" ONE-STEP"SYNTHESIS OF AN INDENO-INDOLIZINE NUCLEUS

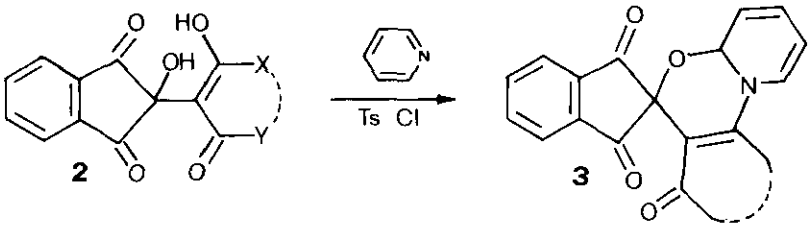
Angelo Carotti* and Giovanni Casini
Dipartimento Farmaco-Chimico dell'Università, Via Amendola 173,BARI ITALY
Enrico Gavuzzo and Fernando Mazza
Istituto di Strutturistica Chimica "G.Giacomello" CNR, Monterotondo
Stazione ROMA, ITALY

Abstract - The reaction of 2-hydroxy-2-phenacyl-1,3-indanedione with tosyl chloride in pyridine directly afforded in high yield the 11-benzoyl-10H-indeno[2,1-b] indolizine-10-one the structure of which has been determined by single crystal X-ray diffraction. A possible pathway of this unexpected novel annulation reaction is discussed.

1,3-indanedione derivatives are an object of continuous studies in view of their multiple pharmacological properties and of the interesting and peculiar reactivity presented by their bicyclic system[1].In this contest we begun a systematic research on the dehydration reaction of several aldol adducts **2** derived from 1,2,3-indanetrione and acyclic or cyclic ß-dicarbonyl compounds [2,3], and on the hydration reaction of the corresponding ethylenic-tetracarbonyl derivatives obtained from **2**[4].The purpose of this study was the preparation of potential biologically active compounds and a better understanding of the structure-reactivity relationship in both elimination and addition reactions. In order to explain a particular reactivity observed in aldol adducts **2** carrying a benzoyl substituent, compound **1** reacted with tosyl chloride in anhydrous pyridine. Most surprisingly a red crystalline product having a molecular formula corresponding to $C_{22}H_{13}NO_2$ was obtained in high yield; it may be derived from **1** through a formal addition of one molecule of pyridine and elimination of two molecules of water.

Actually another similar cyclocondensation reaction had already been observed when treatment of aldol adducts **2** with the same reagent under the same experimental conditions had produced pyrido-oxazine derivatives **3**[5] (Scheme 1).

SCHEME 1



However in the present case evidences of neither analytical nor spectroscopic properties were consistent with a structure like **3**. Careful analysis of spectroscopic data, especially from ^{1}H-NMR (Tab.1) and Mass[6] spectra, provided some clues to the structure elucidation but did not allow any firm conclusion.

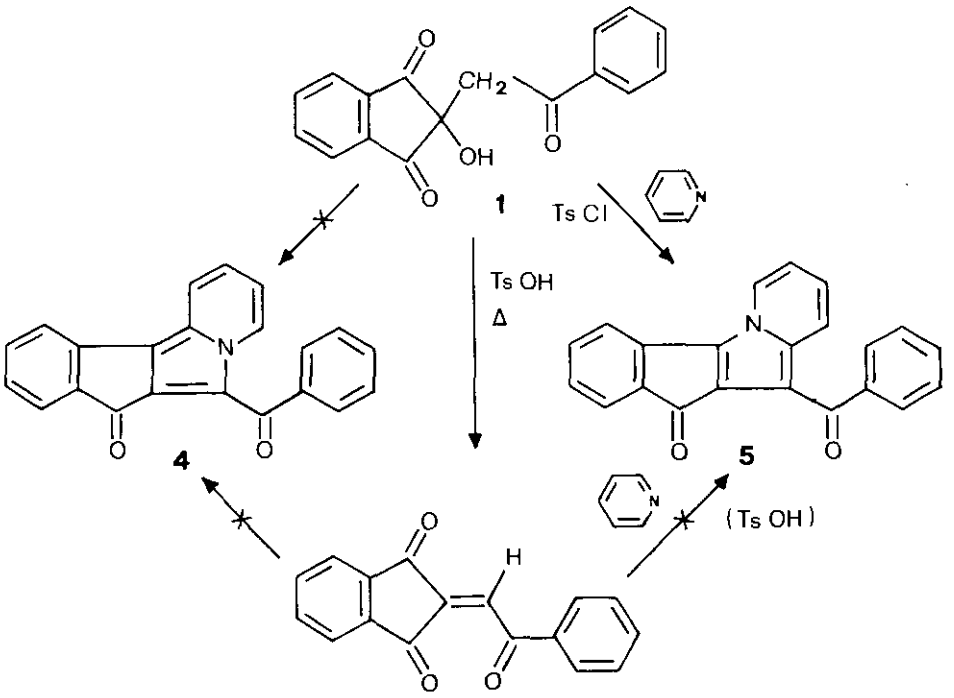
Table 1. 200 MHz ^{1}H-NMR data of compound **5**

