

SYNTHESIS OF DEUTERIUM-LABELLED N,N-DIMETHYL-MORPHOLINIUM- AND N-METHYL-N-ETHYL-MORPHOLINIUM- 7,7,8,8-TETRACYANOQUINODIMETHANE COMPLEXES.

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SUMMARY

Attempted exchange experiments of morpholine, N-methylmorpholine and N-ethylmorpholine with a deuterium donor led to no deuterium incorporation in the morpholine rings. Morpholine- d_8 is not found in the reaction of bromoethanol- d_5 and ammonia, but it can be prepared from ethyleneoxide- d_4 and ammonia. These reaction conditions are given for the H-analog. N-methylmorpholine- d_{11} is prepared from ethyleneoxide- d_4 and methylamine- d_5 ; N-ethylmorpholine- d_{13} is prepared in an analogous manner. N-methyl- d_3 -morpholine is prepared from morpholine and diazomethane- d_2 or from morpholine and methyl iodide- d_3 or from 2,2'-bis-(iodoethyl)ether and methylamine- d_5 . N-methyl-N-ethyl- d_5 -morpholinium(M.E.M.- d_5)-iodide is prepared from N-methylmorpholine and ethyliodide- d_5 . M.E.M.- d_{16} -iodide and M.E.M.-iodide are obtained by a similar route. N,N-di-(methyl- d_2)-morpholiniumiodide is prepared from N-methyl- d_2 -morpholine and methyl iodide- d_3 and also from morpholine and methyl iodide- d_3 . M.E.M.-(T.C.N.Q.- d_4) $_2$; M.E.M.- d_5 -(T.C.N.Q.- d_4) $_2$; M.E.M.- d_{16} -(T.C.N.Q.- d_4) $_2$; M.E.M.- d_{16} -(T.C.N.Q.) $_2$ and N,N-di-(methyl- d_3)-morpholinium-(T.C.N.Q.) $_2$ are prepared from the deuterated or undeuterated morpholiniumiodides and T.C.N.Q. All synthetic methods are described in detail.

Key Words: N,N-dimethylmorpholinium-, N-methyl-N-ethylmorpholiniumiodide, tetracyanoquinodimethane, morpholine, deuterium-labelled.

INTRODUCTION

In our Physical Chemistry Department, in collaboration with the Structural Chemistry Department, much fundamental research has been done on 7,7,8,8-tetracyanoquinodimethane (T.C.N.Q.) complexes. To continue this research we needed for magnetic nuclear resonance- and neutron-diffraction measurements deuterated N-methyl-N-ethylmorpholinium-(T.C.N.Q.) $_2$ complexes, which can be prepared from deuterated N-methyl-N-ethylmorpholinium (M.E.M.)-iodide and T.C.N.Q.

The synthesis of T.C.N.Q.- d_4 is known¹, but nothing was found in the litera-

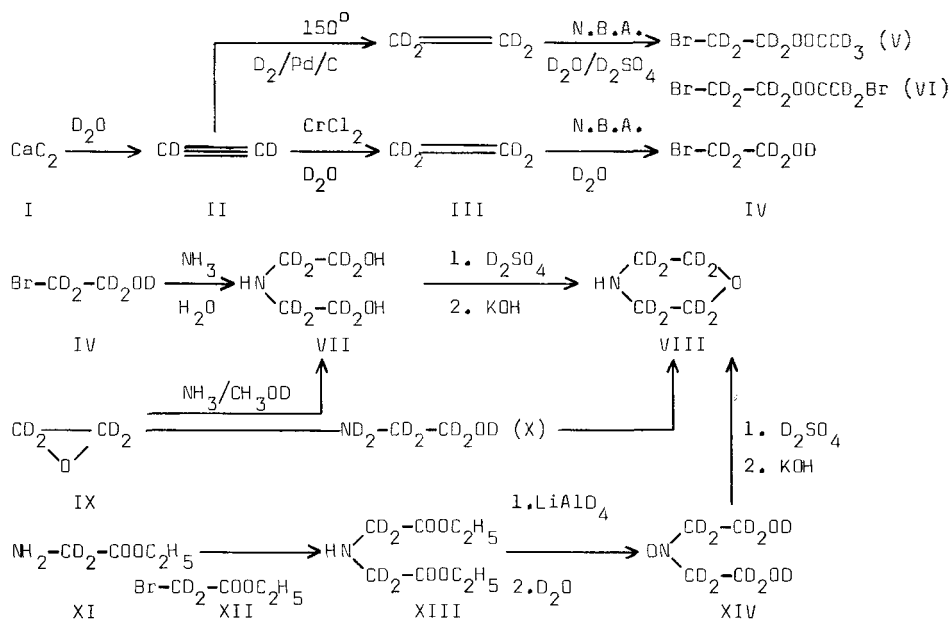
ture about deuterated M.E.M.-iodides.

There are three different approaches for the preparation of deuterated M.E.M.-iodides: first, by exchange of deuterium from a donor to morpholine, N-methylmorpholine or N-ethylmorpholine; second, by synthesis of deuterated morpholine; third, by synthesis of deuterated N-methylmorpholine or N-ethylmorpholine.

Exchange experiments of N-methyl- and N-ethylmorpholine with $\text{DCl}/\text{D}_2\text{O}/\text{PtO}_2$ or $\text{NaOD}/\text{D}_2\text{O}/\text{PtO}_2$ as catalyst led to no deuterium incorporation.

The same exchange experiments with morpholine gives deuterium incorporated at nitrogen. These results are also found on allowing morpholine and chloro-tris-(triphenylphosphine)-iridium-I- or chloro-tris-(triphenylphosphine)-rhodium-I-complexes to react with deuterium gas.^{2,3}

A successful synthetic route to deuterated morpholine is worked out along the lines of the following scheme:

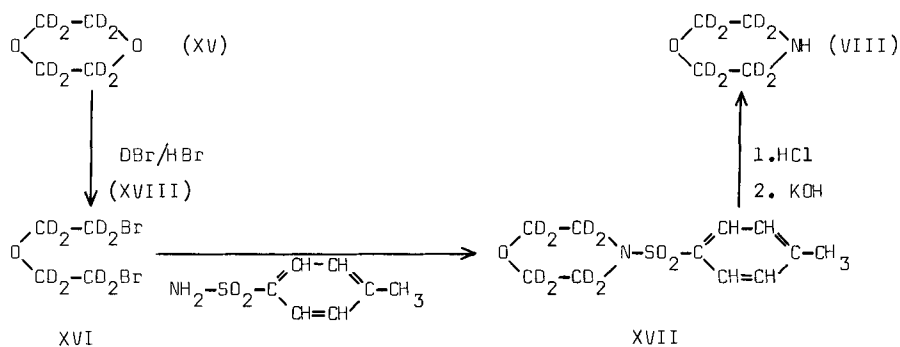


Acetylene- d_2 (II) is prepared from CaC_2 (I) and D_2O ,⁴ ethylene- d_4 (III) from II and chromouschloride/ D_2O .⁵ III can also be prepared from II and deuterium gas/ $\text{Pd}/\text{C}/150^\circ$ ⁶ and bromoethanol- d_5 (IV) from III and N-bromoacetamide (N.B.A.)/ D_2O .⁷ Other products (V) and (VI) are found from III ($\text{D}_2/\text{Pd}/\text{C}/150^\circ$) and N.B.A./ D_2O . 2,2'-Iminodiethanol-1,1,1',1',2,2,2',2'- d_8 (VII) is not

found from IV and ammonia⁸; however VII can be obtained from IX and NH₃ (25% in water or anhydrous in ethanol) in CH₃OD. The high price of ethyleneoxide-d₄ prevented us from doing these experiments and therefore the H-analog results (LIII) are given.²⁷

