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SPIRO-DIHYDROFURAN-PYRAZOLIDINONES FROM TETRAACETYLETHYLENE AND AZO-DICARBONYL COMPOUNDS

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Abstract - Tetraacetylethylene (1) reacted with electron-withdrawing azo compounds to give spiro furan-pyrazoles. Their structure was confirmed by an X-ray crystallographic analysis on a derivative of the spiro|furan-3(2H),5'(7'H)-pyrazolo|1,2-a||1,2,4|triazole-1',3',6'-trione|. The cycloadducts show ring-open chain tautomerism.

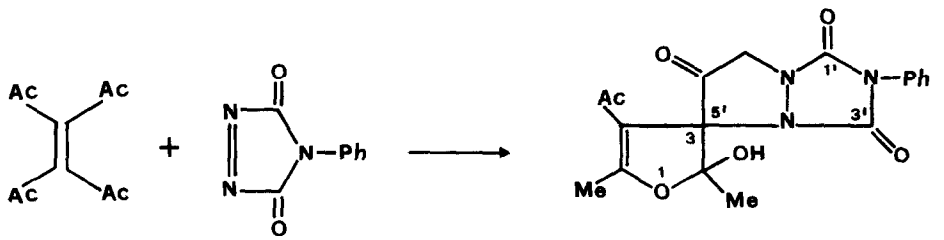
In recent years we undertook a systematic study on the chemistry of tetraacetylethylene (3,4-diacetyl-3-hexen-2,5-dione), (1), which shows a multiform reactivity [1].

In this paper we describe the results observed in the reaction between tetraacetylethylene and electron-withdrawing azo compounds, which gives rise to new hetero spirans.

Refluxing a benzene solution of the ketone **1** with 4-phenyl-1,2,4-triazoline-3,5-dione (**2**), affords the 1:1 cycloadduct **3**, whose structure was assigned on the basis of analytical and spectral data. The ir spectrum shows a very strong band at ca. 1600 cm^{-1}, diagnostic for the presence of a highly polarized O=C-C=C-O-R system[2,3].

The ^{1}H and ^{13}C-nmr spectra in DMSO are consistent with the attributed spiro furan-pyrazole structure.

The ^{1}H-nmr spectrum of **3** in deuteriochloroform displays a duplication of signals (in a ratio of 59:41) attributable to the presence of two

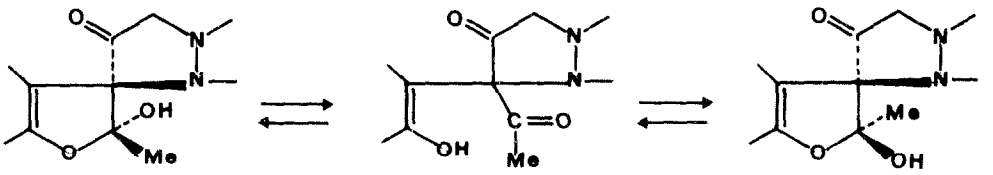


1 **2** **3**

strictly related isomers. This observation is in agreement with the presence of a C-2 hemiacetalic carbon atom which together with the chiral centre at C-3 gives rise to two diastereoisomers, 4 and 5.

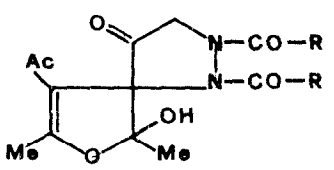
Attempts to separate the isomers 4 and 5 were unsuccessful.

Even if recorded in different solvents the nmr spectrum did never show traces of the open form 6.



4 6 5

The reaction was extended to diethyl azodicarboxylate (7) and to 1,2-diaroyldiazenes 8a-c with which tetraacetylethylene affords the cycloadducts 9 and 10a-c respectively, analogous to 3.



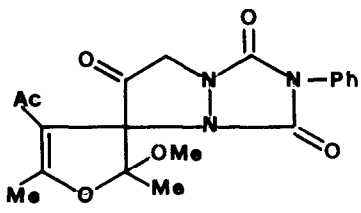
9 R=OEt
10a R=C_6H_5
10b R=C_6H_4-Me(p)
10c R=C_6H_4-Cl(p)

Attempts to obtain suitable crystals of 3 or 9 or 10 a-c for X-ray analysis had been unsuccessful.

