinone is formed and the 3-halogen can easily be replaced as the C$-$3 is susceptible to nucleophilic attack. Further experiments directed towards the synthesis of specific substituted pyrazinones are in progress.

EXPERIMENTAL

Silica gel 60 (grain size 0.063-0.2 mm, Merck) has been used for column chromatography. All melting points are uncorrected. The uv and ir spectra were recorded on the Perkin-Elmer 124 and 257 spectrophotometers. Mass spectra were taken on an AEI-MS-12 (ionization energy 70 eV) apparatus. The mass spectral fragmentations are reported only if supported by high resolution measurements. For the nmr spectra a Jeol JNM-MH-100, a Varian XL-100 and a Bruker WP-80 spectrometer were used. Unless otherwise specified ir spectra were recorded in chloroform, uv spectra in ethanol and nmr spectra in deuteriochloroform. The hydrochloride salts were crystallized from diethylether-methanol.

2-(3-Methoxyphenyl)-2-methylaminopropanenitrile Hydrochloride (Ia).

A solution of 7.5 g of potassium cyanide, 8 g of methylammonium chloride and 21 ml of methylamine 35% in 60 ml water was treated with 15 g (0.1 mole) of 3-methoxyacetophenone, dissolved in 37.5 ml of ethanol 95%. The reaction mixture was stirred during 15 hours at 55°. Ethanol was removed *in vacuo* and the remaining solution was extracted three times with 100 ml of dichloromethane. The organic layer was evaporated under reduced pressure and the residue was treated carefully with 100 ml of ice-cold 1*M* hydrochloric acid. On cooling below 0°, 13.0 g of a white solid, identified as Ia, precipitated (57%), mp 101°; ^{1}H nmr (DMSO-d_6): δ, 2.33 (s, 3H, CMe), 2.60 (s, 3H, NMe), 3.90 (s, 3H, OMe), 7.08 (dxt, 1H, J = 8 × 2 Hz, H$-$4), 7.3-7.7 (m, 3H, H$-$2, H$-$5, H$-$6), 11.3 (s, 2H, $^+$NH$_2$).

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.27; H, 6.67; N, 12.36. Found: C, 57.97; H, 6.67; N, 12.15.

N-Methyl-3-methoxybenzylammonium Chloride (Ib) (2).

2-(3-Methoxyphenyl)-2-methylaminoacetonitrile. Hydrochloride (Ic).

A Strecker synthesis (9) on 13.6 g (0.1 mole) of 3-methoxybenzaldehyde, carried out as in the preparation of Ia, afforded, after hydrogen chloride treatment and crystallization, 14.0 g of the expected salt Ic (66%), mp 110°; ^{1}H nmr (DMSO-d_6): δ 2.64 (s, 3H, NMe), 3.85 (s, 3H, OMe), 6.15 (s, 1H, CH), 7.10 (dxt, 1H, J = 8 × 2 Hz, H$-$4), 7.3-7.7 (m, 3H, H$-$2, H$-$5, H$-$6), 10.5 (s, 2H, $^+$NH$_2$).

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.18. Found: C, 56.23; H, 6.14; N, 12.96.

2-Methylaminobutanenitrile Hydrochoride (Id).

Compound Id resulted from hydrogen chloride treatment of the corresponding aminonitrile, which was prepared from the cyanohydrine (10).

This compound was very hygroscopic, mp 72°; ^{1}H nmr (DMSO-d_6): δ 1.04 (t, 3H, CMe), 2.00 (m, 2H, CH$_2$), 2.66 (s, 3H, NMe), 4.66 (t, 1H, CH), 8.30 (broad s, 2H, $^+$NH$_2$).

2-Methylaminoacetonitrile Hydrochloride (Ie).

This compound was commercially available and allows the preparation of the corresponding hydrobromide (If), used as such without purification.

2-Benzylamino-, 2-Cyclohexylamino- and 2-Phenylaminoacetonitrile Hydrochloride (Ig-i).

The corresponding amines are described in the literature (11). The hydrochloride salts Ig-h have been obtained by treatment of these aminonitriles with gaseous hydrogen chloride in diethyl ether.

Compound Ig melted at 158°; ^{1}H nmr (dimethylsulfoxide-d_6): δ, 4.24 (s, 2H, CH$_2-$CN), 4.34 (s, 2H, CH$_2-$Ar), 7.30-7.80 (m, 5H, H$-$Ar), 10.6 (broad s, 2H, $^+$NH$_2$).

