SYNTHESIS OF 3,4-DIHYDROPYRIDAZINO[1,6-*a*]BENZIMIDAZOLES[#]

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Abstract - 3,4-Dihydropyridazino[1,6-*a*]benzimidazoles (**4a-e**) have been prepared by catalytical hydrogenation of dialkyl *(E)*-2-(substituted 2-nitrophenylhydrazono)glutarates (**1a-e**) to the respective amines (**2**) followed by their base catalyzed cyclization in a tandem reaction proceeding *via* 4,5-dihydropyridazin-6(1H)-one intermediates (**3**).

INTRODUCTION

The synthesis of several pyridazino[1,6-*a*]benzimidazoles from appropriate heterocyclic precursors by means of thermolysis,[1] cyclocondensation,[2-4] and photocyclization[5,6] has been reported. Furthermore, the preparation of both 1,2,3,4-tetrahydro[7] and 6,7,8,9-tetrahydro derivatives[8,9] has been described.

As part of a program on the synthesis of various *N*-heterocycles by reductive cyclization of ortho-nitroaryls[10-13] involved with reactions of different 2-nitrophenylhydrazono compounds we have out of them made

[#] Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

accessible 4*H*-pyrazolo[1,5-*a*]benzimidazoles,[14] (1,2,4-benzotriazin-3-yl)-acetic acid derivatives,[15] benzo[1,2-*b*:5,4-*b'*]bis(1*H*)-imidazo[1,2-*b*]pyrazoles),[16] and substituted 1,2-dihydro-1,2,5-benzotriazepines.[17]

We wish to report here the first synthesis of 3,4-dihydropyridazino-[1,6-*a*]benzimidazoles by reductive cyclization of 2-nitrophenylhydrazones of dialkyl 2-oxoglutarates.

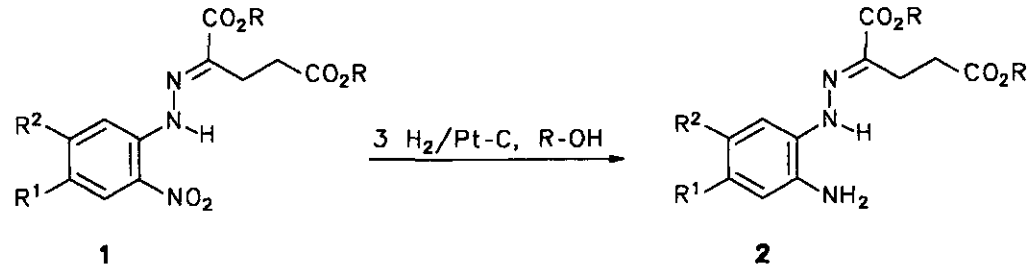
RESULTS AND DISCUSSION

The requisite dimethyl 2-(substituted 2-nitrophenylhydrazono)glutarates (**1a-c**) and (5) were prepared in form of pure *(E)*-isomers from the corresponding substituted 2-nitrophenylhydrazines and dimethyl 2-oxoglutarate similar to the procedure of Schwesinger *et al.* , who recently reported on the tautomerism of such hydrazones.[18] Compounds (**1d-e**) were accessible by transesterification of the methyl esters (**1a-b**).

On hydrogenation over 3% Pt-C catalyst under standard conditions the *(E)*-nitrohydrazones (**1**) reacted to form the dialkyl *(E)*-2-(2-amino-4,5-substituted phenylhydrazono)glutarates (**2**), detectable on tlc plates by condensation with the 4-dimethylaminobenzaldehyde reagent yielding orange coloured azomethines. As examples, amines (**2a**) and (**2d**) have been isolated and characterized.

It was the aim of our investigation to compare the reaction behaviour of the nitrohydrazones (**1**) during catalytical hydrogenation with that of related compounds, which have been reductively cyclized under the same conditions. Hence, it seemed possible, that the amines (**2**) could either cyclize by addition to the azomethine double bond forming a 1,2,4-benzotriazine derivative[15] or by condensation with the 1-alkoxycarbonyl group yielding a 1,2,5-benzotriazepine compound.[17] However, none of these opportunities has been realized.

