FORMATION OF SPIRO-LACTOLS UPON REACTION OF NINHYDRIN WITH METHYLDIAZINES[1,#]

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Abstract - Reaction of ninhydrin (**4**) with 4-methylpyridazine or 4-methylquinoline leads to 2-hydroxy-2-heteroarylmethyl-1,3-indandiones (**5**), which resist dehydration to the corresponding 2-heteroarylmethylene-1,3-indandiones (**2**). In contrast, employing methyl(di)azines with a methyl group in α-position to a ring nitrogen atom (3-methylpyridazine, 4-methylpyrimidine, 2-methylpyrazine, 2-methylquinoline, 2-methylquinoxaline) results in the exclusive formation of novel 3a',8b'-dihydroxy-3'-heteroaryl-3a',8b'-dihydrospiro[indane-2,2'(3'*H*)-4'*H*-indeno [1,2-*b*]furan]-1,3,4'-triones (**7**) which might result from cyclisation of initially formed 2,2'-dihydroxy-2,2'-(heteroarylmethylene)bis-1,3-indandiones (**6**).

Dedicated to Prof. Miha Tišler on the occasion of his 70th anniversary

INTRODUCTION

In the course of a program directed to the synthesis of compounds with potential blood platelet antiaggregatory activity we were interested in 1,2-diazine analogues of the anticoagulant 2-(3-pyridinylmethylene)- and 2-(4-pyridinylmethylene)-1,3-indandiones described by Rehse.[2] Whereas 2-(4-pyridazinylmethylene)-1,3-indandione (**2b**) could be simply obtained in a Knoevenagel-type condensation from 4-pyridazinecarbaldehyde and 1,3-indandione[3] (**1**), a similar reaction with 3-pyridazinecarbaldehyde did not lead to the desired 3-pyridazinyl congener (**2a**).[3] Instead, the exclusive formation of a 2:1 product (**3a**) resulting from Michael addition of a further 1,3-indandione unit to the initially formed condensation product was observed[4] (Scheme 1). The latter reaction behaviour was also observed with other carbaldehydes derived from π-deficient *N*-heteroaromatics having the formyl group in α-position to the ring nitrogen atom[4] (2-pyridinecarbaldehyde, 2-quinolinecarbaldehyde). This prompted us to investigate a "reverse" way of C-C bond formation by transforming the carbonyl moiety to the indandione system (1,3-indandione → 1,2,3-indantrione) and the C-H acidic component to the heterocyclic system ((di)azinecarbaldehyde → methyldiazine) in order to achieve a more general access to the desired methylene compounds. Thus, we here report on some investigations concerning the reaction of ninhydrin (**4**) (= 1,2,3-indantrione hydrate) with methyldiazines and methylazines.

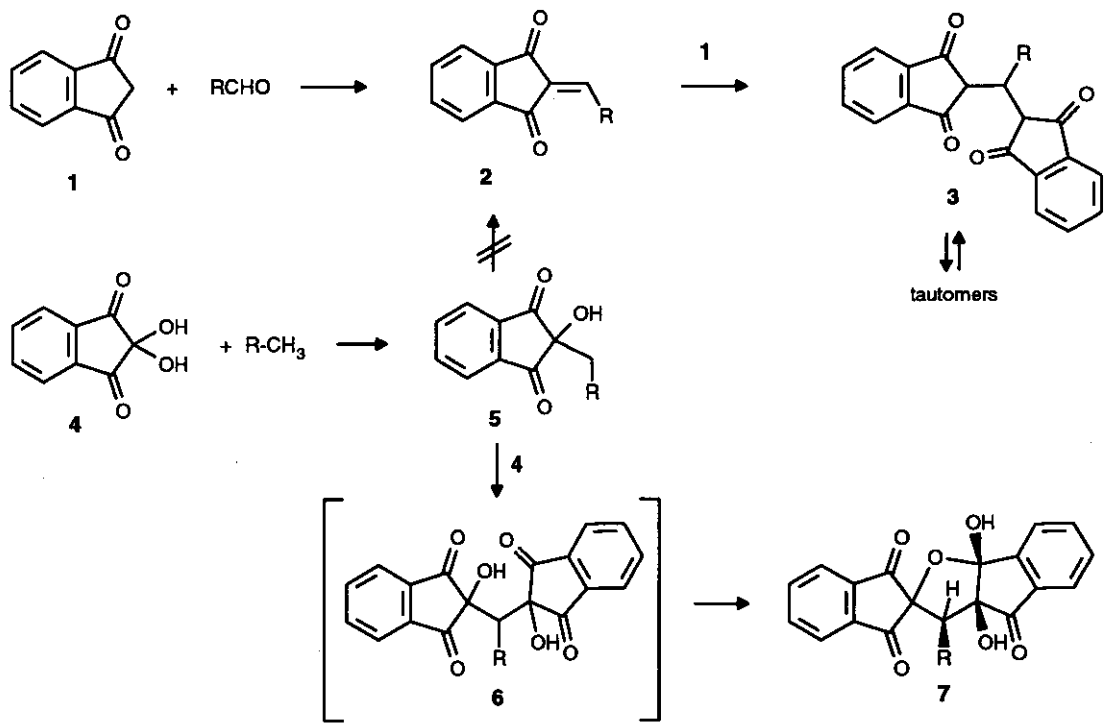
RESULTS AND DISCUSSION

Synthesis

Initial attempts by heating ninhydrin (**4**) with 4-methylpyridazine in xylene (100°C) showed that addition to give the carbinol (**5b**) occurred smoothly (Scheme 1). However, no spontaneous elimination of water to yield the corresponding alkene (**2a**) could be observed. In contrast, under analogous reaction conditions 3-methylpyridazine and **4** did not afford the corresponding alcohol (**5a**). Instead, according to ms data as well as elemental analysis, a compound of the elemental composition $C_{23}H_{14}N_2O_6$ had been obtained as the sole product, which obviously results from reaction of two ninhydrin units with one molecule of the methyldiazine. Similarly, reaction of ninhydrin (**4**) with 4-methylpyrimidine, 2-methylpyrazine,