Anal. Calcd. for $C_9H_{11}ClN_2$: C, 59.18; H, 6.07; N, 15.34. Found: C, 59.28; H, 6.03; N, 15.31.

Compound Ih had mp 169°; ^{1}H nmr (dimethylsulfoxide-d_6): δ, 1.00-2.20 (m, 10 H, H-cyclohexyl), 3.00 (m, 1H, CH$-^+$NH$_2$), 4.30 (s, 2H, CH$_2-$CN), 10.20 (broad s, 2H, $^+$NH$_2$).

Anal. Calcd. for $C_8H_{15}ClN_2$: C, 55.00; H, 8.66; N, 16.04. Found: C, 54.63; H, 8.71; N, 15.65.

The free amine Ii (11) showed the following ^{1}H nmr characteristics: δ, 3.80 (s, 2H, CH$_2$CN), 5.20 (broad s, 1H, NH), 6.50-7.40 (m, 5H, aromatic).

1-Phenethylamino-1-cyclohexanecarbonitrile Hydrochloride (Ij).

This compound resulted from hydrogen chloride treatment of the aminonitrile, which was prepared along the cyanohydrine (10). The white crystals melted at 99° and were very hygroscopic: ^{1}H nmr (dimethylsulfoxide-d_6): δ, 1.00-2.80 (m, 10 H, H-cyclohexyl), 3.28 (broad s, 4 H, CH$_2-$CH$_2-$Ar), 7.36 (s, 5H, aromatic), 9.10 (broad s, 2H, $^+$NH$_2$).

1-Cyano-1,2-dihydro-1,2-dimethyl-7-methoxy-3,4-isoquinolinedione (IIIa) and 1-Cyano-1,2-dihydro-1,2-dimethyl-5-methoxy-3,4-isoquinolinedione (IIIb).

Compound Ia (11.32 g, 50 mmoles) was added to 12.5 ml (145 mmoles) of oxalyl chloride and 75 ml of carbon tetrachloride. The temperature was raised to 65°. When the liberation of hydrogen chloride had stopped, the excess oxalyl chloride and the solvent were removed *in vacuo*. The residue (13.5 g) corresponded to oxamoyl chloride IIa; ^{1}H nmr: δ 2.12 (s, 3H, CMe), 3.08 (s, 3H, NMe), 3.84 (s, 3H, OMe), 6.8-7.2 (m, 3H, H$-$2, H$-$4, H$-$6), 7.39 (t, 1H, J = 8 Hz, H$-$5). When a solution of IIa in 500 ml of ODCB was heated below 100°, no reaction took place. After reflux during four hours at 170° and removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel. The 7-methoxy isomer IIIa and the 5-methoxy isomer IIIb were eluted with 12.5% respectively 25% acetonitrile in dichloromethane. The separated products were crystallized from carbon tetrachloride-chloroform mixtures.

In this way 5.64 g (46%) of IIIa and 0.76 g (6%) of IIIb were isolated. Compound IIIa had mp 192°; ir: ν cm^{-1} 2840 (OMe), 1705, 1690, 1675 (CO$-$CO), 1600, 1585 (C$=$C); ^{1}H nmr: δ 2.10 (s, 3H, CMe), 3.43 (s, 3H, NMe), 4.01 (s, 3H, OMe), 7.13 (dxd, 1H, J = 9 × 2 Hz, H$-$6), 7.21 (d, 1H, J = 2 Hz, H$-$8), 8.17 (d, 1H, J = 9 Hz, H$-$5); ms: 244 (M$^+$, 9), 216 ($-$CO, 45), 201 ($-$CO, $-$Me, 100), 187 (13), 186 (18); exact mass: calculated for $C_{13}H_{12}N_2O_3$: C, 244.0848. Found: C, 244.085.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.55; H, 4.77; N, 11.30.

Compound IIIb had mp 199°; ir: ν cm^{-1} 2840 (OMe), 1725, 1704, 1682

(CO – CO), 1600, 1585 (C=C); ^{1}H nmr: δ 1.99 (s, 3H, CMe), 3.42 (s, 3H, NMe), 3.99 (s, 3H, OMe), 7.14 (d, 1H, J = 8 Hz, H – 6), 7.36 (d, 1H, J = 8 Hz, H – 8), 7.74 (t, 1H, J = 8 Hz, H – 7); ms: 244 (M$^+$, 14), 216 (– CO, 100), 215 (28), 201 (– CO, – Me, 62), 187 (79), 186 (33); exact mass: calculated for $C_{13}H_{12}N_2O_3$: 244.0848. Found: 244.084.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.64; H, 4.78; N, 11.31.