We have, therefore, tried to achieve cyclization by heating the amines



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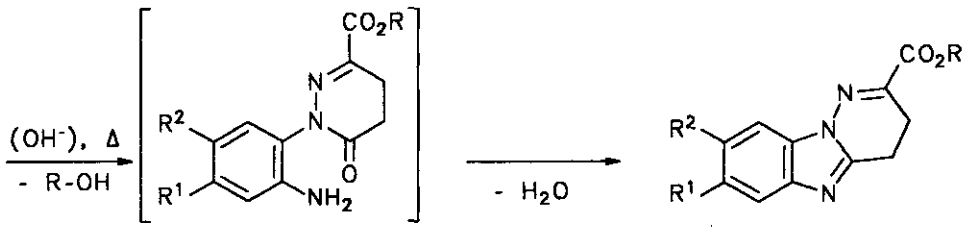

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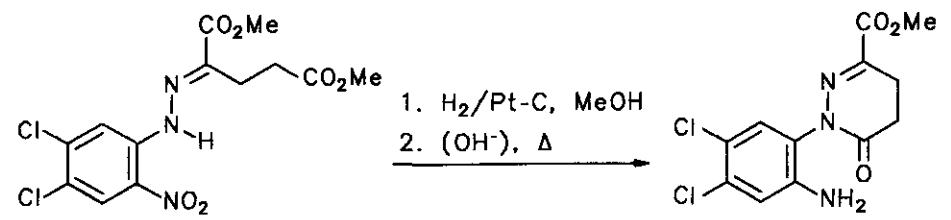
1 - 4	R	R^1	R^2
a	Me	H	H
b	Me	Cl	H
c	Me	H	Cl
d	Et	H	H
e	Et	Cl	H



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(2) in an acidic or basic medium. Whereas acidic catalysis did not influence (2), heating of the filtrated hydrogenation solutions under alkaline catalysis yielded the heterocycles (4) as first representatives of the 3,4-dihydropyridazino[1,6-*a*]benzimidazole system. Obviously, the reaction proceeds *via* the intermediate alkyl [1-(2-amino-4,5-substituted

phenyl)-4,5-dihydropyridazin-6(1*H*)-on-3-yl]carboxylates (**3**), which then undergo another cyclization to form (**4**). This suggestion is supported by the finding, that dimethyl *(E)*-2-(4,5-dichloro-2-nitrophenylhydrazono)glutarate (**5**) under the same conditions underwent only the first cyclization leading to the isolable pyridazine derivative (**6**).

Thus, the formation of the 3,4-dihydropyridazino[1,6-*a*]benzimidazole skeleton by a tandem reaction starting from (**2**) is in principle analogously to the synthesis of 4*H*-pyrazolo[1,5-*a*]benzimidazoles[14] from 2-nitrophenylhydrazones of ß-ketocarboxylic acid esters and may be regarded as a ring-enlarged variant thereof.

Furthermore, we have been interested in comparing the reaction behaviour of the *(E)*- and *(Z)*-isomers of (**1**). Therefore, the thermodynamically more stable *(Z)*-isomers of (**1**) have been prepared by stirring an ethereal solution of a corresponding *(E)*-(**1**) compound after addition of concentrated hydrochloric acid. Completeness of isomerization was detected by tlc and proven by the clear downfield shift of the *(Z)*-NH signal in the ^{1}H-nmr spectra.[17,18] However, the *(Z)*-isomers of (**1**) on hydrogenation yielded only respective *(Z)*-2-aminophenylhydrazones as isomers of (**2**), which could neither be forced to cyclize by acidic nor basic catalysis.