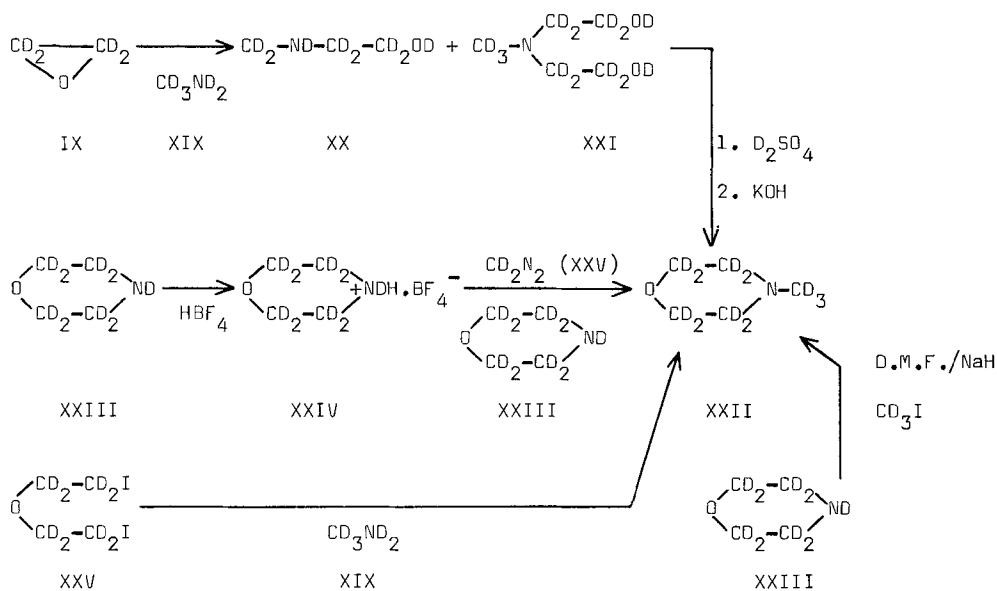
2,2'-Iminodiethanol-d₁₁ (XIV) was not obtained on LiAlD₄ reduction of 2,2'-iminodi-(acetic-d₂)-acid ethylester (XIII). Attempts to prepare IX and X were not begun because of the availability of ethyleneoxide-d₄ from commercial sources,⁹ the easy synthesis of N-methylmorpholine-d₁₁, the difficulty of isolating 2-aminoethanol from KOH/H₂O solutions and the results for the reaction of ethyleneoxide and ammonia as described above.

Aminoethanoic-d₂-acid ethylester (XI) is prepared from acetamidomalonic acid diethylester¹⁰, bromoacetic-d₂-acid ethylester (XII) from acetic acid-d₄¹¹ and 2,2'-iminodi-(acetic-d₂)-acid ethylester (XIII) from XI and XII.



2,2'-Bis-(bromoethyl-d₄) ether (XVI) is prepared from dioxane-d₈ (XV) and DBr/HBr in a low yield.^{12,13} N-4-tosylmorpholine-d₈ (XVII) from XVI and 4-toluene-sulfonic acid amide was not obtained as reported in the literature for the H-analog.¹⁴ Hydrolysis of the water layer with HCl, saturation of this layer with KOH and extraction with diethyl ether gives no detectable amounts of VIII.

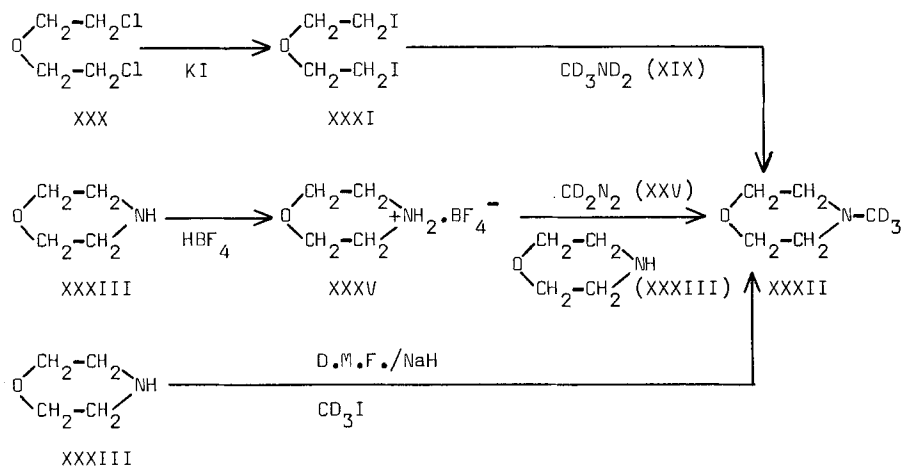
The third approach for the synthesis of deuterated N-methylmorpholine and deuterated N-ethylmorpholine is given below:

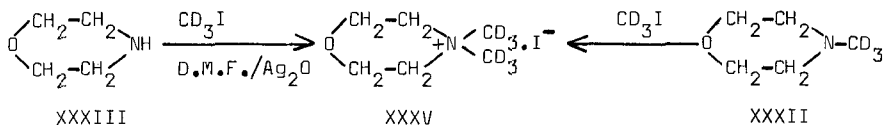


2-(Methylamino)-ethanol-d₉ (XX) and 2,2'-methyliminodiethanol-d₁₃ (XXI) are easily prepared from ethyleneoxide-d₄ (IX) and methylamine-d₅ (XIX).¹⁵ Dehydration of XXI gives in 50% yield N-methylmorpholine-d₁₁ (XXII).

XXII is also formed on allowing diazomethane-d₂ (XXV) to react with morpholinium-d₉-fluoroborate (XXIV) in morpholine-d₉ (XXIII).¹⁶ Two other methods are the direct d₃-methylation of XXIII and the reaction of XIX with 2,2'-bis-(iodoethyl-d₄) ether (XXV).

The high cost of XXIII and XXV forced us to test the reaction conditions with the H-analogs of XXIII and XXV, as given below:

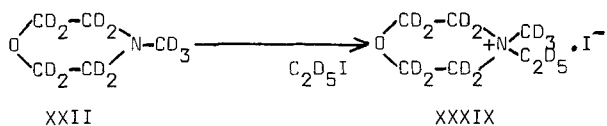
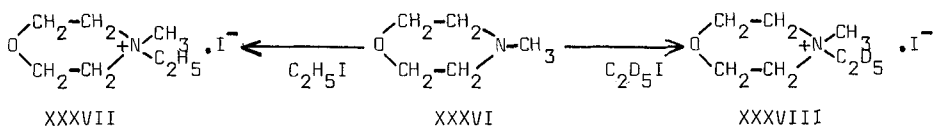




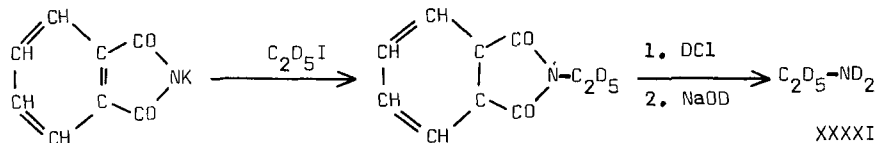
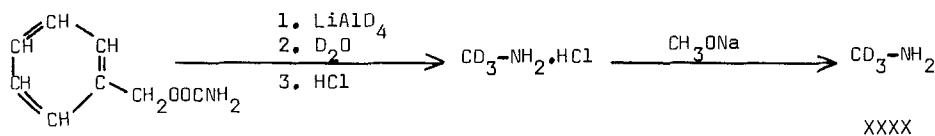
2,2'-Bis-(iodoethyl) ether (XXXXI) is prepared from 2,2'-bis-(chloroethyl) ether and KI,¹⁷ N-methyl-d₃-morpholine (XXXII) from XXXI and XIX, morpholinium-fluoroborate (XXXIV) from morpholine (XXXIII) and HBF₄.¹⁶

XXXIV and XXXIII with diazomethane-d₂ (XXV) gives XXXII. This product is also found from the reaction of XXXIII and methyl iodide-d₃.