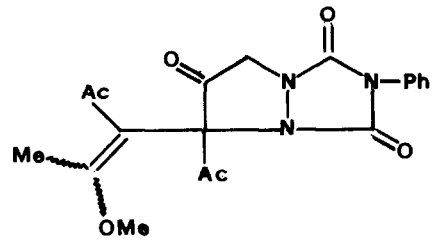
The structure of the cycloadduct 3, and as a consequence the structures of 9 and 10a-c, is confirmed by an X-ray analysis undertaken on the derivative 11 obtained by reaction of 3 with methanol and hydrochloric acid. From the reaction we isolated another methyl-derivative, which we assigned the 5-(1'-acetyl-2'-methoxy-1'-propenyl)-5-acetyl-2-phenylpyrazolo[1,2-a][1,2,4]triazole-1,3,6-trione structure 12. No trace was found of the diastereoisomer of 11.

The molecular model of 11 reported in Figure 1, clearly shows the conformation and the relative configuration of the two asymmetric centers of (2RS,3SR)-4-acetyl-2,5-dimethyl-2'-phenyl-2-methoxyspiro[furan-3(2H),5'(7'H)-pyrazolo[1,2-a][1,2,4 triazole-1',3',6'-trione].

Bond lengths and angles are listed in Table 1. Non-hydrogen atoms fractional coordinates are reported in Table 2.



11



12

The five member rings very slightly deviate from the planarity. As evidenced from the puckering phases and amplitudes[7] reported in Table 3, the preferred conformation for the three pentaatomic rings is a twist envelope with pseudo C_2 symmetry. The corresponding axes pass through N(2) for the triazole, N(2) for the pyrazole and C(2) for the furan ring. The dihedral angle between triazole and pyrazole rings is 140.3°, whereas that between phenyl ring and triazole ring is 115.2°, showing the non-planarity of N(3).

The residual methanol located as described in the experimental section, shows a distance attributable to a hydrogen bond (2.859 Å) with the oxygen of the acetyl group.

Formation of the spiroadducts **3**, **9** and **10a-c** can be rationalized if one admits that the azo compounds behave as bases extracting a hydrogen