3,5-Dihalo-2(1*H*)-pyrazinones (IVa-g).

General Method.

Fifty mmoles or of the salts Ia-h of the free amine (Ii) were added to a mixture of 0.25 mole of oxalyl halide and 65 ml of ODCB. The temperature was raised slowly to the indicated value. After 4-6 hours the reaction was complete. Subsequently the excess oxalyl halide and the solvent were removed under reduced pressure. The residue was subjected to column chromatography on silica gel using acetonitrile-dichloromethane mixtures for elution. The products were stored at low temperature.

3,5-Dichloro-6-(3-methoxyphenyl)-1-methyl-2(1*H*)-pyrazinone (IVa).

The reaction temperature was 100°. After crystallization from diethyl ether-dichloromethane 6.33 g (44%) of IVa was isolated, mp 169°; ir: ν cm^{-1} 2835 (OMe), 1663 (lactam, C=N), 1582, 1562 (C=C); uv: λ max 348 nm (ε = 8900); ^{1}H nmr: δ 3.38 (s, 3H, NMe), 3.90 (s, 3H, OMe), 6.90 (t, 1H, J = 2 Hz, H – 2′), 6.93-7.10 (m, 2H, H – 4′, H – 6′), 7.55 (t, 1H, J = 7 Hz, H – 5′); ^{13}C nmr: δ 36.1 (NMe), 55.6 (OMe), 114.7, 116.2, 121.0 (C – 2′, C – 4′, C – 6′), 123.8 (C – 5), 131.1 (C – 5′), 131.9, 138.9 (C – 6, C – 1′), 145.2 (C – 3), 153.0 (C – 2), 168.6 (C – 3′); ms: 284 (M$^+$, 100), 283 (– H, 13), 269 (– Me, 3), 256 (– CO, 31), 249 (– Cl, 2); exact mass: calculated for $C_{12}H_{10}Cl_2N_2O_2$: 284.0118. Found: 284.012.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.55; H, 3.54; N, 9.82; Cl, 24.87. Found: C, 50.24; H, 3.56; N, 9.75; Cl, 24.76.

3,5-Dichloro-6-ethyl-1-methyl-2(1*H*)-pyrazinone (IVb).

The reaction temperature was 100°. Crystallization from diethyl ether yielded 5.4 g (52%) of IVb, mp 100°; ir: ν cm^{-1} 1661 (lactam, C=N), 1564 (C=C); uv; λ max 349 nm (ε = 8000); ^{1}H nmr: δ 1.30 (t, 3H, J = 7 Hz, CMe), 2.89 (q, 2H, J = 7 Hz, CH_2), 3.70 (s, 3H, NMe); ^{13}C nmr: δ 10.9 (CMe), 23.7 (CH_2), 33.2 (NMe), 122.8 (C – 5), 141.2 (C – 6), 142.9 (C – 3), 152.9 (C – 2); ms: 206 (M$^+$, 85), 178 (– CO, 6), 171 (– Cl, 6), 163 (– CO, – Me, 100); exact mass: calculated for $C_7H_8Cl_2N_2O$: 206.0013. Found: 206.000.

Anal. Calcd. for $C_7H_8Cl_2N_2O$: C, 40.60; H, 3.89; N, 13.53. Found: C, 40.30; H, 3.72; N, 13.31.

3,5-Dichloro-1-methyl-2(1*H*)-pyrazinone (IVc).

The reaction temperature was 80°. After crystallization from diethyl ether-dichloromethane 4.9 g (55%) of IVc was obtained; mp 71°C; ir: ν cm^{-1} 1675, 1660 (lactam, C=N), 1593 (C=C), 885 (=C – H); uv: λ max 344 nm (ε = 6240); ^{1}H nmr: δ 3.65 (s, 3H, NMe), 7.39 (s, 1H, H – 6); ^{13}C nmr: δ 38.5 (qxd, J = 143 × 3.3 Hz, NMe), 123.6 (s, C – 5), 128.5 (dxq, 189 × 3.8 Hz, C – 6), 146.5 (s, C – 3), 152.4 (m, C – 2); ms: 178 (M$^+$, 100), 150 (– CO, 91); exact mass: calculated for $C_5H_4Cl_2N_2O$: 177.9701. Found: 177.970.