N,N-di-(methyl-d₃)-morpholiniumiodide (XXXV) is prepared from XXXIII and methyl iodide-d₃¹⁸ and from XXXII and methyl iodide-d₃.

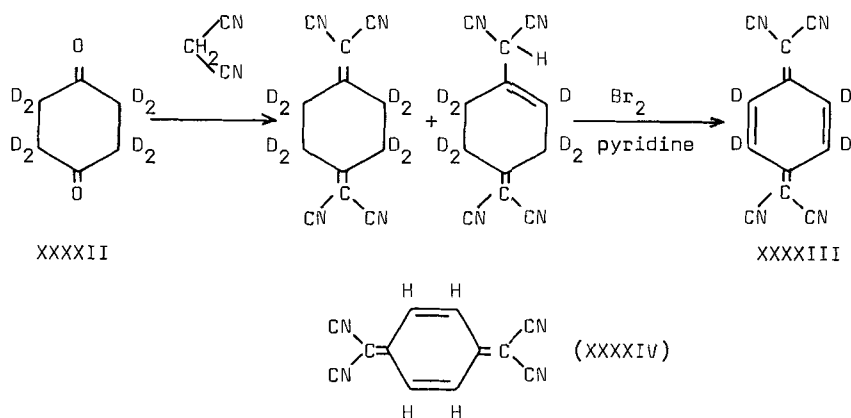


N-Methyl-N-ethylmorpholiniumiodide (XXXVII) is prepared from XXXVI and ethyl iodide.¹⁹ N-Methyl-N-ethyl-d₅-morpholiniumiodide (XXXVIII) from XXXVI and ethyl iodide-d₅ and N-methyl-N-ethylmorpholiniumiodide-d₁₆ (XXXIX) from XXII and ethyl iodide-d₅.



Methylamine-d₃ (XXXX) and ethylamine-d₇ (XXXXI) are prepared as given above.^{20,21}

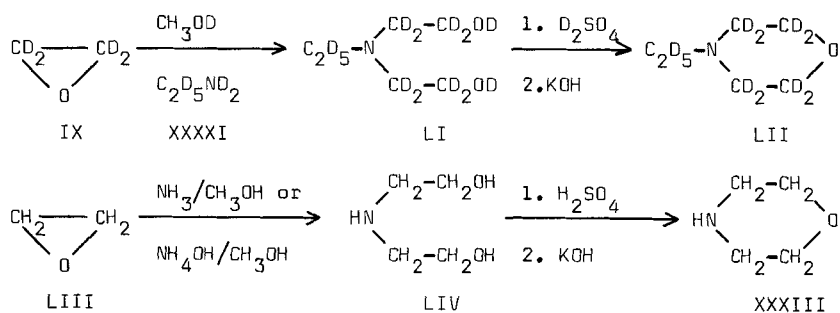
The needed DBr (XVIII) is prepared from deuterium gas and bromine²² or from benzoylbromide and deuteriumoxide.



T.C.N.Q.- d_4 (XXXXIII) is prepared from 1,4-cyclohexanedione- d_8 (XXXXII) in two steps^{1,23} and T.C.N.Q. (XXXXIV) is found starting from 1,4-cyclohexanedione²⁴.

N-Methyl-N-ethylmorpholinium-(T.C.N.Q.)₂ (XXXXV) is prepared from XXXVII and XXXIV²⁵, N-methyl-N-ethyl- d_5 -morpholinium-(T.C.N.Q.- d_4)₂ (XXXXVI) from XXXVIII and XXXIII, N-methyl-N-ethylmorpholinium-(T.C.N.Q.- d_4)₂ (XXXXVII) from XXXVII and XXXIII, the N-methyl- d_3 -N-ethyl- d_5 -morpholinium- d_8 -(T.C.N.Q.)₂ (XXXXVIII) from XXXIX and XXXIV and N-methyl- d_3 -N-ethyl- d_5 -morpholinium- d_8 -(T.C.N.Q.- d_4)₂ (XXXXIX) from XXXIX and XXXIII.

N,N-Di-(methyl- d_3)-morpholinium-(T.C.N.Q.)₂ (L) from XXXV and XXXIV.



2,2'-Ethyliminodiethanol- d_{15} (LI) is prepared from XXXXI and IX, N-ethylmorpholine- d_{13} (LII) from LI after dehydration.

Morpholine (XXXIII) is prepared from LIV after dehydration, the 2,2'-iminodiethanol (LIV) from ethyleneoxide (LIII) and $\text{NH}_3/\text{CH}_3\text{OH}$ or $\text{NH}_4\text{OH}/\text{CH}_3\text{OH}$.

EXPERIMENTAL

The analytical results were obtained with the following instruments:

m.p., Mettler FP 5/51; mass spectra, AEI-MS 9; uv, Beckman, DBG; ir, Unicam SP 1000, liquid samples between KBr plates, solid samples in a KBr pellet; ESR, Varian E 4; refractive index, Abbe/Zeiss-Opton.

Ethyleneoxide-d₄ was purchased from Rohstoff-Einfuhr GMBH, Düsseldorf, Germany; p-dioxane-d₈, D₂O, LiAlD₄, CH₃OD and acetic acid-d₄ from E. Merck, Darmstadt, Germany; D₂ gas from Baker, Deventer, The Netherlands; methyl-iodide-d₃ and ethyliodide-d₅ from Aldrich, Milwaukee, USA; ethyliodide-d₅ from Stöhrler Isotope Comp., Innerberg, Switzerland; methylamine-d₅ from Merck Sharp & Dohme, Canada; ammonium-hexa-chloroiridate III from Alfa, Danvers, Mass., USA and Deutero Diazald Prep. Set from Aldrich-Europe, Beerse, Belgium.

Acetylene-d₂ (II):

To I (100 g, 1.6 mol.) is slowly added under cooling and mixing deuterium oxide (40 g, 2 mol.); yield 9.5 l./76 cm Hg; ir, 10 cm gas cell, main bands: 680, 1020, 1060, 2420 and 2460 cm⁻¹.

Ethylene-d₄ (III); D₂/Pd/C/150° method:

A mixture of II (6 l./76 cm Hg, 0.27 mol.) and deuterium gas (9 l./76 cm Hg, 0.4 mol.) is passed several times through a quartz tube at 150°, filled with 5% Pd/C and mineral-wool. Ir, 10 cm gas cell, main bands: 720, 1020, 1080, 2100 and 2220 cm⁻¹.

Ethylene-d₄ (III); Cr II chloride method:

II (prepared from carefully degassed I, 50 g, 0.8 mol. and deuterium oxide 25 g, 1.2 mol.) is shaken with chromous chloride (0.1 mol.)²⁷ during three days under an inert atmosphere (N₂, oxygen free). The reaction is followed by gas chromatography and stopped when no more II was found in the reactor.