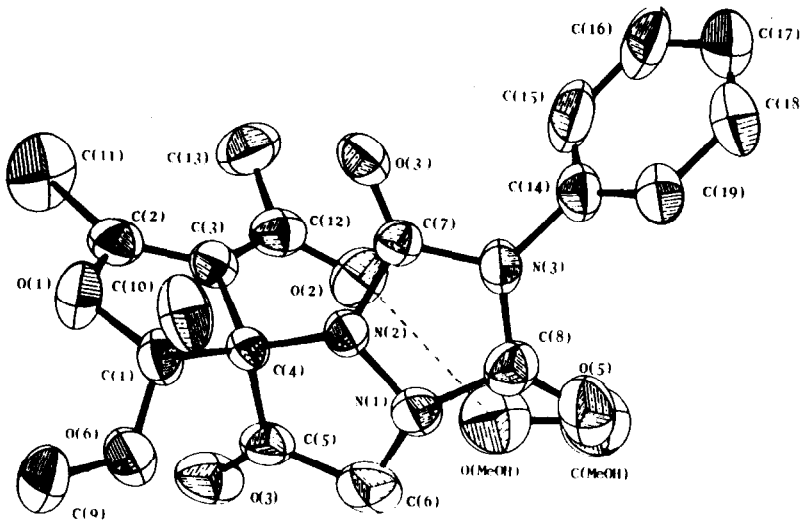
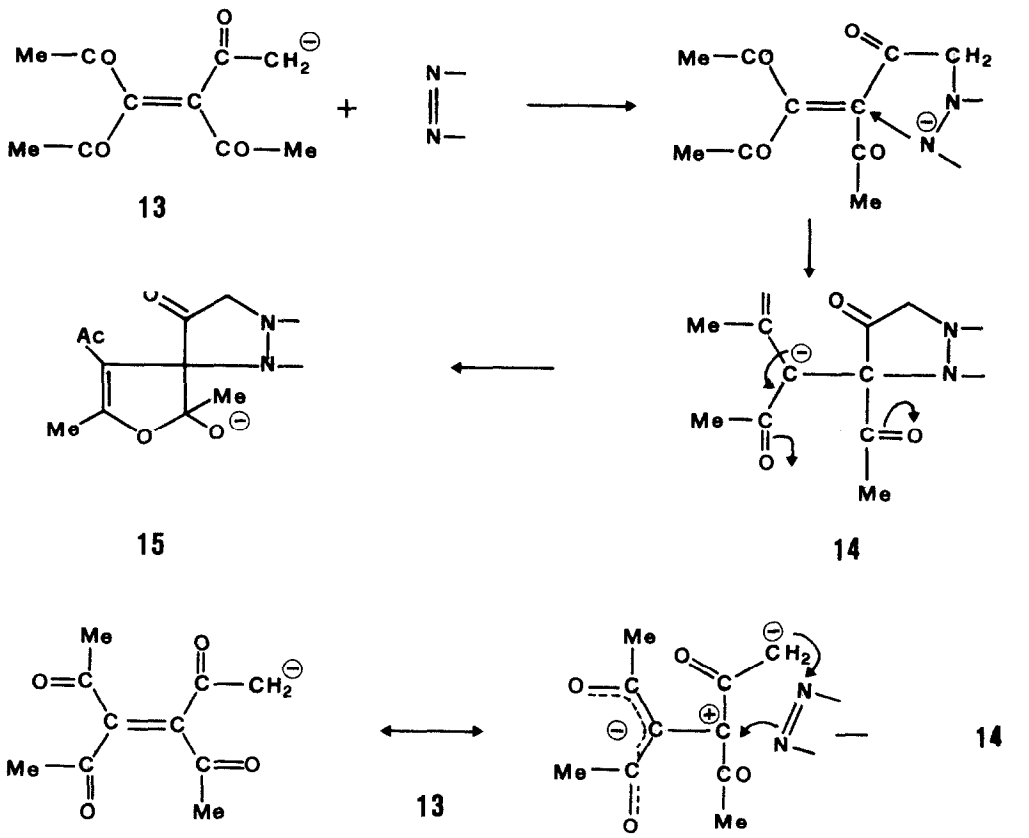


FIGURE - Perspective view of **11** with the number scheme used in crystallographic analysis.

atom from a methyl group of the tetraketone 1. Then the carbanion 13 leads, by a nucleophilic attack on another molecule of azo compound to compound 14 which rearranges to the final spiro derivative 15.

Alternatively, one may postulate a concerted mechanism reaction between the anion 13 and a molecule of azo derivative with the formation of the pyrazole ring. This behaviour would be analogous to that described by Trost for similar systems [4]. Afterwards compound 14 could give the spiro derivative 15.



It is of interest to note that 2,3-diacetylethylene[5] and diethyl 2,3-diacetylbutendioic acid[6] did not react with azo dicarbonyl compounds. This behaviour can be justified either with a lower probability of the formation of an anion analogous to 13, or because the pyrazole ring formation requires the furan ring closure, which in the case of the above compounds is not possible.

TABLE 1 - Significant bond lengths (Å) and angles (°) with the e.s.d.'s in parentheses.