Protons[a]	Mt[b]	δ[c], ppm	J H-H	J Hz[c]
1	dt	8.24 (7.28)	1,2 1,3;1,4	9.10 (9.07) 1.2-1.3
4	dt	8.00 (7.70)	4,3 4,1	7.05 (7.05) 1.20 (1.21)
14,18	dt	7.85	14,15 (18,17)	7.05
16	tt	7.59	16,17 or 15 16,14 or 18	7.40 2.70
15,17	td	7.49	15,16 (17,16)	7.40
6(9)	dt	7.34	6,7 6,8	7.15 1.10
8(7)	td	7.30	8,9 8,7 8,6	7.15 7.20 1.10
9(6)	dd	7.14	9,8 9,7	7.15 1.10
2	td	7.08 (6.52)	2,1 2,3 2,4	9.10 6.95 1.10 (1.07)
7(8)	td	7.06	7,6 7,8 7,9	7.15 7.20 1.10
3	td	6.92 (6.29)	3,4 3,2 3,1	7.05 6.95 1.30 (1.30)

a) An alternative possible assignment for the aromatic protons of the indanone moiety is listed in parentheses. b) Mt: Multiplicity. c) For comparison, in parentheses are reported the corresponding values for indolizine[7].

Then the same reaction was repeated in anhydrous d_5-pyridine and a tetradeuterated product was isolated; its spectroscopic properties when compared to those of the corresponding non-deuterated compound, clearly indicated a benzoyl indeno-indolizine derivative. At this point two isomeric structures **4** and **5** (Scheme 2) derivable from the nucleophylic attack of the pyridine at two different sites, could be proposed.

SCHEME 2



6

So, to definetely discriminate between them, an X-ray structure analysis was carried out[8] which provided the final solution and demonstrated unequivocally that the compound formed was **5**, i.e. 11-benzoyl-10H-indeno [2,1-b] -indolizin-10-one. The interesting heterocyclic system present in **5** has already been synthesized by a different route but only as octahydro derivative[9,10].

Crystal structure of 1,2,3,4-tetradeutero-11-benzoyl-10H-indeno[2,1-b]indolizin-10-one.

Crystal data: $C_{22}H_9D_4NO_2$, M=327.5, monoclinic, s.g. Cc, a=4.238(2), b=22.830(14), c=15.839(11) A, ß=90.76(4)° U=1533(2) A^3, F(000)=672, Z=4, Dc=1.42g/cc, λ(Mokα)=0.71069 A, μ(Mokα)=0.1 mm^{-1}.

Red crystals of low scattering power of the title compound showed complete decay in about two days of X-ray exposure. Intensity data were recorded on an automatic Synthex $P2_1$ diffractometer equipped with Mokα radiation up to a 2ϑ value of 50.0° by the ω-scan technique. Out of the 1459 independent reflections recorded 903 with $I > 2.5\sigma(I)$ were considered observed and used in the calculations. The structure was solved by MULTAN [11]. Least-squares refinement, only isotropic because of the limited number of data, converged to a final R of 0.088. The atomic numbering of the title compound together with a view of the molecular conformation found in the crystal is shown in Fig.1; final fractional coordinates of the non-H atoms and bond lengths and angles are listed on Tables 2 and 3 respectively.