Bromoethanol-d₅ (IV):

III (chromous chloride method, from 0.8 mol. I) is stirred overnight with N-bromoacetamide (24 g, 0.17 mol.), D₂O (80 ml.) and D₂SO₄ (1 ml.) at room-temperature. Solid KBr till saturation and solid NaHCO₃ till neutral are added. The water mixture is extracted 5 times with diethyl ether (60 ml.), the diethyl ether layer is dried with MgSO₄/K₂CO₃ and distilled, b.p. 44°/15 mm Hg. Yielding a colourless oil, 8.1 g; n_D^{21.5} 1.4986; ir, 2095 and 2220 cm⁻¹(CD), 2500 cm⁻¹(OD) and 3360 cm⁻¹(OH); mass anal., m/e 130 (C₂D₅OBr), m/e 128

($C_2D_3H_5OBr$) and small peaks at m/e 174, 270 and 271 are found.

Acetic acid- d_3 -2-bromoethyl- d_4 -ester (V) and acetic acid- d_2 -bromo-2-bromoethyl- d_4 -ester (VI) mixture:

III ($D_2/Pd/C/150^\circ$ method, from 0.26 mol. II) is stirred with *N*-bromoacetamide (35 g, 0.25 mol.), D_2O (90 ml.) and D_2SO_4 (2.5 g) at room temperature, until no acetylene- d_2 (ir measurements) is detected. Solid KBr till saturation and solid $NaHCO_3$ till neutral are added. The water mixture is extracted 5 times with diethyl ether (100 ml.), the diethyl ether layer is dried over $MgSO_4$ and distilled. b.p. $112^\circ/98$ mm Hg; yield 7.35 g; n_D^{20} 1.4290; ir, 1720 cm^{-1} (CO), 2400 cm^{-1} (CD); mass anal. m/e 174 ($C_4D_7O_2Br = V$); m/e 252, 251 ($C_4D_6O_2Br_2 = VI$).

2,2'-Iminodiethanol-1,1,1',1',2,2,2',2'- d_8 (VII):

IV (7.8 g, 0.06 mol.) and ammonia (4.5 ml., 25%, 0.03 mol.) are heated in a sealed tube at 100° during 2 hrs. Solid K_2CO_3 is added and the mixture is distilled, b.p. $90-100^\circ/76$ cm Hg; yield 100 mg; mass anal. m/e 136, 137 and 135, no m/e 113 was found. This reaction can be successful, but starting with ethyleneoxide- d_4 is preferable. See the details given for the H-analog LIV.

Ethyleneoxide- d_4 (IX) and ethanolamine- d_7 (X) are not prepared.

Aminoethanoic- d_2 -acid ethylester (XI) (glycine- d_2 -ethylester):

Acetamidomalonic- d_2 -acid ethylester (21.7 g, 0.1 mol.) is added to a mixture of freshly distilled thionylchloride (30 ml.) and D_2O (126 ml.), refluxed 6 hrs under N_2 , cooled and the D_2O/H_2O distilled off, tetrahydrofuran added and the white crystals filtered off, washed with tetrahydrofuran and dried; yield 9.6 g, glycine-deuteriochloride- d_5 . Glycine-deuteriochloride- d_5 (8.25 g, 0.07 mol.) is added to a solution of ethanol, abs. (41 ml.) and thionylchloride (5.25 g), refluxed for 3 hrs, cooled, diethyl ether added, the solid filtered off, washed with diethyl ether and dried; yield 10.3 g glycine- d_2 -ethylester.HCl.

Glycine- d_2 -ethylester-hydrochloride (8 g, 0.06 mol.) is added to triethylamine (20 ml.) and D_2O (8 ml.), stirred during 30 min., diethyl ether (50 ml.) is added, the upper layer is decanted, this extraction repeated twice, the solvent evaporated to 25 ml., filtered and the final solvent is evaporated under vacuum and distilled, b.p. $40^\circ/40$ mm Hg; yield 2.3 g XI; ir, 1745 cm^{-1} (CO), 2260, 2500, 2520, 3000 and 3380 cm^{-1} (CO, OH and NH).

Bromoacetic-d₂-acid ethyl ester (XII):

Acetic acid-d₄ (10 g, 0.16 mol.) and red phosphorus (0.2 g) are heated at 95° and bromine (30 g, 0.19 mol.) is slowly added. The mixture is heated at 95° for 45 min, excess bromine distilled off, ethanol, abs. (15 ml., 0.26 mol.) added, the reaction mixture refluxed 3 hrs, cooled and distilled. B.p. 153-154°/76 cm Hg; yield 5.8 g; n_D^{23} 1.4491; ir, 1750 cm⁻¹(CO), 2195 and 2300 cm⁻¹(CD), 2920 and 3000 cm⁻¹(C₂H₅) and a small peak at 3480 cm⁻¹ (COOH). •

2,2'-Iminodiacetic-d₂-acid ethylester (XIII):

XI (0.6 g, 4 mmol.) in ethanol, abs. (30 ml.) is filtered at 40° and to this solution XII (1.7 g, 10 mmol.) is added. The mixture is heated 15 min at 40°, evaporated till dryness, diethyl ether (25 ml.) is added, stirred and filtered. The solid product is dried, triethylamine (10 ml.) is added, again evaporated till dryness and the residue is used immediately for further synthesis.

2,2'-Iminodi-(ethan-d₄-ol) (XIV):

XIII (residue above, max. 4 mmol.) is brought in solution with diethyl ether (25 ml.) and LiAlD₄ (336 mg, 8 mmol.) is added in 4 portions. The mixture is refluxed for 30 min, cooled and D₂O (0.5 g) is added. The diethyl ether layer is decanted, the water layer stirred another 3 times with diethyl ether. The combined ether layers are dried over MgSO₄, filtered and evaporated. No XIV was found.

2,2'-Bis-(bromoethyl-d₄) ether (XVI):

p-Dioxane-d₈ (XV), (10 ml., 0.11 mol.), DBr (1.0 g, 0.01 mol.) and HBr (10 g, 0.13 mol.) are brought together under cooling in a 1 l. stainless steel cylinder. The cylinder is allowed to come to room temperature, is shaken for a short time and is put aside for 32 days. After this period the pressure is released and diethyl ether (5 times 100 ml.) is added. Each time the resulting mixture is filtered off, yielding a yellow powder and a dark diethyl ether solution. The combined diethyl ether solutions are distilled, yielding two fractions, b.p. 50°/15 mm Hg; 0.68 g; $n_D^{22.5}$ 1.4830; ir, 1735 cm⁻¹ as a broad peak, 2090 and 2120 cm⁻¹ (CD); b.p. 60°/15 mm Hg; 0.48 g; $n_D^{22.5}$ 1.5032; ir, 2080, 2200 cm⁻¹ (CD) and a small amount 3500 cm⁻¹ (OH).

2,2'-Bis-(bromoethyl-d₄) ether (XVI):

An attempt to get XVI by mixing p-dioane, benzoylbromide²⁷ and D₂O in a pressure vessel was not successful.

N-4-Tosyl-morpholine-d₈ (XVII) and morpholine-d₈ (VIII):

XVI (480 mg, 2 mmol.), p-toluenesulfonamide (342 mg, 2 mmol.), KOH (112 mg, 2 mmol.) and ethanol, abs. (10 ml.) are refluxed for 1 hr. Another portion of KOH (112 mg, 2 mmol.) in ethanol, abs. (10 ml.) is added, refluxed for another ½ hr and the solid material is filtered off, dried, m.p. above 200°; ir, spectrum identical with p-toluenesulfonic acid potassium salt.