2-methylquinoline and 2-methylquinoxaline, respectively, resulted in the formation of congeneric products. However, according to their nmr data (see below) the isolated compounds could not be the primary 1:2 adducts of type (**6**). Detailed nmr spectroscopic investigations and, particularly, X-ray analyses finally enabled us to assign the spiro-ring structure (**7**) to the compounds obtained. Their formation from the initial addition products (**6**) can be easily explained by lactol-ring closure (Scheme 1).

Scheme 1



	R		R
a	3-pyridazinyl	e	2-quinolinyl
b	4-pyridazinyl	f	4-quinolinyl
c	4-pyrimidinyl	g	2-quinoxalinyl
d	2-pyrazinyl		

On the other hand, similar to the formation of **5b**, 4-methylquinoline and **4** afforded the alcohol (**5f**) in 65 % yield (Scheme1). Several attempts to transform the carbinols (**5b**) and (**5f**), respectively, to the corresponding alkenes of type (**2**) employing different methods met with a failure. Obviously, elimination of water from such type of compounds is difficult, which is confirmed by a similar case described in the

literature.[5] Moreover, it should be mentioned that upon reaction of **4** with 2-methylpyridine and 4-methylpyridine no defined reaction products could be isolated under the conditions applied.

In conclusion, reaction of ninhydrin with methyl(di)azines having the methyl group in α-position to the ring nitrogen atom leads to the exclusive formation of 2:1 spiro-ring products of type (**7**), whereas upon employment of methyl(di)azines with "β"- or "γ"-methyl groups the reaction stops on the stage of 1:1 products of type (**5**).

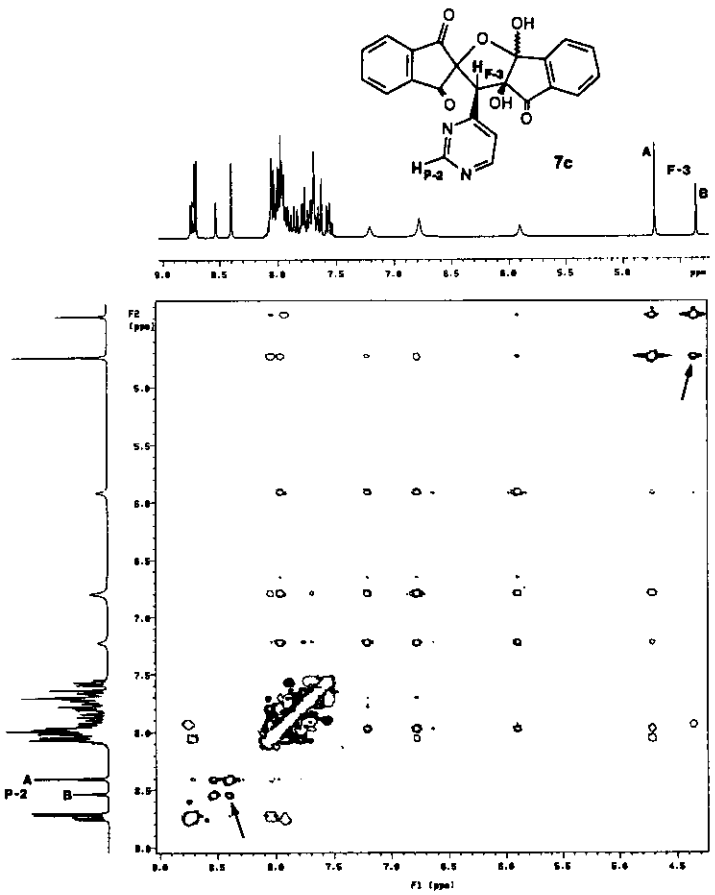
Spectroscopic Investigations

An interesting phenomenon is observed in the ^{1}H- and ^{13}C-nmr spectra of compounds (**7**). Although these products were obtained as homogenous materials, their nmr spectra exhibit two sets of signals (A and B) in a ratio of ~ 2:1 with the predominating species A having the C(sp^3)-H signal of the central tetrahydrofuran ring at higher frequencies. This can be explained by the adjustment of an equilibrium between two stereoisomers due to a ring opening - ring closure process with reversion of configuration on the anomeric C-atom (C-8b in Table 1). This assumption was confirmed by NOESY experiments (phase sensitive) which permit to distinguish cross peaks due to positive NOEs (usual for small molecules in non-viscous solvents) from those originating from chemical exchange on basis of their phase properties: thus, cross peaks resulting from positive NOEs have opposite phase than diagonal peaks or signals originating from negative NOEs and from chemical exchange processes.[6] Accordingly, the 2D-NOESY spectrum of compound (**7c**) (Figure 1) shows cross peaks due to chemical exchange between the corresponding signals of "non-acidic" protons pyrimidine H-2 ("P-2") of A and B (marked with an ➔; minor isomer B δ 8.55 ppm, major isomer A δ 8.42 ppm), the same applies for the two C-H signals of the tetrahydrofuran system ("F-3") at δ 4.72 ppm (major isomer A) and δ 4.40 ppm (minor isomer B, cross peak marked with an ➔).