O(1)-C(1)	1.459(5)	N(3)-C(8)	1.395(5)
O(1)-C(2)	1.353(6)	N(3)-C(14)	1.423(5)
O(2)-C(12)	1.230(5)	N(3)-C(7)	1.385(6)
O(3)-C(5)	1.204(5)	C(1)-C(4)	1.548(6)
O(4)-C(7)	1.211(5)	C(1)-C(10)	1.511(7)
O(5)-C(8)	1.209(5)	C(2)-C(3)	1.353(6)
O(6)-C(1)	1.387(5)	C(2)-C(11)	1.483(8)
O(6)-C(9)	1.449(6)	C(3)-C(4)	1.492(6)
N(1)-N(2)	1.432(4)	C(3)-C(12)	1.443(6)
N(1)-C(6)	1.459(6)	C(4)-C(5)	1.546(6)
N(1)-C(7)	1.387(6)	C(5)-C(6)	1.501(7)
N(2)-C(4)	1.478(5)	C(12)-C(13)	1.495(7)
N(2)-C(8)	1.367(5)		

C(1)-O(1)-C(2)	109.4(3)	C(2)-C(3)-C(12)	132.2(4)
C(1)-O(6)-C(9)	115.8(5)	N(2)-C(4)-C(1)	111.2(3)
N(2)-N(1)-C(6)	111.2(3)	N(2)-C(4)-C(5)	101.7(3)
N(2)-N(1)-C(7)	108.1(3)	C(1)-C(4)-C(5)	114.9(3)
C(6)-N(1)-C(7)	124.7(4)	N(2)-C(4)-C(3)	116.0(3)
N(1)-N(2)-C(4)	111.8(3)	C(1)-C(4)-C(3)	103.6(3)
N(1)-N(2)-C(8)	108.0(3)	C(3)-C(4)-C(5)	109.9(3)
C(4)-N(2)-C(8)	124.2(3)	O(3)-C(5)-C(4)	124.0(4)
C(8)-N(3)-C(14)	123.6(3)	O(3)-C(5)-C(6)	125.1(4)
C(7)-N(3)-C(8)	110.7(3)	C(4)-C(5)-C(6)	110.8(4)
C(7)-N(3)-C(14)	124.9(3)	N(1)-C(6)-C(5)	103.8(4)
O(1)-C(1)-O(6)	108.9(3)	O(4)-C(7)-N(1)	126.2(4)
O(6)-C(1)-C(4)	107.7(4)	O(4)-C(7)-N(3)	128.1(4)
O(1)-C(1)-C(4)	103.8(3)	N(1)-C(7)-N(3)	105.6(4)
O(6)-C(1)-C(10)	114.2(4)	O(5)-C(8)-N(2)	126.8(4)
O(1)-C(1)-C(10)	107.0(4)	O(5)-C(8)-N(3)	126.6(4)
C(4)-C(1)-C(10)	114.7(4)	N(2)-C(8)-N(3)	106.5(3)
O(1)-C(2)-C(3)	113.8(4)	O(2)-C(12)-C(3)	118.2(4)
O(1)-C(2)-C(11)	114.0(4)	O(2)-C(12)-C(13)	120.3(5)
C(3)-C(2)-C(11)	132.2(5)	C(3)-C(12)-C(13)	121.5(5)
C(2)-C(3)-C(4)	108.0(4)	N(3)-C(14)-C(19)	120.1(4)
C(4)-C(3)-C(12)	119.2(4)	N(3)-C(14)-C(15)	118.9(4)

TABLE 2 - Fractional coordinates ($x10^4$) of non-hydrogen atoms with the e.s.d.'s in parentheses.

Atom	x/a	y/b	z/c
O(1)	3602(1)	-101(3)	2996(3)
O(2)	2681(2)	-37(2)	4662(3)
O(3)	2036(1)	2067(2)	1431(2)
O(4)	753(2)	-393(3)	2224(3)
O(5)	1596(2)	1506(2)	3894(3)
O(6)	2219(2)	618(2)	2151(3)
N(1)	1823(2)	-167(2)	2359(3)
N(2)	1266(2)	926(3)	1577(3)
N(3)	3657(1)	1511(2)	3122(3)
C(1)	2666(2)	785(3)	3006(3)
C(2)	3349(2)	723(3)	2616(4)
C(3)	3222(2)	2064(3)	3574(4)
C(4)	1863(2)	1299(3)	1698(3)
C(5)	4255(3)	-260(6)	2756(7)
C(6)	3428(3)	856(6)	1458(5)
C(7)	754(2)	1433(3)	1152(4)
C(8)	1995(3)	-623(4)	3333(5)
C(9)	2476(2)	19(3)	3793(4)
C(10)	1218(2)	71(3)	2077(4)
C(11)	2634(2)	1723(3)	3509(3)
C(12)	2050(2)	2033(3)	3950(3)
C(13)	463(2)	1121(4)	265(4)
C(14)	-211(3)	2453(6)	317(6)
C(15)	566(3)	2246(5)	1635(6)
C(16)	1989(4)	2970(4)	4455(5)
C(17)	77(3)	2746(6)	1199(7)
C(18)	-29(3)	1630(5)	-141(5)
C(19)	3480(3)	2923(5)	4056(6)
C(MeOH)	-65(18)	5013(48)	-277(46)
O(MeOH)	-714(16)	4795(26)	-277(29)