The water layer is brought to pH 1, heated at 60° for 15 min, cooled, saturated with KOH and extracted with diethyl ether (50 ml.). The diethyl ether layer is dried over MgSO₄, filtered and distilled. There is no morpholine-d₈ detectable in the residue.

Deuteriumbromide, DBr (XVIII):

Deuterium gas saturated with bromine at room temperature is slowly bubbled through a quartz tube, filled with ceramic wool and heated at 700°. The DBr is dried over mol. sieves (4A) and condensed in a cold trap at -70°. The yield is very low. One gram is used for the synthesis of XVI. Ir, as in the lit.²⁸

2-(Methylamino)-ethanol-d₉ (XX) and 2,2'-methyliminodiethanol-d₁₃ (XXI):

Methylamine-d₅ (XIX) (4 g, 111 mmol.) in CH₃OD (25 ml.) at -25° and ethylene-oxide-d₄ (IX) (8 g, 250 mmol.) in CH₃OD (25 ml.) at -20° are brought together in a 100 ml. stainless steel cylinder. The cylinder is closed and allowed to come to room temperature under stirring, then is heated 2 hrs at 100°, cooled and diethyl ether added. The mixture is distilled, b.p. 35-53°/10 mm Hg; yield 0.22 g (XX); n_D²⁵ 1.4119; ir, 2070, 2190 cm⁻¹(CD) and 2400 cm⁻¹(OD/ND); mass anal., m/e 84 (12%, C₃D₉NO), m/e 83 (37%, C₃D₈HNO), m/e 82 (38%, C₃D₇H₂NO), m/e 81 (7%, C₃D₆H₃NO), m/e 80 (6%, C₃D₅H₄NO). B.p. 124-126°/10 mm Hg; yield 4.5 g (XXI); n_D²⁵ 1.4629; ir, 2070, 2215 cm⁻¹(CD), 2520 cm⁻¹(OD), 2800 and 3360 cm⁻¹ are peaks analogous to 2,2'-methyliminodiethanol in small amount; mass anal., m/e 133 (3%, C₄¹³CD₁₃NO₂), m/e 132 (13%, C₅D₁₃NO₂), m/e 131 (22%, C₅D₁₂HNO₂), m/e 130 (23%, C₅D₁₁H₂NO₂), m/e 129 (17%, C₅D₁₀H₃NO₂), m/e 128 (12%, C₅D₉H₄NO₂), m/e 127 (9%, C₅D₈H₅NO₂), m/e 126 (3%, C₅D₇H₆NO₂).

N-Methylmorpholine-d₁₁ (XXII):

2,2'-Methyliminodiethanol-d₁₃ (XXI) (4.3 g, 29 mmol.) is cooled to -20^o and D₂SO₄ (9 ml., 96-98%) is added in small portions under stirring. A vigorous reaction sets in and after this has subsided, the mixture is heated 1.5 hrs at 100^o, cooled and diethyl ether (100 ml.) is added. The mixture is neutralised with NaOD (0.1 mol.) in D₂O (25 ml.) and NaOH (25 g, 0.5 mol.). The diethyl ether layer is decanted, another portion diethyl ether (20 ml.) is added to the water layer, stirred, decanted and the procedure is repeated another two times. The combined ether layers are dried over MgSO₄ for two hours, filtered and distilled. B.p. 112-114^o/76 cm Hg; yield 2.3 g; n_D²⁰ 1.4311; ir, 2030, 2080, 2170 and 2210 cm⁻¹(CD). Peaks for the H-analog at 2790, 2850 and 2950 cm⁻¹ are not found. Mass anal., m/e 113 (6%, C₄¹³CD₁₁NO), m/e 112 (74%, C₅D₁₁NO), m/e 111 (8%, C₅D₁₀HNO), m/e 110 (8%, C₅D₉H₂NO), m/e 109 (3%, C₅D₈H₃NO).

2,2'-Bis-(iodoethyl) ether (XXXI):

2,2'-Bis-(chloroethyl) ether (XXX) (28.6 g, 0.2 mol.), sodium iodide (120 g, 0.8 mol.) and dry acetone (500 ml.) are heated under reflux and stirring during 10 hrs. The acetone is evaporated, the residue stirred with diethyl ether (350 ml.) and filtered. The solid product is washed once more with diethyl ether (100 ml.). The combined diethyl ether layers are washed with aqueous NaHSO₃, followed by water and then dried over MgSO₄. The solid MgSO₄ is filtered off and the solution is distilled, b.p. 130^o/10 mm Hg; yield 17.5 g XXXI. Ir, 690 cm⁻¹(CCl) is absent.

N-Methyl-d₃-morpholine (XXXII), from 2,2'-bis-(iodoethyl) ether:

XIX (0.5 g, 14 mmol.) in ethanol, abs. (20 ml.), XXXI (9 g, 28 mmol.) and KOH (2 ml. 33% in water) are mixed at -20^o in a stainless steel cylinder. The valve is closed and the cylinder is heated at 90-100^o during 5 hrs. The cylinder is cooled, opened, diethyl ether (100 ml.) and KOH (1.7 g, 30 mmol.) are added and the diethyl ether layer is decanted. The water layer is extracted another 4 times with diethyl ether (100 ml.), the diethyl ether layers are combined, dried, filtered and distilled. B.p. 90^o/76 cm Hg; yield 420 mg; ir, 2210 cm⁻¹(CD) and a large water peak at 3460 cm⁻¹. B.p. above 90^o/76 cm; yield 100 mg; ir, 2210 and 2550 cm⁻¹(CD) and a large water peak at 3460 cm⁻¹. Mass anal., m/e 104 (C₅D₃H₂NO), also m/e 117, 131 and 162 are found for both fractions in minor amounts.

methane-d₂ (XXV) /diethyl ether mixture is distilled. This diazomethane-d₂ solution is prepared from Diazald (p-tolylsulfonylmethylnitrosamide, 11 g, 51 mmol.) in diethyl ether (110 ml.), dropwise added to a mixture of carbitol-d (2-(2-ethoxy-ethoxy)-ethanol-d, 25 g), diethyl ether (10 ml.) and sodium deuterioxide (10 g, 30% in D₂O), stirred magnetically at 50°. After the Diazald solution is added, diethyl ether (25 ml.) is used twice for cleaning the distillation apparatus. The mixture in the receiver stays yellow, so another portion of morpholine (1.4 g, 16 mmol., not N-deuterated) is added and is allowed to react 30 min. DCl (5.5 ml., 20% in D₂O) and D₂SO₄ (2 ml., 98%) are added. The colourless solution is evaporated, diethyl ether (50 ml.) is added, followed by concentrated KOH solution and KOH pellets. The diethyl ether is decanted, another portion of diethyl ether (30 ml.) is added, stirred and decanted. This procedure is repeated another time, the combined diethyl ether layers are dried over MgSO₄, filtered and distilled. B.p. 116°/76 cm Hg; yield 1.5 g; n_D²⁵ 1.4370; ir, 2040, 2180 and 2230 cm⁻¹(CD), 2700, 2760 and 2900 cm⁻¹(CH) and a small water peak at 3250 cm⁻¹; mass anal., m/e 105 (6%, C₄¹³CD₃H₈NO), m/e 104 (53%, C₅D₃H₈NO); m/e 103 (32%, C₅D₂H₉NO), m/e 102 (9%, C₅DH₁₀NO).