Assignments were performed on basis of different nmr techniques such as NOE difference experiments, fully ^{1}H-coupled ^{13}C-nmr spectra, ^{13}C,^{1}H-shift correlations (HMQC and HMBC)[7] as well as on 1D-HETCOR[8] and long-range INEPT spectra[9] with selective DANTE excitation. However, owing to severely overlapping signals in the aromatic and heteroaromatic region of the ^{1}H- and ^{13}C-nmr spectra complete and unambiguous assignments of all resonances were not possible with compounds of type (**7**). Thus, in Table 1, only selected ^{13}C-nmr data of compounds (**7**) are presented. Isomers A and B differ with respect

to their configuration at the anomeric C-atom C-8b (marked with an *). The question which isomer corresponds to the configuration of compounds (**7**) found in the X-ray structures of **7c** (Figure 2) and **7g** (Figure 3) cannot be unequivocally decided on basis of the present data.

Figure 1. Phase-sensitive NOESY spectrum of compound (**7c**) (DMSO-d_6, mixing time 1.2 s).#

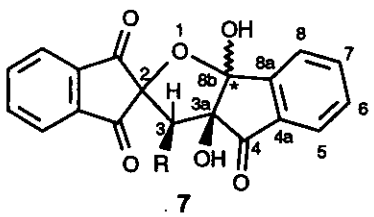


Positive peaks (diagonal peaks and peaks resulting from chemical exchange) are plotted with several contour levels, negative peaks resulting from positive NOEs are plotted as "empty" contours (one level).

Crystal Structures of Compounds (7c)·CH_3NO_2·H_2O (Nitromethane Water Solvate of 7c) and (7g)

Yellow crystals suitable for X-ray work were obtained by recrystallization of **7c** from unpurified nitromethane and turned out to be a stoichiometric nitromethane water solvate. Technical details of the structure determination work are given in the experimental section. Atomic parameters are listed in Table 2. A view of the asymmetric unit of **7c**·CH_3NO_2·H_2O and selected bond lengths are given in Figure 2. The

Table 1. Selected ^{13}C-nmr data (δ, ppm) of compounds (**7**) (isomers A and B)[$]



7

No.	C=O	C-2[§]	C-3	C-3a[§]	C-8b	(Di)azine-C (C of R)
7a (A)	198.4, 195.6, 195.4	80.8	54.4	83.3	108.3	156.1 (3), 150.7 (6), 127.4 (4), 126.1 (5)
7a (B)	199.0, 196.7, 195.1	84.4	54.6	86.7	111.3	156.2 (3), 150.6 (6), 128.1 (4), 126.8 (5)
7c (A)	198.2, 196.0, 195.4	80.6	55.9	83.3	108.4	161.6 (4), 156.5 (2), 155.7 (6), 121.3 (5)
7c (B)	198.7, 196.7, 195.1	84.3	55.8	86.4	111.3	161.5 (4). 156.7 (2), 156.7 (6), 121.9 (5)
7d (A)	198.1, 196.0, 195.3	80.8	55.2	83.5	108.3	149.0 (2), 145.3 (3), 142.6 (5), 141.6 (6)
7d (B)	198.7, 196.7, 194.9	84.3	54.9	86.8	111.2	148.7 (2), 146.0 (3), 142.9 (5), 142.0 (6)
7e (A)	198.0, 196.4, 196.2	81.2	58.3	83.6	108.6	#
7e (B)	199.0, 197.7, 195.5	84.4	58.2	86.9	111.7	#
7g (A)	198.4, 196.5, 195.8	80.8	56.3	83.8	108.4	#
7g (B)	199.0, 197.4, 195.2	84.5	56.5	86.7	111.6	#

$ Isomers A and B differ with respect to the configuration at the anomeric C-atom C-8b (•).

§ May be interchanged.

Not unequivocally determined.

7c molecule is built up from two essentially flat indane moieties and a planar 4-pyrimidinyl moiety. Most interesting part of the molecule is the central spiro-ring system with a lactol-type tetrahydrofuran ring. The tetrahydrofuran ring adopts an envelope conformation in which the least squares-planes through C(25)-C(13)-C(14)-O(24) (r.m.s. deviation from planarity 0.011 Å) subtends an angle of 35° with the plane O(24)-C(2)-C(25). The angle between the l.s. plane C(25)-C(13)-C(14)-O(24) and the second indane moiety, C(12) through C(20), is 65°. The observed bond lengths (cf. Figure 2) are consistent with the chemical structure diagram **7** (Scheme 1 and Table 1): mean bond lengths are C=O = 1.215 Å, C-O(H) = 1.395 Å, C-O(THF ring) = 1.436 Å, C_{al}-C_{al} = 1.545 Å, C_{al}-C_{ar} = 1.483 Å, C_{ar}-C_{ar} = 1.383 Å, and C_{ar}-N_{ar} = 1.329 Å (al = aliphatic, ar = aromatic). The formation of the lactol ring is likely facilitated by a simultaneous formation of an intramolecular hydrogen bond from O(23h) as the donor to the carbonyl oxygen O(10) of the first indane moiety as the acceptor, O(23h)...O(10) = 2.846 Å. This hydrogen bond may compensate the loss in Hückel stabilization when, on lactol-ring formation, C(14) transforms from sp^2- to sp^3-hybridized state. The second hydroxyl group, O(22h)-H(22), donates one hydrogen bond to a

water molecule H_2O(36w) and accepts in turn one hydrogen bond from another symmetry equivalent molecule H_2O(36w). The second hydrogen bond donated by H_2O(36w) - it has a trigonal planar coordination type - is accepted by the terminal pyrimidinyl nitrogen N(29). The nitromethane molecule is stereochemically inactive and fills a gap in the crystal structure. It is well ordered and shows comparatively low thermal displacement parameters, indicating that it contributes distinctly to the stability of the unusual solvate structure of **7c·CH_3NO_2·H_2O**.