Anal. Calcd. for $C_5H_4Cl_2N_2O$: C, 33.55; H, 2.25; N, 15.65; Cl, 39.61. Found: C, 33.81; H, 2.46; N, 15.47; Cl, 39.58.

3,5-Dibromo-1-methyl-2(1*H*)-pyrazinone (IVd).

The reaction temperature was 80°. After crystallization from dichloromethane 6.57 g (49%) of IVd was obtained, mp 98°C; ir: ν cm^{-1} 1675 (lactam, C=N), 1590 (C=C), 863 (=C – H); uv: λ max 345 nm (ε = 5070); ^{1}H nmr: δ 3.62 (s, 3H, NMe), 7.45 (s, 1H, H – 6); ^{13}C nmr: δ 39.3 (NMe), 110.7 (C – 5), 131.65 (C – 6), 140.0 (C – 3), 152.4 (C – 2); ms: 266 (M$^+$, 100), 238 (– CO, 81), 187 (– Br, 8); exact mass: calculated for $C_5H_4Br_2N_2O$: 265.8691. Found: 265.869.

Anal. Calcd. for $C_5H_4Br_2N_2O$: C, 22.42; H, 1.51; N, 10.46. Found: C, 22.31; H, 1.89; N, 10.37.

1-Benzyl-3,5-dichloro-2(1*H*)-pyrazinone (IVe).

The reaction temperature was 90°C. Crystallization from diethyl ether yielded 8.44 g (67%) of IVe, mp 80°; ir: ν cm^{-1} 1666 (lactam, C=N), 1590 (C=C), 884 (=CH); uv: λ max 346 nm (ε = 5920); ^{1}H nmr: δ 5.11 (s, 2H, CH_2Ph), 7.18 (s, 1H, H – 6), 7.36 (broad s, 5H, aromatic); ^{13}C nmr: δ 53.8 (CH_2), 124.1 (C – 5), 126.9 (C – 6), 128.8, 129.2, 129.4 and 133.9 (aryl-C), 147.0 (C – 3), 152.0 (C – 2); ms: 254 (M$^+$, 13), 91 (100); exact mass: calculated for $C_{11}H_8Cl_2N_2O$: 254.0013. Found: 254.001.

Anal. Calcd. for $C_{11}H_8Cl_2N_2O$: C, 51.79; H, 3.16; N, 10.98; Cl, 27.80. Found: C, 51.89; H, 3.27; N, 11.02; Cl, 27.71.

3,5-Dichloro-1-cyclohexyl-2(1*H*)-pyrazinone (IVf).

The reaction temperature was 100°. Crystallization from hexane yielded 7.63 g (62%) of IVf, mp 122°; ir: ν cm^{-1} 2930, 2860 (CH_2), 1660 (lactam, C=N), 1590 (C=C); uv: λ max 342 nm (ε = 8400); ^{1}H nmr: δ 1.00-2.40 (m, 10H, cyclohexyl-H), 4.74 (broad m, 1H, H – 1′), 7.40 (s, 1H, H – 6); ^{13}C nmr: δ 25.1, 25.5, 32.0 (C-cyclohexyl), 57.6 (C – 1′), 123.5 (C – 6), 124.2 (C – 5), 147.0 (C – 3), 151.6 (C – 2); ms: 246 (M$^+$, 29), 164 (– C_6H_{10}, 100); exact mass: calculated for $C_{10}H_{12}Cl_2N_2O$: 246.0327. Found: 246.033.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O$: C, 48.60; H, 4.90; N, 11.34; Cl, 28.69. Found: C, 48.71; H, 4.99; N, 11.41; Cl, 28.41.

3,5-Dichloro-1-phenyl-2(1*H*)-pyrazinone (IVg).

The reaction temperature was 100°. Crystallization from hexane-dichloromethane yielded 6.8 g (56%) of IVg, mp 157°; ir: ν cm^{-1} 1670 (lactam, C=N), 1585 (C=C), 883 (=C – H); uv: λ max 346 nm (ε = 8900); ^{1}H nmr: δ 7.32 (s, 1H, H – 6), 7.48 (m, 5H, aryl-H); ^{13}C nmr: δ 124.2 (C – 5), 127.0 (C – 6), 148.4 (C – 3), 151.4 (C – 2), 125.7, 129.9 and 138.7 (aryl-C); ms: 240 (M$^+$, 88), 212 (– CO, 30), 77 (100); exact mass: calculated for $C_{10}H_6Cl_2N_2O$: 239.9857. Found: C, 239.986.