N-Methyl-d₃-morpholine (XXXII), from methyl iodide-d₃ and morpholine:

XXXIII (1.0 g, 11.5 mmol.) in D.M.F. (6 ml.) and NaH (0.4 g, 55% oil dispersion, 9 mmol.) are mixed and methyl iodide-d₃ (1.0 g, 6.9 mmol.) is added. A vigorous reaction sets in and after this has subsided the solution is refluxed another 30 min, cooled and distilled. B.p. 90°/76 cm Hg; yield 0.85 g; ir, 2020, 2170 and 2210 cm⁻¹(CD), 2860 and 2950 cm⁻¹(CH); mass anal., m/e 104 (C₅D₃H₈NO, 84%), m/e 103 (C₅D₂H₉NO, 16%) and 2 peaks at m/e 108 and 186, respectively 31% and 16% (m/e 104=100%).

Morpholine (XXXIII):

LIV (5 g, 48 mmol.) and H₂SO₄ (10 ml., 96-98%) are mixed and heated for 2 hrs at 200° and cooled. Diethyl ether (50 ml.) is added, followed by KOH (20 ml., saturated in water) and KOH (50 g, pellets). The diethyl ether layer is decanted, another portion of diethyl ether (30 ml.) is added, stirred and decanted. This procedure is repeated twice. The combined diethyl ether layers are dried over MgSO₄, filtered and distilled. B.p. 35°/15 mm Hg; yield 1.0 g; n_D²⁵ 1.4520;

ir, 2900 cm^{-1} (CH) and 3320 cm^{-1} (NH), identical with a commercial sample (Aldrich).

Morpholiniumfluoroborate (XXXIV):

XXXIII (17.4 g, 0.2 mol.) and water (10 ml.) are cooled at 0° and under stirring tetrafluoroboric acid (HBF_4 , 41.2 ml., 48% in water, 0.2 mol.) is added in 4 portions. The solution is stirred for 1 hr, poured in a mixture of T.H.F. (150 ml.) and diethyl ether (30 ml.) and cooled at -28° for 3 days. A small amount of white crystals is isolated. The mother liquor is evaporated, the residue and the small amount of white crystals are dissolved in boiling ethanol, abs. and cooled. The white crystals are filtered off under N_2 and dried. Yield 23.5 g; m.p. 143.0° ; lit. $141-143^{\circ}$.

N,N-Di-(methyl- d_3)-morpholiniumiodide (XXXV):

XXXII (0.5 g, 5.7 mmol.) in diethyl ether (5 ml.) is mixed with methyl iodide- d_3 (1.0 g, 6.9 mmol.) and refluxed for 1 hr. The solvent is distilled off and to the residue diethyl ether (5 ml.) is added. The solid is filtered off, washed 3 times with diethyl ether (5 ml.), dried, yielding 0.12 g XXXV. Ir, 2250 cm^{-1} (CD), 2880 and 2970 cm^{-1} (CH). The solid is used for the next step without further purification.

N,N-Di-(methyl- d_3)-morpholiniumiodide (XXXV), in 1 step from morpholine:

Methyl iodide- d_3 (2.2 g, 15 mmol.) in D.M.F. (10 ml.) is stirred, XXXIII (0.65 g, 7.5 mmol.) is added, followed by Ag_2O (0.87 g, 3.75 mmol.). The solution becomes clear. After 5 min the solution is heated at 90° for 1 hr. On cooling a solid precipitates. This solid is filtered off, washed with ethanol, abs. and diethyl ether and dried. Yield 3 portions of product, 500, 700 and 250 mg. Ir, 2260 cm^{-1} (CD), 2880 and 2970 cm^{-1} (CH). C.H.-analysis: resulted in bad results, also after several recrystallizations from acetonitril; however the atomic ratios are correct.

N-Methyl-N-ethylmorpholiniumiodide (XXXVII):

XXXVI (20 ml., 0.16 mol.) is cooled at -10° and under stirring methyl iodide (14 ml., 0.22 mol.) is added. Some ethanol, dry is added to give a solid, which is filtered off and recrystallized from ethanol, abs.. The white product is dried, yielding 15.1 g; ir, 2870, 2970 and 3030 cm^{-1} (CH).

N-Methyl-N-ethyl-d₅-morpholiniumiodide (XXXVIII):

XXXVI (495 mg, 4.9 mmol.) and ethyliodide-d₅ (805 mg, 5 mmol.) are mixed and heated 1 hr at 70^o. A solid product is formed on cooling. Ethanol, abs. (5 ml.) is added, the mixture is stirred and the solid is filtered off, washed 3 times with cold n-hexane (10 ml.) and dried. Yield 180 mg; ir, 2220 cm⁻¹(CD), 2870, 2970 and 3020 cm⁻¹(CH); mass anal. m/e 161 (C₂D₅I). This peak is from ethyliodide-d₅. The M.E.M.-iodides are not volatile enough for a mass spectrum.

N-Methyl-d₃-N-ethyl-d₅-morpholinium-d₅-iodide (XXXIX):

XXII (2.0 g, 17.8 mmol.) is added to ethyliodide-d₅ (4.0 g, 25.2 mmol.) at 0^o. After 5 min the mixture is heated 1 hr at 70^o, the mixture becomes solid, n-hexane (5 ml.) is added. The reaction mixture is shaken and refluxed. After cooling the n-hexane is taken off with a pipette, another portion n-hexane (5 ml.) is added, shaken and again the n-hexane is taken off. This procedure is repeated another 5 times. Then the solid is filtered off under N₂, washed 3 times with n-hexane (5 ml.) and dried. Yield 1.27 g white product; ir, 2110 cm⁻¹(CD), no peaks are found at 2870, 2970 and 3020 cm⁻¹ (CH in the H-analog); anal. calcd., C, 30.8; D, 11.8; I, 46.5; found, C, 30.5; D, 11.5; I, 46.6; mass anal., as XXXVIII.

Methyl-d₃-amine (XXXX):

Benzylcarbamate (17 g, 0.11 mol.) in diethyl ether (500 ml.) is stirred and in small portions LiAlD₄ (20 g, 0.48 mol.) is added. Then it is stirred 24 hrs at room temperature, cooled to 0^o and D₂O (10 ml.) and KOH (20 ml., 15% in D₂O) are added very slowly. The mixture is allowed to stand overnight and the CD₃NH₂ is distilled off by adding KOH (20 ml., 15% in D₂O, followed by 40 g solid) to this mixture. The CD₃NH₂ is absorbed by a diethyl ether/HCl solution in the receiver. A solid product is formed, which is filtered off under N₂, washed with diethyl ether and dried, yielding 2.4 g CD₃NH₂.HCl; ir, 2300 cm⁻¹(CD) and 3100 cm⁻¹(NH). To prepare a solution of XXXX, CD₃NH₂.HCl (2.4 g, 34 mmol.) is added to D₂O (5 ml.) and diethyl ether (500 ml.). To this mixture sodium methoxide (2.0 g, 37 mmol.) is added. This diethyl ether solution is stored at 0^o and used in a further experiment.