TABLE 3 - Puckering phases and amplitudes with the e.s.d.'s in parentheses.

Ring	Furan	Pyrazole	Triazole
Q_2	0.117(4)	0.083(5)	0.087(4)
Φ_2	-161(2)	-123(2)	90(2)

EXPERIMENTAL

Melting points were taken on a Kofler melting point apparatus and are uncorrected. Unless otherwise stated, the ^{1}H-nmr spectra were recorded for deuteriochloroform solutions with a Hitachi-Perkin-Elmer R-600 instrument and ^{13}C-nmr spectra with a Varian FT-80 A spectrometer; chemical shifts (J in Hz) are reported downfield from internal tetramethylsilane. The ir spectra were recorded on a Perkin-Elmer 782 spectrophotometer using samples in potassium bromide pellets.

Materials

The following compounds were prepared by the literature procedure cited: tetraacetylethylene, **1**,[8], diaroylhydrazines[9], diaroyldiazenes[10,11].

4-Acetyl-2-hydroxy-2,5-dimethyl-2'-phenyl spiro [furan-3(2H),5'(7'H)-pyrazolo[1.2-a] [1.2.4]triazolo-1',3',6'-trione] (3).

A mixture of tetraacetylethylene (1) (1g, 5.1 mmoles) and 4-phenyl-3,5-dihydro-1,2,4-triazole-3,5-dione (0.893 g, 5.1 mmoles) in benzene (22 ml) was refluxed for 7 hours. The cooled solution was evaporated to dryness. The residue was crystallized from ethyl acetate to yield the spiro derivative **3**, m.p. 169-170° (1.9 g, 70%). Ir, νmax: 3180(OH), 1790(CO), 1775(CO), 1720(CO), 1590(CO-C=C-O-) cm^{-1}; uv λmax (log ε): 265 (4.06) nm; ^{1}H-nmr (DMSO) δ :1.69(s,3H,Me), 2.25(s,3H,Me), 2.36(s,3H,Me), 4.32(AB,2H, CH_2,J=18), 7.42(s,5H,C_6H_5); ^{13}C-nmr (DMSO):199.8(CO), 193.35 (CO), 171.3(C-5), 154.0(CO-N), 153.0(CO-N), 131.5-126.4 (aromatic C), 113.2(C-2 or C-4), 110.3(C-4 or C-2), 80.25(C-3), 50.6(CH_2N), 27.7(MeCO), 24.9 (Me-C=C), 15.8(Me); ^{1}H-nmr ($CDCl_3$) δ: 1.59(s,1.8H,Me), 1.75(s,1.2H,Me), 2.26(s,1.2H,Me), 2.30(s,1.8H,Me), 2.33(s,1.2H,Me), 2.37(s,1.8H,Me), 4.30 (AB,2H,CH_2, J=18.0), 4.56(bs,1H,OH), 7.42(s,5H,C_6H_5). Anal. Calcd for $C_{18}H_{17}N_3O_6$: C,58.28; H,4.61; N,11.32. Found: C,58.27; H,4.67; N,11.23.

Diethyl 9-Acetyl-6,8-dimethyl-6-hydroxy-4-oxo-7-oxa-1,2-diaza spiro[4.4] non-8-ene-1,2-dicarboxylate (9).