Technical data on the structure determination of the quinoxalinyl compound (**7g**) are reported in the experimental section, atomic parameters are presented in Table 3. A view of the molecule is shown in Figure 3. In its main characteristics - i.e. bond lengths, bond angles and conformation - **7g** agrees well with the pyridazinyl compound (**7c**)·CH_3NO_2·H_2O. Equivalent bond lengths of the two compounds differ only by 0.004 Å to 0.013 Å and bond angles by 0.5° to 1.6°. In crystalline state **7g** contains two hydrogen bonds: an intramolecular bond O(23h)→O(10) = 2.908 Å, slightly longer than in **7c·CH_3NO_2·H_2O**, and an intermolecular bond O(22h)→N(30).

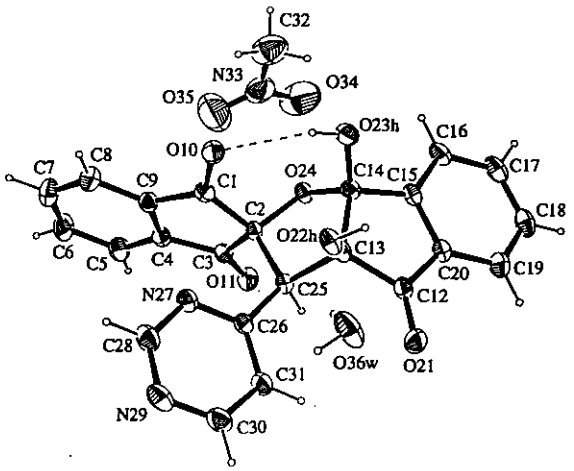
A search in the Cambridge Structural Database[10] did not reveal any analogous compounds. Structurally partly related condensation products of ninhydrin, like ninhydrylurea monohydrate, were reported in refs.[4,11]

EXPERIMENTAL

General

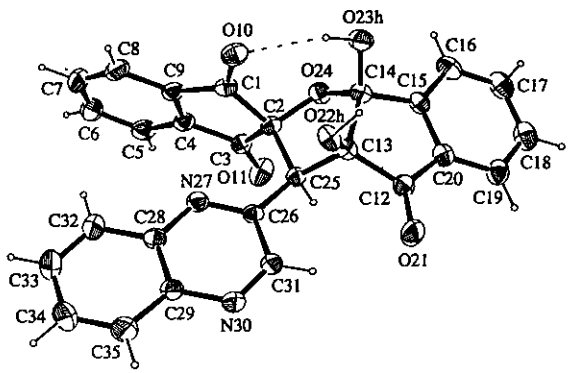
Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were obtained on a Perkin Elmer FTIR 1605 instrument. Mass spectra were recorded on a Varian MAT 311A spectrometer (70 eV). The nmr spectra were obtained from DMSO-d_6 solutions on a Varian Unity*Plus* 300 instrument (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°C. The solvent signal was used as an internal standard which was related to tetramethylsilane with δ 2.49 ppm (^{1}H) and δ 39.5 ppm (^{13}C). Chromatographic separations were carried out using Merck Kieselgel 60 (230-400 mesh) as stationary phase. The yields given below are not optimized.

Figure 2. View of the asymmetric unit of **7c**·CH_3NO_2·H_2O (Ortep plot, 30% ellipsoids, crystallographic numbering scheme).



Selected bond lengths in Å (esd's ~ 0.003 Å): C(1)-C(2)=1.535, C(1)-C(9)=1.476, C(1)-O(10)=1.220, C(2)-C(3)=1.537, C(2)-O(24)=1.430, C(2)-C(25)=1.543, C(3)-C(4)=1.472, C(3)-O(11)=1.211, C(12)-C(13)=1.541, C(12)-C(20)=1.462, C(12)-O(21)=1.214, C(13)-C(14)=1.564, C(13)-O(22h)=1.405, C(13)-C(25)=1.549, C(14)-C(15)=1.504, C(14)-O(23h)=1.384, C(14)-O(24)=1.442, C(25)-C(26)=1.505. Hydrogen bonds (donor→acceptor): O(22h)→O(36w)=2.696, O(23h)→O(10)=2.873, O(36w)→N(29)=2.846, O(36w)→O(22h)=2.864.

Figure 3. View of the asymmetric unit of **7g** (Ortep plot, 30% ellipsoids, crystallographic numbering scheme).



Selected bond lengths in Å (esd's ~ 0.002 Å): C(1)-C(2)=1.548, C(1)-C(9)=1.478, C(1)-O(10)=1.212, C(2)-C(3)=1.543, C(2)-O(24)=1.422, C(2)-C(25)=1.539, C(3)-C(4)=1.471, C(3)-O(11)=1.203, C(12)-C(13)=1.539, C(12)-C(20)=1.463, C(12)-O(21)=1.211, C(13)-C(14)=1.568, C(13)-O(22h)=1.405, C(13)-C(25)=1.543, C(14)-C(15)=1.503, C(14)-O(23h)=1.391, C(14)-O(24)=1.437, C(25)-C(26)=1.508. Hydrogen bonds (donor→acceptor): O(22h)→N(30)=2.834, O(23h)→O(10)=2.908.