Ethylamine-d₅ (XXXXI):

Potassium phthalimide (10 g, 54 mmol., dried at 200^o) and ethyliodide-d₅ (6 g, 37 mmol.) are sealed in an ampul and heated at 110^o during 24 hrs, then 24 hrs at 120^o and thereafter cooled. The ampul is opened, water (50 ml.) is added, the solid is filtered off, washed with water and crystallized from ethanol, abs.. Yield 4.2 g N-ethyl-d₅-phthalimide; ir, 2110, 2140 and 2230 cm⁻¹(CD); m.p. 74.9^o; mass anal., m/e 180 (C₁₀D₅H₄NO₂). This N-ethyl-d₅-phthalimide (4.2 g, 23 mmol.) and DCl (9.3 ml., 44 mmol., 20% in D₂O) are refluxed 4 hrs. The mixture is cooled, CH₃ONa (2.7 g, 50 mmol.) and CH₃OD (5 ml.) are added and the liquid is distilled up to 100^o. Before the distillation is started, CH₃OD (1 ml.) is added in the receiver. At the end of the distillation there was 11 ml. in the receiver. Mass anal., m/e 52 (7%); m/e 51 (17%); m/e 50 (24%, C₂D₇N); m/e 49 (27%, C₂D₆HN); m/e 47 (5%, C₂D₄H₃N); m/e 48 (20%, C₂D₅H₂N). This 11 ml. is stored at 0^o and used in further experiments.

Tetracyanoquinodimethane-d₄ (XXXXIII):

XXXXII (4.0 g, 33 mmol., prepared analogous to an earlier publication²³) and malonitrile (4.76 g, 72 mmol.) are melted together and added in 3 portions to a mixture of β-alanine (40 mg, 0.4 mmol.) and water (8 ml.) heated at 100^o. A solid forms, the mixture is allowed to react for an additional 15 min, then cooled and filtered off under N₂. The solid is washed with a small amount of water and dried, yielding 8.2 g product; m.p. 214.3^o. This product is added to acetonitril, dry (134 ml.) and bromine (12.8 g, 160 mmol.). This solution is cooled below 10^o and over 15 min pyridine (12.8 ml., 158 mmol.) in acetonitrile (20 ml.) is added with stirring. After 30 min two thirds of the acetonitrile is distilled off and then D₂O (30 ml.) is added. The solid is filtered off, washed twice with D₂O (10 ml.) and once with acetonitrile (10 ml.). The solid is crystallized from boiling acetonitrile under N₂ and sublimed twice, yielding 3.5 g; ir, 2285 cm⁻¹(CD) and 2210 cm⁻¹(CN); mass anal., m/e 208 (C₁₂D₄N₄); anal. calcd. C, 69.2; D, 3.9; N, 26.9; found C, 69.4; D, 3.9; N, 26.5.

Tetracyanoquinodimethane (XXXXIV):

Prepared analogous to XXXXIII from 1.4-cyclohexanedione (150 g, 1.34 mol.), malonitrile (178 g, 2.7 mol.) and a solution of β-alanine (1.5 g, 17 mmol.) in water (300 ml.), yielding 242 g intermediate, m.p. 208-212^o.

In several portions the intermediate is converted to XXXXIV, yielding 207 g. After 2 recrystallizations from acetonitrile is the yield 145 g; ir, 2210 cm^{-1} (CN) and 3050 cm^{-1} (CH). Mass anal., m/e 204 ($\text{C}_{12}\text{H}_4\text{N}_4$). A typical conversion of the intermediate is given below:

Intermediate (24 g, 0.12 mol.) in acetonitrile (400 ml.) and bromine (34.8 g, 0.48 mol.) are cooled at 0° . Under stirring is added in 15 min a mixture of pyridine (38.4 ml., 0.48 mol.) and acetonitrile (60 ml.). A solid precipitates. Stirring is continued 30 min at 0° and the mixture is warmed up to room temperature in 1 hr. The mixture is poured into cold water (600 ml.), the solid is filtered off, washed with cold water and dried. After crystallization from acetonitrile green-yellow crystals are obtained. Yield 25.5 g XXXXIV.

N-Methyl-N-ethylmorpholinium-(T.C.N.Q.)₂ (XXXXV):

XXXVII (510 mg, 2.0 mmol.) in acetonitrile, pure (5 ml.) is heated to reflux under N_2 and then a boiling mixture of XXXXIV (160 mg, 0.8 mmol.) and acetonitrile, pure (25 ml.) is added. A dark solution is formed, which is filtered hot and cooled. The dark solid is filtered off, washed with a little acetonitrile and dried, yielding 110 mg dark needles. Ir, 2160 cm^{-1} (CN), a characteristic peak for M.E.M.-(T.C.N.Q.)₂ complexes; anal. calcd. C, 69.1; H, 4.5; N, 23.4; found C, 68.9; H, 4.5; N, 23.25; uv, in acetonitrile, 1 cm quartz cell, absorption max. at 742 and 394 nm; N-methyl-N-ethylmorpholinium-(T.C.N.Q.)₁ gives absorption max. at 742 and 420 nm; ESR, a normal ESR signal for XXXXV is found³¹, consisting of one line at $G = 2.0030 \pm 0.0002$, for a powder spectrum at room temperature.

N-Methyl-N-ethyl-d₅-morpholinium-(T.C.N.Q.-d₄)₂ (XXXXVI):

XXXVIII (180 mg, 0.69 mmol.) in boiling acetonitrile (3 ml.) is added to a boiling solution of XXXXIII (70 mg, 0.34 mmol.) in acetonitrile (15 ml.); boiling is continued 5 min. The dark solution is filtered hot, cooled, yielding 50 mg dark crystals. Ir, 2160 cm^{-1} (CN); anal. calcd. C, 67.5; H+D, 6.8; N, 22.8; found C, 66.7; H+D, 6.8; N, 22.8; uv and ESR as XXXXV.

N-Methyl-N-ethylmorpholinium-(T.C.N.Q.-d₄)₂ (XXXXVII):

XXXVII (1.5 g, 5.8 mmol.) in boiling acetonitrile (10 ml.) is added to a boiling solution of XXXXIII (580 mg, 2.8 mmol.) in acetonitrile (150 ml.). The mixture

is filtered hot, cooled, filtered off, washed with acetonitrile and dried. Yield 409 mg; ir, 2160 cm^{-1} (CN); anal. calcd. C, 68.1; D+H, 5.9; N, 23.1; found C, 68.2; D+H, 5.9; N, 22.6; uv and ESR as XXXXV.

N-Methyl-d₃-N-ethyl-d₅-morpholinium-d₈-(T.C.N.Q.)₂ (XXXXVIII):

XXXIX (64 mg, 0.25 mmol.) in acetonitrile (1 ml.) is heated to reflux and then a boiling mixture of XXXXIV (28 mg, 0.14 mmol.) and acetonitrile (10 ml.) is added. The mixture is filtered hot and cooled. The next day the solid is filtered off, washed with a small amount of acetonitrile and dried, yielding 15 mg dark needles. Ir, 2160 cm^{-1} (CN); anal. calcd. C, 67.1; D+H, 7.3; N, 22.7; found C, 67.2; D+H, 7.1; N, 22.5; uv and ESR as XXXXV.

N-Methyl-d₃-N-ethyl-d₅-morpholinium-d₈-(T.C.N.Q.-d₄)₂ (XXXXIX):

XXXXIX (200 mg, 0.73 mmol.) in boiling acetonitrile (2 ml.) is added to a boiling solution of XXXXIII (77 mg, 0.37 mmol.) in acetonitrile (20 ml.). The dark solution is filtered hot and slowly cooled. The solid is filtered off, washed with a small amount of acetonitrile and dried. Yield 98 mg; ir, 2160 cm^{-1} (CN); anal. calcd. C, 66.2; D, 8.6; N, 22.4; found C, 66.0; D, 8.5; N, 22.2; uv and ESR as XXXXV.