In summary, we are now able to evaluate the behaviour of 2-nitrophenylhydrazones of dialkyl 2-oxodicarboxylates under the conditions of reductive cyclization. The 2-nitrophenylhydrazones of dialkyl mesoxalates can be cyclized to form 3-alkoxycarbonyl-4-hydroxy-1*H*-1,2,5-benzotriazepines.[19] Similarly, the *(Z)*-2-nitrophenylhydrazones of dialkyl 2-oxalacetates react to form 3-alkoxycarbonylmethylen-4-hydroxy-1,2-dihydro-1,2,5-benzotriazepines,[17] whereas the *(E)*-isomers yield uncyclized amines only. Finally, in contrast to their lower homologues, *(E)*-2-nitrophenylhydrazones of dialkyl 2-oxoglutarates (**2**) have been transformed to 3,4-dihydro-

pyridazino[1,6-a]benzimidazoles (4).

The financial support for this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

EXPERIMENTAL

Melting points were determined on a Boetius micro hotstage and are corrected. Ir spectra were measured on a *Carl Zeiss Jena spectrophotometer* Specord M80. Nmr spectra were recorded with a Varian Gemini 200 spectrometer at 199.975 MHz and a Varian 400 spectrometer at 399.952 MHz, resp., for ^{1}H and with a Varian Gemini 200 spectrometer at 50.289 MHz for ^{13}C. Chemical shifts for nmr signals are reported in ppm from tetramethylsilane. Mass spectra were collected at 70 eV with a Finnigan MAT 212 spectrometer at an ion source temperature of 200 °C. Elemental analyses were performed on *a Heraeus CHN-O-RAPID analyzer*.

General procedure for the synthesis of dimethyl *(E)*-2-(substituted 2-nitrophenylhydrazono)glutarates (1a-c) and (5): To a suspension of 10 mmol of the corresponding substituted phenylhydrazine in 10 ml of methanol were added 150 mg of acetic acid (for **(1a)** or 150 mg of concentrated hydrochloric acid (for **(1b)**, **(1c)** and **(5)**). The resulting mixture was stirred for 1 h at 20 °C, became clear in between times and finally separated the hydrazones **(1a-c)** and **(5)** as crystals.

Dimethyl *(E)*-2-(2-nitrophenylhydrazono)glutarate (1a): Yield 2.24 g (72%) orange crystals, mp 108-110 °C (MeOH); lit.,[18] mp 109-111 °C. Ir (KBr): ν =1700 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 11.44 (s,1H), 8.23-6.98 (m, 4H), 3.88 (s,3H), 3.66 (s,3H), 2.95 (t,J=6.5 Hz,2H), 2.74 (t,J=6.5 Hz,2H).

Dimethyl *(E)*-2-(4-chloro-2-nitrophenylhydrazono)glutarate (1b): Yield 2.34 g (68%), dark orange crystals, mp 104-106 °C (MeOH). Ir (KBr): ν = 1725 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$): δ = 11.40 (s,1H), 8.18-7.49 (m,3H), 3.88 (s,3H), 3.68 (s,3H), 2.92 (t,J=5.8 Hz,2H), 2.74 (t,5.8 Hz,2H). Anal. Calcd for $C_{13}H_{14}N_3O_6Cl$: C, 45.42; H, 4.10; N, 12.22; Cl,10.31. Found: C, 45.23; H, 4.26; N, 12.17; Cl, 10.39.

Dimethyl *(E)*-2-(5-chloro-2-nitrophenylhydrazono)glutarate (1c): Yield 2.58 g (75%), yellow crystals, mp 99-101 °C (MeOH). Ir (KBr): ν = 1720 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 11.47 (s,1H), 8.17-6.91 (m,3H), 3.90 (s,3H), 3.67 (s,3H), 2.91 (t,J=5.9 Hz,2H), 2.78 (t,J=5.9 Hz,2H). Anal. Calcd for $C_{13}H_{14}N_3O_6Cl$: C, 45.52; H, 4.10; N, 12.22; Cl, 10.31. Found: C, 45.13; H, 4.31; N, 12.40; Cl, 10.26.