Anal. Calcd. for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62; Cl, 29.41. Found: C, 49.68; H, 2.59; N, 11.63; Cl, 29.21.

Reaction of Ij and its Transformation into IIj.

When Ij was treated with oxalyl chloride in the same way as Ia-h, the ^{1}H nmr spectrum of the reaction mixture (after evaporation of excess oxalyl chloride and solvent *in vacuo*) showed a broad multiplet (10H) between 1.0 and 2.5 ppm, 2 multiplets respectively at ± 2.90 and 3.60 ppm (2 × 2H) and a broad singlet at 7.20 ppm (5H). The ^{13}C nmr spectrum revealed the presence of a C≡N group at 117.78 ppm and of 2 carbonyl-C atoms respectively at 159.92 and 162.87 ppm. From the mass spectrum it became clear that the substance contains one chlorine atom (M$^+$ 318.100). Structure IIj is in agreement with these experimental facts.

Compound IIj, being an oil, was further characterized as the corresponding methyl ester. After crystallization from hexane it melted at 80°; ir: ν cm^{-1} 2950, 2870, 1735 (ester) and 1670 (amide); ^{1}H nmr: δ 1.10-2.40 (m, 10H, cyclohexyl-H), 2.97 and 3.50 (2 x m, 2 × 2H, $CH_2 - CH_2Ar$), 3.83 (s, 3H, OMe) and 7.23 (m, 5H, H – Ar); ^{13}C nmr: δ 23.6, 24.6, 33.5 and 60.3 (C-cyclohexyl), 37.9 and 49.1 ($CH_2 - CH_2$), 53.0 (OMe), 118.6 (C≡N), 127.4, 129.0, 129.2 and 137.5 (C – Ar), 162.7 and 162.9 (CO), ms: 314 (M$^+$, 26), 223 (– C_7H_7), 42), 110 (100); exact mass: calculated for $C_{18}H_{22}N_2O_3$: 314.1630. Found: 314.1627.

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.06; N, 8.91. Found: C, 68.73; H, 7.09; N, 8.85.

Ethyl *N*-Cyanomethyl-*N*-methyloxamate (V).

Compound Ie (1.065 g, 10 mmoles) was added to 3.4 ml (30 mmoles) of ethyl chlorooxoacetate. The temperature was raised to 120°. Prolonged heating did not affect the reaction product, which after removal of the excess ethyl chlorooxoacetate and chromatography on silica gel with dichloromethane as eluent, was identified as V; ir: ν cm^{-1} 2264 (CN), 1748 (ester), 1680 (amide); ^{1}H nmr: δ 1.38 (t, 3H, J = 7 Hz, CMe), 3.18 (s, 3H, NMe), 4.40 (q, 2H, J = 7 Hz, OCH_2), 4.41 (s, 2H, NCH_2); ms: 170 (M$^+$, 26), 98 (57), 97 (100), 69 (42).

5-Chloro-1,4-dihydro-1-methyl-2,3-pyrazinedione (VIa), 5-Chloro-3-methoxy-1-methyl-2(1*H*)-pyrazinone (VIb) and 5-Chloro-1,4-dihydro-1,4-dimethyl-2,3-pyrazinedione (VIc).

Compound IVc (1.79 g, 10 mmoles) dissolved in 10 ml of dioxane was treated with a solution of 0.56 g (10 mmoles) of potassium hydroxide in 10 ml of dioxane-water (1:1). The starting material quickly disappeared as indicated by tlc analysis. After removal of the solvent under reduced pressure and crystallization of the residue from ethanol, compound VIa resulted with the following characteristics, mp 253.5°; ir (potassium bromide): ν cm^{-1} 1685 (secondary amide) and 1650 (tertiary amide); ^{1}H nmr (DMSO-d_6): δ, 3.39 (s, 3H, NMe), 6.34 (s, 1H, H – 6), 8.05 (s, 1H, NH).

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.40; H, 3.14; N, 17.44. Found: C, 37.66; H, 3.25; N, 17.52.