N,N-Di-(methyl-d₃)-morpholinium-(T.C.N.Q.)₂ (L):

XXXV (120 mg, 0.48 mmol.) in acetonitrile (2 ml.) is heated to reflux and added to a boiling solution of XXXXIV (60 mg, 0.27 mmol.) in acetonitrile (10 ml.), filtered hot and cooled. The very fine needles are filtered, washed with a small amount of acetonitrile and dried, yielding 42 mg. Ir, 2170 cm^{-1} (CN); anal. calcd. C, 67.9; H+D, 5.3; N, 23.8; found C, 66.6; H+D, 5.5; N, 23.0; a better analysis was not obtained by recrystallization from acetonitrile. This purification problem is also found for the H-analog.

2,2'-Ethyliminodiethanol-d₁₅ (LI):

Ethylamine-d₅ (XXXXI) (0.75 g, 14 mmol.) in CH₃OD (6 ml.) and D₂O (5 ml.) is brought in a 100 ml. stainless steel cylinder, cooled at -20° and ethyleneoxide-d₄ (IX) (1.6 g, 50 mmol.) is condensed in the cylinder. The valve is closed, the products are stirred and allowed to come to room temperature, next heated at 100° for 45 min and cooled. The CH₃OD is distilled off, yielding 0.1 g; ir, 2100 and 2230 cm^{-1} (CD), 2540 cm^{-1} (OD), the peaks at 2830, 2950 and

3400 cm^{-1} are from the starting IX; mass anal., m/e 149 (7%, $\text{C}_5^{13}\text{CD}_{15}\text{NO}_2$), m/e 148 (20%, $\text{C}_6\text{D}_{15}\text{NO}_2$), m/e 147 (26%, $\text{C}_6\text{D}_{14}\text{HNO}_2$), m/e 146 (22%, $\text{C}_6\text{D}_{13}\text{H}_2\text{NO}_2$), m/e 145 (18%, $\text{C}_6\text{D}_{12}\text{H}_3\text{NO}_2$), m/e 144 (7%, $\text{C}_6\text{D}_{11}\text{H}_4\text{NO}_2$).

N-Ethylmorpholine- d_{13} (LII):

LI (0.1 g, 0.7 mmol.) is cooled at -20° and D_2SO_4 (2 ml., 96-98%) is added. The mixture is heated at 100° for 90 min, cooled and diethyl ether (25 ml.) added, followed by small portions of KOH (6 g). The upper layer is decanted and the lower layer is extracted twice with diethyl ether (25 ml.). The combined diethyl ether layers are dried over MgSO_4 , filtered and concentrated to 1 ml., this solution is used for mass analysis. Mass anal., m/e 129 (7%, $\text{C}_5^{13}\text{CD}_{13}\text{NO}$), m/e 128 (64%, $\text{C}_6\text{D}_{13}\text{NO}$), m/e 127 (12%, $\text{C}_6\text{D}_{12}\text{HNO}$), m/e 126 (17%, $\text{C}_6\text{D}_{11}\text{H}_2\text{NO}$). The results are analogous to N-ethylmorpholine.

2,2'-Iminodiethanol (LIV), from NH_4OH and ethyleneoxide:

LIII (8 g, 182 mmol.) in methanol (100 ml.) is cooled at -30° , ammonia (10 ml., 25% in water, 134 mmol.) is added. The stainless steel cylinder is closed, allowed to come to room temperature and then heated at $150-200^\circ$ for 1 hr. After cooling the solution is removed and distilled in two fractions, b.p. $120-140^\circ/13$ mm Hg; yield 3.4 g; ir and NMR as a distilled commercial product (Fluka); b.p. $140-150^\circ/13$ mm Hg; yield 2.7 g; ir and NMR as above; mass anal., m/e 118, 100, 74 and a small amount m/e 143.

2,2'-Iminodiethanol (LIV), from NH_3 and ethyleneoxide:

LIII (9 g, 205 mmol.) in methanol (50 ml.) is reacted as above with NH_3 in ethanol, abs. (40 ml., 2.5 mmol. NH_3/ml ethanol). The solution is distilled in two fractions, b.p. $120-140^\circ/13$ mm Hg; yield 4.8 g; ir and NMR as above; b.p. $140-150^\circ/13$ mm Hg; yield 2.2 g; ir and NMR as the 4.8 g. Mass anal., m/e 118, 100 and 74, m/e 143 is found in a very small amount. The results are analogous to the literature³².

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REFERENCES

1. Lunelli B. and Pecile C.-Gazz. Chim. Ital. 99: 496 (1969)
2. Inorganic Synthesis XIV: 94,95
3. Eberhardt G.G., Maher E. Tadros and Vaska L.-J.C.S. Chem. Comm.:290 (1972)
4. Nicholas P.P. and Carroll R.T.-J. Org. Chem. 33: 2345 (1968)
5. Cox J.D. and Warne R.J.-J. Chem. Soc.: 1893 (1951)
6. Bournsnel J.C., Francis G.E. and Wormall A.-Biochem. J. 40: 744 (1946)
7. Petrov A.A.-J. Gen. Chem. U.S.S.R. 13: 481 (1943)
8. Wurtz A.-Ann. der Chem. 121: 226 (1862)
9. Ethyleneoxide-d₄ was available from Stohler Isotope Chemicals and from Rohstoff Einfuhr G.M.B.H.
10. Blomquist A.T., Hiscock B.F. and Harpp D.N.-J. Org. Chem. 31:338 (1966)
11. Quast H. und Gelléri A.-Justus Liebigs Ann. Chem.: 939 (1975)
12. Van Cleave A.B. and Blake R.I.-Can. J. of Chem. 29: 785 (1951)
13. Prelog V., Fausy El-Neweihy M. und Häflinger O.-Helv. Chim. Acta 33:1937(1950)
14. Sand J.-Chem. Ber. 34: 2906 (1901)
15. Knorr L. und Schmidt W.-Chem. Ber. 31: 1072 (1898)
16. Müller E., Huber-Emden H. und Rundel W.-Ann. der Chemie 623: 34 (1959)
17. Gibson C.S. and Johnson J.D.A.-J. Chem. Soc.: 2526 (1930)
18. Olsen R.K.-J. Org. Chem. 35: 1912 (1970)
19. Wedekind E. und Bruch E.-Ann. der Chemie 471: 73 (1929)
20. Wessely F. und Swoboda W.-Monatsheft für Chemie 82: 621 (1951)
21. Cox J.D. and Warne R.J.-J. Chem. Soc.: 1896 (1951)
22. Boitsova V.F., Rusinova K.D., Komers G.I. and Grigor'eva L.P.-Tr. Gos. Inst. Prikl. Khim. 52: 98 (1964)
23. Kwant B.H.-This journal XIV: 397 (1978)
24. Acker D.S. and Hertler W.R.-J. A. C. S. 84: 3370 (1962)
25. Kuindersma P.I.-Ph. D. Thesis, University of Groningen, Physical Chem., 1975
26. Rozenkranz G., Mancera O., Cativa J. and Djerassi C.-J.A.C.S. 72: 4077 (1950)
27. Duldner I., Georgescu V., Serban S., Weidenbacher A. and Buzas A.-Rev. Chim. (Bucharest) 19: 566 (1968)
28. Pinchas S. and Laulich I.-Infrared Spectra of Labelled Compounds, Acad. Press, London, 1971
29. Claisen L.-Chem. Ber. 14: 2473 (1881)
30. Aldrich-Europe, Beerse, Belgium: Technical information product no. 16484
31. Private communication S. Huizinga
32. Stenhagen E. et al-Atlas of Mass Spectral Data, Interscience publ., 1969