Table 2. Atomic coordinates and equivalent isotropic thermal displacement parameters for **7c**·CH_3NO_2·H_2O; H atoms omitted.

	x/a	y/b	z/c	U_{eq} [Å^2]
C(1)	0.4121(2)	0.5587(2)	0.1681(2)	0.033(1)
C(2)	0.3674(2)	0.5194(2)	0.2710(2)	0.029(1)
C(3)	0.4948(2)	0.6236(2)	0.3768(2)	0.032(1)
C(4)	0.6108(2)	0.7008(2)	0.3327(2)	0.033(1)
C(5)	0.7476(3)	0.8017(3)	0.3961(2)	0.046(1)
C(6)	0.8350(3)	0.8619(3)	0.3341(3)	0.055(1)
C(7)	0.7878(3)	0.8251(3)	0.2139(3)	0.056(1)
C(8)	0.6532(3)	0.7245(3)	0.1510(2)	0.045(1)
C(9)	0.5638(2)	0.6622(2)	0.2119(2)	0.034(1)
O(10)	0.3277(2)	0.5247(2)	0.0722(1)	0.043(1)
O(11)	0.4959(2)	0.6362(2)	0.4778(1)	0.044(1)
C(12)	0.0895(2)	0.2103(2)	0.2718(2)	0.034(1)
C(13)	0.1705(2)	0.2943(2)	0.2040(2)	0.030(1)
C(14)	0.1060(2)	0.4186(2)	0.2189(2)	0.031(1)
C(15)	-0.0053(2)	0.3976(2)	0.2912(2)	0.033(1)
C(16)	-0.0933(2)	0.4797(2)	0.3281(2)	0.041(1)
C(17)	-0.1855(3)	0.4416(3)	0.3973(2)	0.047(1)
C(18)	-0.1911(3)	0.3263(3)	0.4296(2)	0.047(1)
C(19)	-0.1041(3)	0.2445(3)	0.3927(2)	0.043(1)
C(20)	-0.0110(2)	0.2808(2)	0.3225(2)	0.034(1)
O(21)	0.1101(2)	0.1047(2)	0.2806(2)	0.053(1)
O(22h)	0.1502(2)	0.2118(2)	0.0862(1)	0.038(1)
O(23h)	0.0388(2)	0.4266(2)	0.1148(1)	0.041(1)
O(24)	0.2302(2)	0.5438(1)	0.2863(1)	0.032(1)
C(25)	0.3390(2)	0.3665(2)	0.2651(2)	0.029(1)
C(26)	0.4395(2)	0.2907(2)	0.2120(2)	0.031(1)
N(27)	0.5213(2)	0.3465(2)	0.1492(2)	0.041(1)
C(28)	0.6108(3)	0.2792(3)	0.1038(2)	0.049(1)
N(29)	0.6268(2)	0.1625(2)	0.1131(2)	0.049(1)
C(30)	0.5439(3)	0.1081(3)	0.1761(3)	0.052(1)
C(31)	0.4497(3)	0.1701(2)	0.2291(2)	0.044(1)
C(32)	0.1575(5)	0.7892(4)	0.1881(4)	0.101(2)
N(33)	0.2509(4)	0.8477(3)	0.3068(3)	0.087(2)
O(34)	0.1871(4)	0.8563(4)	0.3849(3)	0.138(2)
O(35)	0.3821(4)	0.8790(4)	0.3177(4)	0.158(3)
O(36w)	-0.1453(2)	0.0707(2)	0.0226(2)	0.065(1)

Table 3. Atomic coordinates and equivalent isotropic thermal displacement parameters for **7g**; H atoms omitted

	x/a	y/b	z/c	U_{eq} [Å^2]
C(1)	0.5681(2)	0.1354(1)	0.4069(2)	0.0412(5)
C(2)	0.6967(2)	0.2176(1)	0.3802(1)	0.0373(4)
C(3)	0.7228(2)	0.2873(1)	0.5074(1)	0.0416(5)
C(4)	0.6118(2)	0.2520(1)	0.5928(1)	0.0414(5)
C(5)	0.5903(2)	0.2960(2)	0.7139(2)	0.0511(6)
C(6)	0.4703(2)	0.2569(2)	0.7705(2)	0.0621(7)
C(7)	0.3755(2)	0.1754(2)	0.7095(2)	0.0650(7)
C(8)	0.3979(2)	0.1287(2)	0.5905(2)	0.0540(6)
C(9)	0.5185(2)	0.1682(1)	0.5330(2)	0.0422(5)
O(10)	0.5257(1)	0.0515(1)	0.3405(1)	0.0552(4)
O(11)	0.8156(1)	0.3617(1)	0.5274(1)	0.0638(5)
C(12)	0.8248(2)	0.2800(2)	0.0642(1)	0.0440(5)
C(13)	0.7231(2)	0.2172(1)	0.1521(1)	0.0379(4)
C(14)	0.8213(2)	0.1206(1)	0.2248(1)	0.0412(5)
C(15)	0.9699(2)	0.1400(1)	0.1810(2)	0.0422(5)
C(16)	1.0968(2)	0.0789(2)	0.2186(2)	0.0548(6)
C(17)	1.2207(2)	0.1115(2)	0.1629(2)	0.0608(7)
C(18)	1.2210(2)	0.2021(2)	0.0725(2)	0.0604(7)
C(19)	1.0966(2)	0.2634(2)	0.0345(2)	0.0533(6)
C(20)	0.9705(2)	0.2312(1)	0.0906(2)	0.0435(5)
O(21)	0.7854(1)	0.3549(1)	-0.0149(1)	0.0654(5)
O(22h)	0.5977(1)	0.1716(1)	0.0849(1)	0.0456(3)
O(23h)	0.7774(2)	0.0031(1)	0.2002(1)	0.0526(4)
O(24)	0.8214(1)	0.1486(1)	0.3589(1)	0.0440(3)
C(25)	0.6790(2)	0.2990(1)	0.2612(1)	0.0355(4)
C(26)	0.5355(2)	0.3621(1)	0.2379(1)	0.0354(4)
N(27)	0.4455(1)	0.3527(1)	0.3267(1)	0.0399(4)
C(28)	0.3193(2)	0.4159(1)	0.3110(1)	0.0405(5)
C(29)	0.2883(2)	0.4886(1)	0.2023(2)	0.0424(5)
N(30)	0.3840(1)	0.4964(1)	0.1092(1)	0.0457(4)
C(31)	0.5035(2)	0.4340(1)	0.1271(1)	0.0412(5)
C(32)	0.2204(2)	0.4100(2)	0.4051(2)	0.0582(6)
C(33)	0.0962(2)	0.4753(2)	0.3913(2)	0.0670(7)
C(34)	0.0659(2)	0.5467(2)	0.2836(2)	0.0735(8)
C(35)	0.1590(2)	0.5533(2)	0.1901(2)	0.0634(7)