Dimethyl *(E)*-2-(4,5-dichloro-2-nitrophenylhydrazono)glutarate (5): Yield 2.46 g (65%), yellow crystals, mp 122-124 °C (MeOH). Ir (KBr): ν = 1730, 1700 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 11.43 (s,1H), 8.32 (s,1H), 8.13 (s,1H), 3.91 (s,3H), 3.67 (s,3H), 2.90 (t,J=6.3 Hz,2H), 2.77 (t,J=6.3 Hz,2H). Anal. Calcd for $C_{13}H_{13}N_3O_6Cl_2$: C, 41.29; H, 3.46; N, 11.11; Cl, 18.75. Found: C, 41.12; H, 3.59; N, 10.99; Cl, 18.79.

General procedure for the synthesis of diethyl *(E)*-2(substituted 2-nitrophenylhydrazono)glutarates (1d-e): Sodium carbonate (1.06 g, 10 mmol) was added to a solution of the appropriate methyl precursor (**1a**) or (**1b**), resp., in 100 ml of absolute ethanol. After refluxing for 1 h, the mixture was filtered. The filtrate separated the hydrazones (**1d-e**) on standing as crystals.

Diethyl *(E)*-2-(2-nitrophenylhydrazono)glutarate (1d): Yield 1.44 g (85%), yellow crystals, mp 90-92 °C (EtOH). Ir (KBr): ν = 1745, 1710 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 11.39 (s,1H), 8.18-6.96 (m,4H), 4.23 (q,J=7.0 Hz,2H), 4.11 (q,J=7.0 Hz,2H), 2.93 (t,J=7.0 Hz,2H), 2.69 (t,J=7.0 Hz,2H), 1.37 (t,J=7.0 Hz,3H), 1.21 (t,J=7.0 Hz,3H). Anal. Calcd for $C_{15}H_{19}N_3O_6$: C,

53.40; 5.68; N, 12.46. Found: C, 53.18; H, 5.89; N, 12.60.

Diethyl *(E)*-2-(4-chloro-2-nitrophenylhydrazono)glutarate (1e): Yield 1.38 g (74%), orange crystals, mp 69 -71 °C (EtOH). Ir (KBr): ν = 1735, 1725 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 11.41 (s,1H), 8.20-7.,51 (m,3H), 4.34 (q,J=7.1 Hz,2H), 4.13 (q,J=7.1 Hz,2H), 2.93 (t,J=6.3 Hz,2H), 2.73 (t,J=6.3 Hz,2H), 1.40 (t,J=7.1 Hz,3H), 1.23 (t,J=7.1 Hz,3H). Anal. Calcd for $C_{15}H_{18}N_3O_6Cl$: C, 48.45; H, 4.88; N, 11.30; Cl 9.94. Found: C, 48.70; H, 5.02; N, 11.13; Cl, 9.31.

General procedure for the isomerization of *(E)*-hydrazones (1a-e) to the corresponding *(Z)*-isomers: 1 mmol of concentrated hydrochloric acid was added to a solution of 1 mmol of the appropriate *(E)*-hydrazone (**1a-e**) in 50 ml of diethyl ether. After stirring for 6 h the solution separated the corresponding *(Z)*-hydrazone on slow evaporation of the solvent. A characteristic feature of all *(Z)*-isomers is the downfield shift of their NH signal in the ^{1}H-nmr to values of about 13.8 ppm in $CDCl_3$, which has already been described elsewhere.[18]

General procedure for the synthesis of dialkyl (E)-2-(substituted 2-amino-phenylhydrazono)glutarates (2a-e): The respective hydrazones (**1**) (3 mmol) in methanol (50 ml) (for methyl esters **1a-c**) or in ethanol (50 ml) (for ethyl esters (**1d**) and (**1e**)) were hydrogenated over 3% Pt on carbon powder (100 mg) under normal pressure at 20 °C until no more hydrogen was consumed (uptake 200 ml). The catalyst was filtered off and the filtrates allowed to stand overnight in an open beaker. In the cases of (**2a**) and (**2d**) the products separated as crystalline solids and were characterized. (**2b**), (**2c**), and (**2e**) separated as oily liquids, pure according to tlc, which were not further characterized.