FIGURE 1

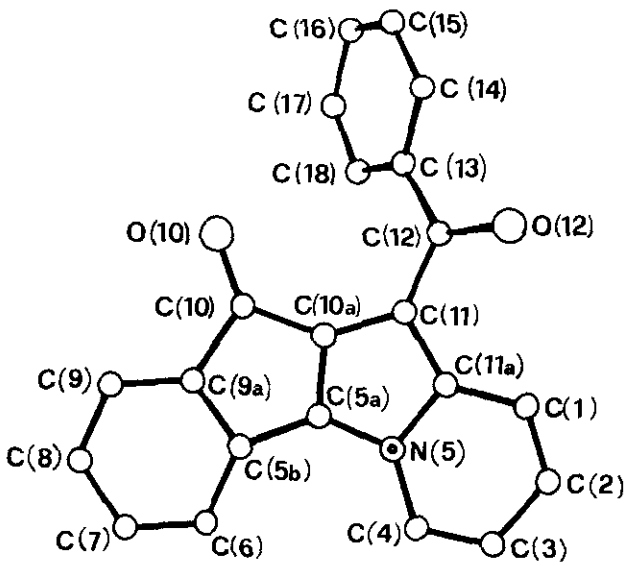


TABLE 2. Final fractional coordinates of the non-H atoms and isotropic temperature factors B ($Å^2$) with e.s.d's. in parentheses for 5

	x/a	y/b	z/c	B
C(1)	1.2326(45)	.1205(5)	-.1003(11)	3.7(2)
C(2)	1.3848(49)	.1438(6)	-.1646(12)	4.9(3)
C(3)	1.3922(50)	.2056(6)	-.1772(13)	4.4(3)
C(4)	1.2364(45)	.2410(5)	-.1247(12)	3.8(2)
N(5)	1.0725(43)	.2164(4)	-.0573(11)	3.5(2)
C(5a)	.9003(42)	.2426(5)	.0051(11)	2.9(2)
C(5b)	.7980(45)	.3019(5)	.0245(11)	3.5(2)
C(6)	.8453(45)	.3578(5)	-.0113(12)	4.0(2)
C(7)	.7155(45)	.4058(5)	.0281(12)	3.8(2)
C(8)	.5375(47)	.3997(6)	.0998(12)	4.3(2)
C(9)	.4802(46)	.3455(5)	.1351(11)	3.7(2)
C(9a)	.6212(43)	.2975(5)	.0966(11)	3.5(2)
C(10)	.5975(44)	.2332(5)	.1211(11)	2.9(2)
O(10)	.4505(39)	.2143(4)	.1802(10)	4.2(2)
C(10a)	.7909(43)	.2012(4)	.0583(11)	2.6(2)
C(11)	.8834(42)	.1449(5)	.0297(10)	2.8(2)
C(11a)	1.0597(44)	.1560(5)	-.0433(11)	3.4(2)
C(12)	.8094(46)	.0868(5)	.0617(12)	4.1(2)
O(12)	.8138(43)	.0445(4)	.0121(11)	5.6(2)
C(13)	.7563(42)	.0755(5)	.1526(11)	3.5(2)
C(14)	.5751(45)	.0272(6)	.1744(12)	4.5(3)
C(15)	.5349(51)	.0144(8)	.2579(14)	6.4(4)
C(16)	.6941(*)	.0450(6)	.3201(*)	5.0(3)
C(17)	.8777(49)	.0933(6)	.2974(12)	5.0(3)
C(18)	.9019(43)	.1089(5)	.2143(11)	3.8(2)

(*) These coordinates were held fixed during the refinement.

TABLE 3. Bond lengths (Å) and angles (°) with e.s.d'.s in parentheses for **5**.