General Procedure for the Reaction of Ninhydrin (**4**) with Methyl(di)azines

To a solution of 10 mmol of the methyl(di)azine in 70 ml of xylene (isomeric mixture) 1.78 g (10 mmol) of ninhydrin (**4**) were added and the resulting mixture was stirred at 100-110°C under an argon atmosphere (an initially formed, colored precipitate of 1,2,3-indantrione dissolved with time). After completion of the reaction (8 - 80 h) the mixture was cooled and the colorless precipitate was filtered off and washed with cold diisopropyl ether.

2-Hydroxy-2-(4-pyridazinylmethyl)-1,3-indandione (**5b**) (Reaction of **4** with 4-Methylpyridazine)

The reaction time was 8 h. Recrystallization from 2-propanol afforded 1.550 g (61%) of almost colorless crystals, mp 220-222°C; ^{1}H-nmr (DMSO-d_6): δ (ppm) 9.05 (dd, $J_{6,5}$ = 5.4 Hz, $J_{6,3}$ = 1.2 Hz, 1H, pyridazine H-6), 8.99 (dd, $J_{3,5}$ = 2.4 Hz, $J_{3,6}$ = 1.2 Hz, 1H, pyridazine H-3), 8.04-7.96 (m, 4H, indane H-4,5,6,7), 7.45 (dd, $J_{5,6}$ = 5.4 Hz, $J_{5,3}$ = 2.4 Hz, 1H, pyridazine H-5), 6.58 (s, 1H, OH), 3.06 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 199.7 (indane C-1,3), 153.5 (pyridazine C-3), 150.5 (pyridazine C-6), 139.1 (indane C-3a,7a), 137.0 (indane C-5,6), 134.9 (pyridazine C-4), 128.2 (pyridazine C-5), 123.5 (indane C-4,7), 78.5 (indane C-2), 36.1 (CH_2); ms: m/z (%) 254 (M^+, 59), 133 (50), 121 (14), 105 (35), 104 (37), 94 (42), 77 (55), 76 (60), 75 (15), 74 (12), 66 (11), 65 (19), 63 (11), 51 (64), 50 (61), 40 (13), 39 (100), 38 (22); ir (KBr): 3420, 3000, 2760 (O-H), 1740, 1700 (C=O) cm^{-1}. *Anal.* Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.17; H, 3.99; N, 10.79.

2-Hydroxy-2-(4-quinolinylmethyl)-1,3-indandione (**5f**) (Reaction of **4** with 4-Methylquinoline)

The reaction time was 45 h. Recrystallization of the raw product from 1,4-dioxane afforded 1.974 g (65%) of colorless crystals, mp 206-209°C; ^{1}H-nmr (DMSO-d_6): δ (ppm) 8.65 (d, $J_{2,3}$ = 4.4 Hz, 1H, quinoline H-2), 7.96 (m, 1H, quinoline H-5), 7.90-7.75 (m, 5H, quinoline H-8 and indane H-4,5,6,7), 7.66 (m, 1H, quinoline H-7), 7.51 (m, 1H, quinoline H-6), 7.21 (d, $J_{3,2}$ = 4.4 Hz, 1H, quinoline H-3), 6.53 (s, 1H, OH), 3.58 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ (ppm) 200.3 (indane C-1,3), 149.3 (quinoline C-2), 147.7 (quinoline C-8a), 140.7 (quinoline C-4), 139.5 (indane C-3a,7a), 136.7 (indane C-5,6), 129.3 (quinoline C-8), 128.9 (quinoline C-7), 127.3 (quinoline C-4a), 126.0 (quinoline C-6), 124.7 (quinoline C-5), 123.7 (quinoline C-3), 123.0 (indane C-4,7), 77.8 (indane C-2), 36.1 (CH_2, ^1J = 131.8 Hz); ms: m/z (%) 304 (M^++1, 13), 303 (M^+, 60), 170 (15), 144 (20), 143 (100), 142 (51), 133 (24), 129 (14), 115 (43), 105

(19), 104 (26), 77 (25), 76 (17), 43 (16); ir (KBr): 1753, 1718 (C=O) cm^{-1}. *Anal.* Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 74.96; H, 4.30; N, 4.51.