A solution of tetraacetylethylene (1) (1g, 5.1 mmoles) and ethyl azodicarboxylate (1 ml, 6.4 mmoles) in benzene (5 ml) was refluxed for 48 hours. The yellow solution was filtered through a small quantity of silica gel and evaporated. The residue was crystallized from benzene to give the spiro derivative **9**, as white needles (1.22g, 67.8%), m.p. 131-132° . Ir ν max.: 3170(OH), 1785(CO), 1745(CO), 1720(CO), 1600(CO-C=C-O-) cm^{-1}; uv λ max. (log ε): 262.5 (3.96) nm; ^{1}H-nmr δ : 1.23(t,3H,Me), 1.30(t,3H,Me),

1.42(s,1.7H,Me), 1.69(s,1.3H,Me), 2.26(s,4.7H,Me), 2.33(s,4.3H,Me), 4.10-4.29(m,6H,3xCH_2). Anal.Calcd for $C_{16}H_{21}N_2O_8$: C,51.89; H,5.99; N,7.76. Found: C,52.05; H,5.95; N,7.48.

9-Acetyl-1,2-diaroyl-6,8-dimethyl-6-hydroxy-4-oxa-1,2-diaza spiro [4.4] non-8-enes (**10a-c**).

A solution of diaroyldiazene (1.2 mmoles) and tetraacetylethylene (1 mmole) in benzene (15 ml) was refluxed for 30 hours. The solution changed from red to yellow. The cooled solution was treated with carbon, filtered and evaporated to give a residue which was extracted with ether. Ethereal extracts were filtered through a small amount of silica gel and then evaporated to yield the spiro compounds **10a-c**.

Compound **10a**, mp 158-160° (from cyclohexane) (46%). Ir, ν max: 3400(CH), 1770(CO), 1680(CO), 1625(CO-C=C-O-) cm^{-1}; ^{1}H-nmr δ : 1.49(s,3H,Me), 1.62 (s,2H,H_2O), 2.24(s,3H,Me), 2.34(s,3H,Me), 4.41(AB,2H,CH_2,J=16.8), 6.59 (bs,1H,OH), 7.41(s,10H,2xC_6H_5). Anal.Calcd for $C_{24}H_{22}N_2O_6.H_2O$: C,63.72; H,5.30; N,6.19. Found: C,63.76; H,5.10; N,6.30.

Compound **10b**, mp 169-170° (from chloroform/petroleum ether) (51%). Ir ν max: 3200(OH), 1770(CO), 1685(CO), 1615(CO-C=C-O-) cm^{-1}; ^{1}H-nmr δ : 1.47(s,1.8H,Me), 1.57(s,1.2H,Me), 2.23(s,3H,Me), 2.35(bs,9H,3xMe), 4.41 (AB,2H,CH_2,J=16.8), 6.70(bs,1H,OH), 7.07-7.69 (m,8H, 2xC_6H_4). Anal.Calcd for $C_{26}H_{26}N_2O_6$: C,67.53; H,5.63; N,6.06. Found: C,67.32; H,5.74; N,5.95.

Compound **10c**, mp 186-189° (from ethyl acetate/cyclohexane), (45%): Ir ν max: 3380(OH), 1710(CO), 1680(CO), 1590(CO-C=C-O-) cm^{-1}; ^{1}H-nmr δ : 1.47 (s,2.0H,Me), 1.54(s,1.0H,Me), 2.25(bs,3H,Me), 2.35(bs,3H,Me), 4.40 (AB,2H, CH_2,J=16.8), 6.42(bs,1H,OH), 7.38-7.70(m,8H,2xC_6H_4). Anal. Calcd for $C_{24}H_{20}Cl_2N_2O_6$: C,57.37; H,3.98; Cl,13.94; N,5.58. Found: C,57.20; H,3.97; Cl,13.52; N,5.59.

Methylation of the Spiro derivative **3**.