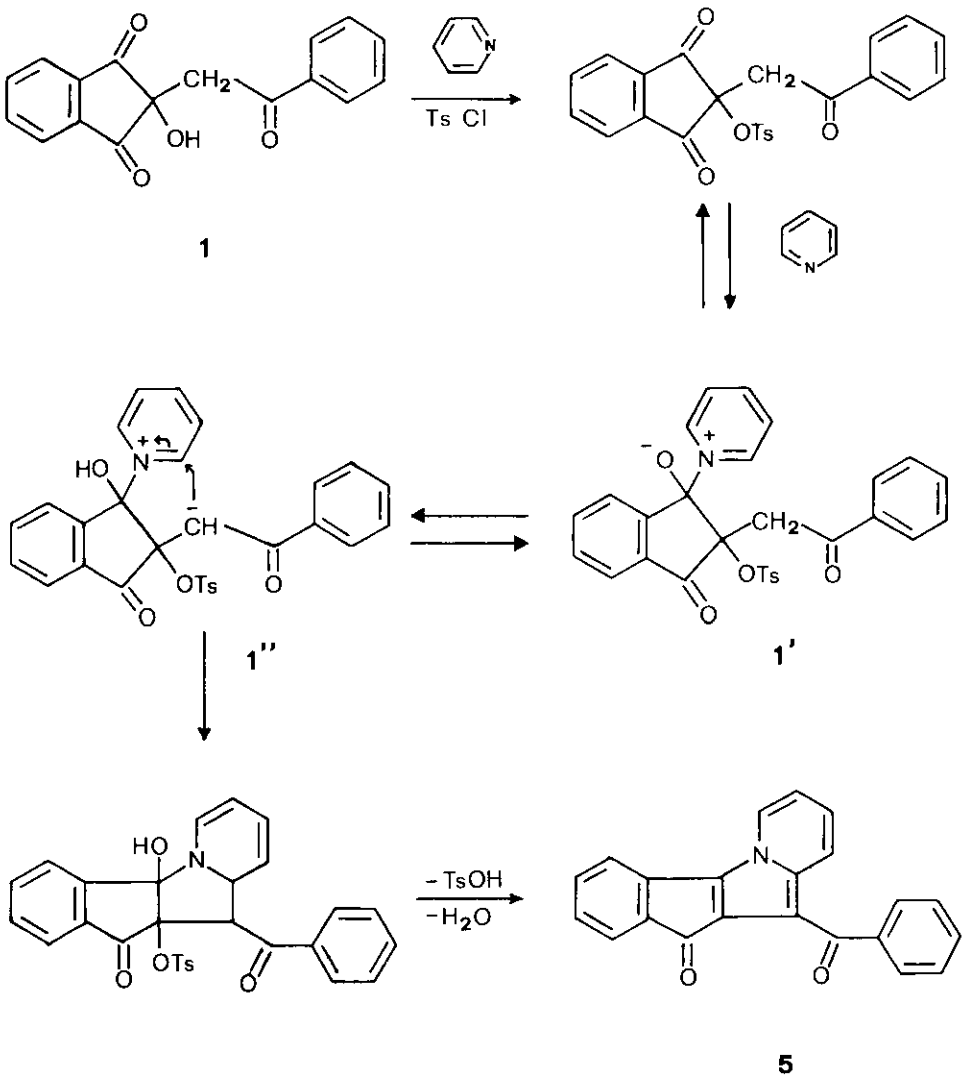
C(1)-C(2)	1.32(3)	C(9a)-C(10)	1.52(2)
C(1)-C(11a)	1.42(2)	C(10)-C(10a)	1.49(2)
C(2)-C(3)	1.43(2)	C(10)-O(10)	1.21(2)
C(3)-C(4)	1.34(2)	C(10a)-C(11)	1.42(2)
C(4)-N(5)	1.40(2)	C(11)-C(11a)	1.41(2)
N(5)-C(5a)	1.37(2)	C(11)-C(12)	1.46(2)
N(5)-C(11a)	1.40(2)	C(12)-O(12)	1.25(2)
C(5a)-C(5b)	1.46(2)	C(12)-C(13)	1.48(3)
C(5a)-C(10a)	1.35(2)	C(13)-C(14)	1.39(2)
C(5b)-C(6)	1.41(2)	C(13)-C(18)	1.38(2)
C(5b)-C(9a)	1.38(3)	C(14)-C(15)	1.37(3)
C(6)-C(7)	1.38(2)	C(15)-C(16)	1.38(2)
C(7)-C(8)	1.38(3)	C(16)-C(17)	1.40(2)
C(8)-C(9)	1.38(2)	C(17)-C(18)	1.37(3)
C(9)-C(9a)	1.39(2)		