Reaction of **4** with 3-Methylpyridazine (Compound **7a**)

The reaction time was 12 h. The raw material was recrystallized twice from ethanol to afford 787 mg of **7a** (38% related to **4**) of a nearly colorless powder, mp 195-197°C; ^{1}H-nmr (DMSO-d_6): mixture of isomers A:B ~ 2.5:1, δ (ppm) 8.94 (m, 1H, pyridazine H-6 of B), 8.90 (m, 1H, pyridazine H-6 of A), 8.24 (m, 1H, pyridazine H-4 of A), 8.13[12] (m, 1H, pyridazine H-4 of B), 8.10[12] (s, 1H, OH of A), 7.71[13] (m, 1H, pyridazine H-5 of B), 7.68[13] (m, 1H, pyridazine H-5 of A), 8.18-7.50 (m, indane-H of A and B), 7.26 (s, 1H, OH of B), 6.93 (s, 1H, OH of A), 5.96 (s, 1H, OH of B), 4.82 (s, 1H, C(sp^3)-H of A), 4.53 (s, 1H, C(sp^3)-H of B); ms: m/z (%) 414 (M^+, 2), 254 (36), 253 (40), 238 (10), 237 (13), 225 (29), 133 (17), 121 (30), 105 (30), 104 (68), 94 (39), 77 (38), 76 (100), 75 (17), 74 (17), 65 (30), 63 (10), 52 (13), 51 (38), 50 (83), 39 (52), 38 (20); ir (KBr): 3432 (OH), 1747, 1714 (C=O) cm^{-1}. *Anal.* Calcd for $C_{23}H_{14}N_2O_6$: C, 66.67; H, 3.41; N, 6.76. Found: C, 66.41; H, 3.58; N, 6.62.

Reaction of **4** with 4-Methylpyrimidine (Compound **7c**)

The reaction time was 20 h. Recrystallization from methanol - ethanol (1:1) afforded 1.38 g (67%) of **7c** as a nearly colorless powder, mp 200-201°C; ^{1}H-nmr (DMSO-d_6): mixture of isomers A:B ~ 2:1, δ (ppm) 8.77 (d, $J_{6,5}$ = 5.1 Hz, 1H, pyrimidine H-6 of B), 8.73 (d, $J_{6,5}$ = 5.1 Hz, 1H, pyrimidine H-6 of A), 8.55 (s, 1H, pyrimidine H-2 of B), 8.42 (s, 1H, pyrimidine H-2 of A), 8.10[12] (s, 1H, OH of A), 8.05[12] (d, $J_{5,6}$ = 5.1 Hz, 1H, pyrimidine H-5 of A), 7.93[12] (d, $J_{5,6}$ = 5.1 Hz, 1H, pyrimidine H-5 of B), 8.15-7.52 (m, indane-H of A and B), 7.32 (s, 1H, OH of B), 6.92 (s, 1H, OH of A), 5.98 (s, 1H, OH of B), 4.72 (s, 1H, C(sp^3)-H of A), 4.40 (s, 1H, C(sp^3)-H of B); ms: m/z (%) 414 (M^+, 2), 254 (46), 253 (100), 239 (12), 238 (71), 237 (52), 226 (11), 225 (70), 121 (32), 105 (24), 104 (37), 94 (23), 93 (19), 77 (19), 76 (37), 50 (13); ir (KBr): 3466 (OH), 1753, 1720 (C=O) cm^{-1}. *Anal.* Calcd for $C_{23}H_{14}N_2O_6 \cdot H_2O$: C, 63.89; H, 3.73; N, 6.48: Found: C, 64.06; H, 3.82; N, 6.24.

Reaction of **4** with 2-Methylpyrazine (Compound **7d**)

The reaction time was 80 h. Flash-chromatography (eluent: ethyl acetate) afforded 604 mg (29%) of **7d** as a nearly colorless powder, mp 214°C; ^{1}H-nmr (DMSO-d_6): mixture of isomers A:B ~ 1.7:1, δ (ppm) 9.20

(s, 1H, pyrazine H-3 of A), 9.04 (s, 1H, pyrazine H-3 of B), 8.40 (d, $J_{5,6}$ = 1.9 Hz, 1H, pyrazine H-5 of B), 8.34 (d, $J_{5,6}$ = 1.8 Hz, 1H, pyrazine H-5 of A), 8.03[13] (d, 1H, pyrazine H-6 of B), 7.98[12] (s, 1H, OH of A), 7.85[12] (d, 1H, pyrazine H-6 of A), 8.10-7.52 (m, indane-H of A and B), 7.15 (s, 1H, OH of B), 6.82 (s, 1H, OH of A), 6.03 (s, 1H, OH of B), 4.81 (s, 1H, C(sp^3)-H of A), 4.43 (s, 1H, C(sp^3)-H of B); ms: m/z (%) 414 (M^+, 1), 254 (71), 253 (100), 239 (12), 238 (78), 237 (65), 236 (10), 226 (19), 225 (93), 207 (25), 197 (14), 181 (19), 149 (13), 121 (33), 105 (42), 104 (54), 94 (32), 93 (32), 77 (25), 76 (41), 50 (13); ir (KBr): 3408 (OH), 1754, 1719 (C=O) cm^{-1}. *Anal.* Calcd for $C_{23}H_{14}N_2O_6$: C, 66.67; H, 3.41; N, 6.76. Found: C, 66.90; H, 3.59; N, 6.62.

Reaction of **4** with 2-Methylquinoline (Compound **7e**)

The reaction time was 8 h. Compound (**7e**) was obtained as a nearly colorless powder (1.77 g, 76%) of mp 204°C; ^{1}H-nmr (DMSO-d_6): mixture of isomers A:B ~ 1.7:1, δ (ppm) 8.34-7.37 (m, quinoline-H and indane-H of A and B, OH of A), 7.03 (s, 1H, OH of B), 6.74 (s, 1H, OH of A), 6.60 (m, 1H, quinoline H-3 of B), 6.47 (m, 1H, quinoline H-3 of A), 5.88 (s, 1H, OH of B), 4.90 (s, 1H, C(sp^3)-H of A), 4.53 (s, 1H, C(sp^3)-H of B); ms: m/z (%) 445 (M^+-H_2O, 2), 303 (28), 302 (44), 287 (67), 286 (100), 274 (62), 230 (52), 228 (21), 170 (65), 143 (69), 142 (47), 129 (28), 128 (47), 115 (60), 114 (22), 106 (22), 105 (80), 104 (72), 101 (23), 97 (20), 91 (40), 89 (22), 83 (23), 77 (80), 76 (86), 75 (29), 74 (32), 73 (21), 71 (26), 69 (28), 63 (26), 62 (22), 57 (51), 55 (42), 51 (56), 50 (72), 44 (86), 43 (48); ir (KBr): 3506 (OH), 1750, 1731, 1704 (C=O) cm^{-1}. *Anal.* Calcd for $C_{28}H_{17}NO_6$: C, 72.57; H, 3.70; N, 3.02. Found: C, 72.28; H, 3.55; N, 2.95.