Dimethyl *(E)*-2-(2-aminophenylhydrazono)glutarate (2a): Yield 0.72 g (85%), pale yellow crystals, mp 80-82 °C (MeOH). Ir (KBr): ν = 3410, 3350, 3300

(NH_2), 1720, 1695 (CO). ^{1}H-Nmr ($CDCl_3$): δ = 12.04 (s,1H), 7.18-6.76 (m,4H), 4.71 (br s,2H), 3.82 (s,3H), 3.69 (s,3H), 2.87 (t,J=6.3 Hz,2H), 2.70 (t,J=6.3 Hz,2H). Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 56.21; H, 6.18; N, 15.29.

Diethyl *(E)*-2-(2-aminophenylhydrazono)glutarate (2d): Yield 0.76 g (82%), yellow crystals, mp 68-70 °C (cyclohexane). Ir (KBr): ν = 3400, 3350, 3280 (NH_2), 1740, 1690 (CO). ^{1}H-Nmr ($CDCl_3$): δ = 12.01 (s,1H), 7.30-6.73 (m,4H), 4.29 (q,J=7.0 Hz,2H), 4.14 (q,J=7.0 Hz,2H), 3.75 (br s,2H), 2.87 (t,J=6.6 Hz,2H), 2.71 (t,J=6.6 Hz,2H), 1.35 (t,J=7.0 Hz,3H), 1.25 (t,J=7.0 Hz,3H). Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.47; H, 6.96; N, 13.55.

General procedure for the synthesis of alkyl (substituted 3,4-dihydropyridazino[1,6-*a*]benzimidazol-2-yl)carboxylates (4a-e): 0.2 ml of 10% aqueous NaOH were added to the filtered hydrogenation solution of a 3 mmol run for the respective amine (2). After refluxing for 1 min, the hot solution was diluted with 5 volumes water and afforded on standing overnight crystals of the crude pyridazino[1,6-*a*]benzimidazole (4).

Methyl (3,4-dihydropyridazino[1,6-*a*]benzimidazol-2-yl)carboxylate (4a): Yield 0.55 g (80%), colourless crystals, mp 136-138 °C (cyclohexane). Ir (KBr): ν = 1710 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 7.72-7.29 (m,4H), 3.98 (s,3H) 3.24 (t,J=8.2 Hz,2H), 3.06 (t,J=8.2 Hz,2H). ^{13}C-Nmr ($CDCl_3$): δ = 163.8, 148.1, 143.6, 141.5, 132.6, 124.2, 123.9, 119.8, 109.1, 53.2, 21.5, 19.6. Ms (m/z, relative intensity) 229 (M^+,100), 197 (15), 169 (27), 142 (15). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.83; N, 18.33. Found: C, 62.64; H, 5.35; N, 18.14.

Methyl (7-chloro-3,4-dihydropyridazino[1,6-*a*]benzimidazol-2-yl)carboxylate (4b): Yield 0.40 g (50%), colourless crystals, mp 208-210 °C (MeOH). Ir (KBr): ν = 1740 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 7.65-7.29 (m,3H), 3.96 (s,3H), 3.23 (t,J=8.1 Hz,2H), 3.06 (t,J=8.1 Hz,2H). Ms (m/z, relative in-

tensity) 263 (M^{+},100), 231 (11), 203 (28), 177 (23). Anal. Calcd for $C_{12}H_{10}N_3O_2Cl$: C, 54.66; H, 3.82; N, 15.93; Cl, 13.45. Found: C, 54.72; H, 3.67; N, 15.60; Cl 13.79.