C(2)-C(1)-C(11a)	121(1)	O(10)-C(10)-C(10a)	129(1)
C(1)-C(2)-C(3)	121(2)	C(10)-C(10a)-C(5a)	106(1)
C(2)-C(3)-C(4)	120(2)	C(10)-C(10a)-C(11)	145(1)
C(3)-C(4)-N(5)	119(1)	C(5a)-C(10a)-C(11)	110(1)
C(4)-N(5)-C(11a)	122(1)	C(10a)-C(11)-C(11a)	105(1)
C(4)-N(5)-C(5a)	130(1)	C(10a)-C(11)-C(12)	131(2)
C(5a)-N(5)-C(11a)	107(1)	C(11a)-C(11)-C(12)	125(1)
N(5)-C(5a)-C(5b)	136(1)	C(1)-C(11a)-N(5)	116(1)
N(5)-C(5a)-C(10a)	110(1)	C(1)-C(11a)-C(11)	135(1)
C(5b)-C(5a)-C(10a)	114(1)	N(5)-C(11a)-C(11)	109(1)
C(5a)-C(5b)-C(6)	135(2)	C(11)-C(12)-O(12)	119(2)
C(5a)-C(5b)-C(9a)	106(1)	C(11)-C(12)-C(13)	122(1)
C(6)-C(5b)-C(9a)	119(1)	O(12)-C(12)-C(13)	119(1)
C(5b)-C(6)-C(7)	118(2)	C(12)-C(13)-C(14)	118(1)
C(6)-C(7)-C(8)	121(1)	C(12)-C(13)-C(18)	121(1)
C(7)-C(8)-C(9)	122(1)	C(14)-C(13)-C(18)	120(2)
C(8)-C(9)-C(9a)	117(2)	C(13)-C(14)-C(15)	119(2)
C(9)-C(9a)-C(5b)	123(1)	C(14)-C(15)-C(16)	121(2)
C(9)-C(9a)-C(10)	128(2)	C(15)-C(16)-C(17)	119(1)
C(5b)-C(9a)-C(10)	109(1)	C(16)-C(17)-C(18)	120(1)
C(9a)-C(10)-O(10)	125(1)	C(17)-C(18)-C(13)	120(1)
C(9a)-C(10)-C(10a)	105(1)		

The aromatic character of the moiety formed by the four fused rings is deducible from the bond lengths and from the planarity of this system. The largest displacement from the least-squares plane of the four rings is that of C(10a) with a value of 0.04 Å. The benzoylic carbonyl group is out of the plane of both the phenyl and indolizine nuclei. The dihedral angles that the mean plane of the atoms C(11),C(12),O(12) and C(13) makes with the mean planes of the indolizine and of the phenyl ring are 29° and 31° respectively. The dihedral angle between the mean planes of the phenyl and indolizine nuclei is 56°.The conformation of the benzoyl substituent can be described by the following torsion angles computed according to the convention of Klyne and Prelog [12]: C(10a)-C(11)-C(12)--C(13)=-32(3)°and C(11)-C(12)-C(13)-C(18)=-30(3)°.The structural features of the benzoyl-indolizine moiety in **5** are in good agreement with those found for the same moiety present in the more complex structure 1.1-Bis- 5-methyl-2-phenyl-1-benzoyl-indolizinyl (3)-ethylene[13],but are quite different from those obtained from the 1-(2-pyridyl)-3-benzoyl-6-bromo-indolizine[14], in which particularly the benzoylic carbonyl group lies on the same plane of the indolizine nucleus.The crystallographic structure of **5** depicted in Fig.1 is also fully consistent with the ^{1}H-NMR data analysis reported in Table 1. In addition, the conformation with the carbonyl group oriented towards the C-1 proton must be maintained also in the chloroformic solution since a strong deshielding effect has been observed on that proton, which is shifted downfield of about 1ppm compared to the corresponding proton of the indolizine. A similar effect, leading to the same conclusion about the preferred conformation in solution, has been already observed in indolizine derivatives carrying benzoyl (or similar) substituents in 1 or 3 position [15,16].

Finally with the aim of delineating a possible formation route to **5**, we synthesized the 2-phenacylidene-1,3-indandione **6**[17], which remained unchanged upon treatment either with pyridine alone or with pyridine and p-toluensolfonic acid (Scheme 2), that is to say, in the same experimental conditions in which compound **5** was formed. These results demonstrated that **6** is not an intermediate in the formation of **5** and therefore a probable reaction pathway can be formulated as shown in Scheme 3; after the initial tosylation of the alcoholic hydroxyl, a nucleophylic attack by pyridine to one indanedione carbonyl group takes place and then an intramolecular proton transfer from the phenacyl group to the alkoxide anion yields the betaine **1"**. Analogously to some intramolecular 1,5-cycloaddition reactions of intermediate ylides from pyridine and acyl(aryl)-substituted allyl halides leading to indolizine derivatives [18,19], betaine **1"** can easily cyclize to form a tetracyclic system which by the loss of p-toluensolfonic acid and water molecules, produced the more conjugated and stable final compound **5**.