Reaction of **4** with 2-Methylquinoxaline (Compound **7g**)

The reaction time was 20 h. Recrystallization from 2-propanol afforded 1.532 g (66%) of **7g** as a nearly colorless powder, mp 235-236°C; ^{1}H-nmr (DMSO-d_6): mixture of isomers A:B ~ 2.4:1, δ (ppm) 9.43 (s, 1H, quinoxaline H-3 of A), 9.35 (s, 1H, quinoxaline H-3 of B), 8.20-7.52 (m, quinoxaline-H and indane-H of A and B, OH of A), 6.97 (s, 1H, OH of A), 6.93 (s, 1H, OH of B), 6.85 (m, 1H, quinoxaline-H of B), 6.70 (m, 1H, quinoxaline-H of A), 6.22 (s, 1H, OH of B), 4.79 (s, 1H, C(sp^3)-H of A), 4.70 (s, 1H, C(sp^3)-H of B); ms: m/z (%) 446 (M^+-H_2O, 6), 305 (19), 304 (100), 303 (89), 289 (18), 288 (89), 287 (69), 286 (20), 276 (18), 275 (87), 257 (14), 247 (11), 231 (25), 229 (14), 171 (33), 162 (13), 144 (85), 143 (40), 133 (10), 132 (23), 129 (25), 105 (47), 104 (77), 103 (12), 102 (29), 91 (16), 77 (36), 76 (46),

75 (12), 74 (11), 51 (15), 50 (22), 44 (13), 43 (10); ir (KBr): 3398 (OH), 1749, 1714 (C=O) cm^{-1}. *Anal.* Calcd for $C_{27}H_{16}N_2O_6$: C, 69.83; H, 3.47; N, 6.03. Found: C, 69.91; H, 3.37; N, 6.00.

X-Ray Structure Determination of Compound (**7c**)·CH_3NO_2·H_2O (Nitromethane Water Solvate of **7c**)[14]

Crystals of **7c** suitable for X-ray diffraction could be obtained by recrystallization from unpurified nitromethane affording the stoichiometric nitromethane water solvate **7c**·CH_3NO_2·H_2O: $C_{23}H_{14}N_2O_6$·CH_3NO_2·H_2O = $C_{24}H_{19}N_3O_9$, M_r = 493.42, triclinic, space group *P*-1 (No. 2), a = 9.562(2) Å, b = 10.560(2) Å, c = 12.343(2) Å, α = 107.54(1)°, β = 94.62(1)°, γ = 105.03(1)°, V = 1112.0(4) Å^3, Z = 2, D_c = 1.474 g cm^{-3}, μ = 0.115 mm^{-1}, $F(000)$ = 512, T = 24 °C. A yellow crystal (0.06 x 0.28 x 0.61 mm) was used for data collection (Philips PW1100 diffractometer, Mo $K\alpha$ radiation, λ = 0.71069 Å). 3933 independent reflections were collected (θ-2θ scans, θ_{max} = 25°, correction for *LP*, absorption neglected) and all were used for structure solution by direct methods (program XTAL3.2)[15] and subsequent least-squares refinement on F^2 (program SHELXL93).[16] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms, all located in a difference Fourier synthesis, were inserted in idealized positions and were refined either riding with the C to which they were bonded or as rigid groups $OH/H_2O/CH_3$. Final $R1 = \Sigma\,||F_o|-|F_c||/\Sigma|F_o| = 0.084$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.112$ and S = 1.02 for all data and 332 parameters; $R1$ = 0.045 for the 2591 reflections with $F_o \geq 4\sigma(F_o)$. The final difference Fourier map showed minimum and maximum values of -0.18 and +0.24 e Å^{-3}.

X-Ray Structure Determination of Compound (**7g**)[14]

Compound (**7g**): $C_{27}H_{16}N_2O_6$, M_r = 464.42, *monoclinic*, space group $P2_1$ (No. 4), a = 9.281(1) Å, b = 11.154(2) Å, c = 10.465(2) Å, β = 94.62(1)°, V = 1079.8(3) Å^3, Z = 2, D_c = 1.428 g cm^{-3}, μ = 0.103 mm^{-1}, $F(000)$ = 480, T = 24 °C. A yellow crystal was used for data collection (0.44 x 0.46 x 0.55 mm, Philips PW1100 diffractometer, Mo $K\alpha$ radiation, λ = 0.71069 Å). Of 4240 reflections collected (θ-2θ scans, θ_{max} = 25°, correction for *LP*, absorption neglected) 3807 were independent (Friedel pairs not merged) and all were used for structure solution by direct methods and subsequent least-squares refinement on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined either without constraints (two OH hydrogen atoms) or riding with the C atoms to which they were bonded. Final $R1 = \Sigma\,||F_o|-|F_c||/\Sigma|F_o| = 0.029$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.067$ and S

= 1.05 for all data and 325 parameters; $R1$ = 0.027 for the 3616 reflections with $F_o \geq 4\sigma(F_o)$. Final difference electron densities between -0.12 and +0.14 e Å^{-3}.

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