After dissolution of the crude product VIa in 50 ml methanol and 1 day treatment with excess diazomethane in diethyl ether, two new products could be isolated after column chromatography on silica gel: 0.82 g (47%) of IVb was eluted with 5% acetonitrile in dichloromethane and 0.59 g (34%) of VIc with 25% acetonitrile in dichloromethane. These compounds were recrystallized from carbon tetrachloride. Compound VIb had mp 140°; ir: ν cm^{-1} 2845 (OMe), 1665 (lactam), 1602 (C = N), 1549 (C = C), 910 (= C – H); uv: λ max 315 nm (ϵ = 7050); ^{1}H nmr: δ 3.57 (s, 3H, NMe), 4.04 (s, 3H, OMe), 6.93 (s, 1H, H – 6); ms: 174 (M$^+$, 100), 159 (– Me, 13), 145 (– CO, – H, 56), 131 (– CO, – Me, 80), 90 (45); exact mass: calculated for $C_6H_7ClN_2O_2$: 174.0196. Found: 174.0193.

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.27; H, 4.04; N, 16.05. Found: C, 41.59; H, 4.28; N, 15.66.

Compound VIc had mp 202°; ir: ν cm^{-1} 1700, 1690 (CO – CO), 1642 (C = C); uv: λ max 318 nm (ϵ = 5200); ^{1}H nmr: δ 3.43 (s, 3H, NMe – 1), 3.55 (s, 3H, NMe – 4), 6.39 (s, 1H, H – 6); ms: 174 (M$^+$, 100), 146 (– CO, 15), 131 (– CO, – Me, 9), 117 (27), 90 (9); exact mass: calculated for $C_6H_7ClN_2O_2$: 174.0196. Found: C, 174.0194.

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.27; H, 4.04; N, 16.05. Found: C, 41.22; H, 3.99; N, 16.03.

5-Chloro-3-ethoxy-1-methyl-2(1*H*)-pyrazinone (VII).

Compound IVc (1.79 g, 10 mmoles) dissolved in 10 ml of absolute ethanol was treated with 10 ml of 1*M* potassium ethoxide in ethanol. The reaction mixture was kept at room temperature during two hours, evaporated and chromatographed on silica gel. The ethoxy derivative VII was eluted with 6% acetonitrile in dichloromethane. Crystallization from a dichloromethane-diethyl ether mixture yielded 1.51 g (79%) of pure VII, mp 144°; ir: ν cm^{-1} 1664 (lactam), 1601 (C = N), 1542 (C = C), 911 (= C – H); uv: λ max 316 nm (ϵ = 6150); ^{1}H nmr: δ 1.45 (t, 3H, J = 7 Hz, CMe), 3.56 (s, 3H, NMe), 4.42 (q, 2H, J = 7 Hz, OCH_2), 6.90 (s, 1H, H – 6); ^{13}C nmr: δ 13.7 (CMe), 36.7 (NMe), 64.0 (OCH_2), 120.1 (C – 6), 122.4 (C – 5), 150.5 (C – 3), 154.4 (C – 2); ms: 188 (M$^+$, 85), 160 (– C_2H_4, 100), 132 (– C_2H_4, – CO, 46), 103 (32), 90 (25); exact mass: calculated for $C_7H_9ClN_2O_2$: 188.0353. Found: 188.0352.

Anal. Calcd. for $C_7H_9ClN_2O_2$: C, 44.57; H, 4.81; N, 14.86; Cl, 18.80. Found: C, 44.68; H, 4.91; N, 14.79; Cl, 18.73.

3-Amino-5-chloro-1-methyl-2(1*H*)-pyrazinone (VIII).

Compound IVc (1.79 g, 10 mmoles) dissolved in 30 ml of dioxane was treated with 4 ml of 25% ammonia. On standing a pink solid was deposited. After suction filtration, washing with water, ethanol and dichloromethane and crystallization from chlorofrom, 1.32 g (83%) of VIII remained, mp 265°C; ir (potassium bromide): ν cm^{-1} 3365, 3180 (NH_2), 1670 (lactam), 1630 (C = N), 1611, 1598, 1583, 1541 (C = C, C – NH_2), 927 (= C – H); uv: λ max 326 nm (ϵ = 8200); ^{1}H nmr (DMSO-d_6): δ 3.39 (s, 3H, NMe), 6.75 (s, 2H, NH_2), 6.92 (s, 1H, H – 6); ms: 159 (M$^+$, 100), 132 (– HCN, 8), 130 (– CO, – H, 19), 116 (– CO, – Me, 22), 89 (– CO, – Me, – HCN, 13).

Anal. Calcd. for $C_5H_6ClN_3O$: C, 37.64; H, 3.79; N, 26.33; Cl, 22.22. Found: C, 37.53; H, 3.96; N, 25.95; Cl, 22.17.

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