Methyl (8-chloro-3,4-dihydropyridazino[1,6-a]benzimidazol-2-yl)carboxylate (4c): Yield 0.52 g (65%), colourless crystals, mp 134-136 °C (cyclohexane) Ir (KBr): ν = 1740 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 7.65-7.19 (m,3H), 3.95 (s,3H), 3.19 (t,J=8.0 Hz,2H), 3.04 (t,J=8.0 Hz,2H). Ms (m/z, relative intensity) 263 (M^{+},100), 232 (6), 203 (19), 177(18). Anal. Calcd for $C_{12}H_{10}N_3O_2Cl$: C, 54.66; H, 3.82 N, 15.93; Cl 13.45. Found: C, 54.41; H, 3.86; N, 15.61; Cl, 13.29.

Ethyl (3,4-dihydropyridazino[1,6-a]benzimidazol-2-yl)carboxylate (4d): Yield 0.44 g (60%), colourless crystals, mp 94-96 °C (cyclohexane). Ir (KBr): ν = 1705 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 7.69-7.29 (m,4H), 4.43 (q, J=7.1 Hz, 2H), 3.24 (t,J=8.0 Hz,2H), 3.06 (t,J=8.0 Hz,2H), 1.43 (t,J=7.1 Hz,3H). ^{13}C-Nmr ($CDCl_3$): δ = 163.3, 148.4, 143.6, 141.5, 132.7, 124.1, 132.9, 119.8, 110.1, 62.6, 21.6, 19.6, 14.2. Ms (m/z, relative intensity) 243 (M^{+},100), 197 (25), 169 (27), 143 (12). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.06; H, 5.36; N, 17.20.

Ethyl (7-chloro-3,4-dihydropyridazino[1,6-a]benzimidazol-2-yl)carboxylate (4e): Yield 0.44 g (52%), colourless crystals, mp 115-117 °C (cyclohexane) Ir (KBr): ν = 1715 cm^{-1} (CO). ^{1}H-Nmr ($CDCl_3$): δ = 7.65-7.30 (m,3H), 4.43 (q,J=7.1 Hz,2H), 3.23 (t,J=8.0 Hz,2H), 3.06 (t,J=8.0 Hz,2H), 1.43 (t,J=7.1 Hz,3H). Ms (m/z, relative intensity) 277 (M^{+},100), 231 (13), 203 (24), 178 (16). Anal. Calcd for $C_{13}H_{12}N_3O_2$: C, 56,22; H, 4,36; N, 15.13; Cl, 12.77. Found: C, 56.49; H, 4.56; N, 15.03; Cl, 13.13.

Methyl [1-(2-amino-4,5-dichlorphenyl)-4,5-dihydropyridazin-6(1*H*)-on-3-yl]-carboxylate (6): Nitrohydrazone (5) (3 mmol) was hydrogenated as described for hydrazones (1). The resulting hydrogenation solution was further

treated as reported for the synthesis of heterocycles (**4**) from amines (**2**). Compound (**6**) in contrast to (**4**) separated already during refluxing and showed no tendency for further cyclization under the conditions given. Yield: 0.75 g (79%), colourless crystals, mp 185-186 °C (MeOH). Ir (KBr): ν = 3410, 3340, (NH_2), 1735, 1675 (CO) cm^{-1}. ^{1}H-Nmr ($CDCl_3$): δ= 7.28(s,1H) 6.91 (s,1H), 4.58 (br s,2H), 3.89 (s,3H), 3.06 (t,J=8.0 Hz,2H), 2.76 (t,J=8.0 Hz,2H). ^{13}C-Nmr (DMSO-d_6): δ = 171.4, 169.0, 151.3, 149.6, 136.8, 136.0, 131.0, 121.3, 120.9, 58.1, 32.0, 27.3. Ms (m/z, relative intensity) 315 (M^+,75), 298 (18), 256 (48), 175 (100), 139 (75). Anal. Calcd for $C_{12}H_{11}N_3O_3Cl_2$: C, 45.59; H, 3.51; N, 13.29; Cl, 22.43. Found: C, 45.48; H, 3.71; N, 13.03; Cl, 22.73.

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Received, 14th July, 1993