A solution of compound **3** (0.6 g) in methanol (30 ml) was saturated with a stream of hydrogen chloride until the starting product disappeared (tlc). The white solid obtained (0.18 g, 29%) was filtered and crystallized from ethyl acetate/cyclohexane to give the methyl derivative **11**, mp 177-180°. Ir ν max: 1775(CO), 1760(CO), 1710(CO), 1615(CO-C=C-O-) cm^{-1}; ^{1}H-nmr δ : 1.77(s,3H,Me), 2.27(s,3H,Me), 2.36(s,3H,Me), 3.48(s,3H,OMe), 4.25(AB,2H,CH_2,J=17.6), 7.42(s,5H,C_6H_5). Anal.Calcd for $C_{19}H_{19}N_3O_6$: C,

59.22; H,4.93; N,10.9. Found: C,59.06; H,4.68; N,10.78.

The methanolic solution was concentrated to yield another crop of compound **11** (0.1 g, 16%). Then the solution was evaporated to dryness and the residue was dissolved in methylene chloride, treated with anhydrous potassium carbonate, filtered and evaporated to dryness. The residue was crystallized from ethyl acetate to yield the methyl derivative **12**, mp 170-173 (0.17 g, 27%). Ir ν max: 1780(CO), 1710(CO), 1665(CO) cm^{-1}; ^{1}H-nmr δ : 2.23(s,3H,Me), 2.39(s,3H,Me), 2.59(s,3H,Me), 3.78(s,3H,OMe), 4.11(AB,2H, CH_2,J=17.2), 7.57(m,5H,C_6H_5). Anal.Calcd for $C_{19}H_{19}N_3O_6$: C,59.22; H,4.93; N,10.9. Found: C,59.35; H,4.88; N,10.9.

Crystal Data: $C_{19}H_{19}N_3O_6$, M = 385.368. Orthorhombic, space group P_{cab}, a = 21.408(6), b = 14.306(4), c = 12.864(3), V = 3939.7 $Å^3$, Z = 8, F(000) = 1616, D_c = 1.30 $g.cm^{-3}$, graphite-monochromated Mo-Kα, λ = 0.71069 A, μ = 0.61 cm^{-1}.

Data collection and refinement: Crystals suitable for crystallographic measurements were grown from methanol. Elemental analysis and ^{1}H-nmr integration of samples taken from the same batch from which the crystal used for the X-ray analysis was chosen, showed the presence of residual methanol in the range of 10-15%. Attempts to obtain crystals free from methanol, good enough for X-ray structure determination, were unsuccessful.

A colourless prismatic crystal of dimension 0.49x0.6x0.55 mm was mounted on a Philips automated diffractometer, ω-2ϑ scan in the range $4 < 2\vartheta < 50°$, three standard reflections showed no significant variations. After corrections of Lorentz and polarization 1591 reflections with $I > 3\sigma(I)$ were considered observed and used for structure analysis and refinements. Absorption corrections were not applied.

The structure was solved by SHELX 76 system programs [12]. All non-hydrogen atoms were located in the E-maps. Difference Fourier maps showed, together the hydrogen atoms, a residual electronic density at 0,0,0.5 fractional coordinates. Taking into consideration both nmr data and elemental analysis of samples chosed from the same batch of the crystal used in the diffractometric data collection, this density was interpretated as a residual 10-15% of methanol randomly distributed across the 0,0,0.5 and the other symmetry related positions. Refinement inserting a carbon and oxygen at fixed distance of 1.43 Å between them, fixed thermal factor (U = 0.08 $Å^2$) and site occupation factor as free variable, converged giving a site occupation factor of 0.12, so

reasonably confirming the presence of a residual percentage of the crystallization solvent.

In the final refinement three least-squares cycles with non-hydrogen atoms anisotropical and hydrogen atoms with a common thermal parameter of 0.08 A^2, converged at R = 0.055 and R_w = 0.057. The weighting schema used was $w = (\sigma^2(F_o)+0.004\ F_o^2)^{-1}$

Full lists of hydrogen atoms fractional coordinates, anisotropical thermal parameters and observed and calculated structure factors are available as Supplementary Material and have been deposited at the Cambridge Crystallographic Data Centre.

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