SCHEME 3



An interesting aspect of the pathway in scheme 3 is the nucleophylic attack of the pyridine to the carbonyl leading to the betaines **1'** and then to **1"**. These should be, most likely the rate limiting steps since all the following transformations should be strongly thermodynamically favoured. At any rate, we never observed a similar nucleophylic attack in the reaction of acyclic or cyclic aldol adducts **2** with electrophilic reagents like trifluoroacetic anhydride and tosyl chloride in the presence of pyridine. Depending on the nature of the X and Y substituents, on the position of the keto--enolic equilibrium of **2** and sometimes on the work-up procedure, products resulting either from a dehydration reaction[2] or from pyridine displacement of the tosyloxy group[3] deriving from the esterification of the alcoholic or enolic hydroxyl, could be formed.

Of course, the different nature of aldol adduct **1**, which unlikely compounds **2** possesses two acidic methylene protons whose elimination can afford a full aromatic structure, may be responsible of this amazing different reactivity.

We are now working to explore scope and limitations of this new cyclocondensation reaction, aiming to the "one-step" synthesis of new heterocyclic ring system of chemical and pharmacological importance.Preliminary results have shown that the reaction can be successfully applied to other similar starting ketones and that different aromatic bases can be used instead of the pyridine.

EXPERIMENTAL

Melting points were determined by the capillary method on Electrothermal (Mark II) apparatus and are uncorrected. Elemental analyses were made by Mr. G. Dipinto using a Hewlett-Packard 185 C,H,N autoanalyser. The IR spectra were recorded as KBr pellets on a Perkin-Elmer spectrophotometer (Mod. 283); only the most significant absorption bands were reported. UV-Vis spectra were recorded on a Cary 219 spectrophotometer. ^{1}H-NMR spectra were taken on a Varian EM-390 or XL-200 spectrometers using TMS as internal standard; chemical shifts were expressed in δ (ppm) and the coupling constants J in Hz. Exchange with D_2O was used to identify hydroxyl protons. Mass spectra were carried out on Kratos MS 80 spectrometer.

Preparation of 2-hydroxy-2-phenacyl-1,3-indanedione (**1**)

A solution of ninhydrin (5.34 g, 30 mmol) and acetophenone (3.50 ml, 30 mmol) in glacial acetic acid (70 ml) was kept under reflux for 4 h. The solvent was evaporated *in vacuo* and the residue crystallized upon addition of a small volume of ethyl ether to give 6.50 g of **1** (77% yield), mp 107-108 °C, from chloroform-hexane. IR ν_{max}:3440,1740,1710,1680 cm^{-1}. ^{1}H-NMR($CDCl_3$):3.96(s,2H,CH_2),4.20(s,1H, OH),7.3-7.6(m,3H, m- and p-benzoyl),7.7-8.2(m,6H, 4H indan.+2H o-benzoyl). *Anal.* Calcd. for $C_{17}H_{12}O_4$:C,72.85; H,4.32. Found: C,72.80, H,3.98.

Preparation of 2-phenacylidene-1,3-indanedione (**6**)[17]

A solution of **1** (1.40g, 5 mmol) and p-toluensolfonic acid (200 mg) in anhydrous benzene (15-20 ml) was kept under reflux for 4 h using a Dean-Stark apparatus to remove the water produced during the reaction. After cooling the p-toluensolfonic acid was filtered off and the solution was first decoloured with silica gel and then saturated with n-hexane until the precipitation occurred. The title compound (0.79g, 60% yield) were obtained. Mp 129-132 °C dec. (from benzene-n-hexane). UV-Vis (Dioxane) λ_{max} (log ε):249(4.52),315(3.55) nm. IR ν_{max}:1735,1700,1660 cm^{-1}.^{1}H-NMR($CDCl_3$):7.2-7.6(m,3H,m- and p-benzoyl),7.66(s,1H,=CHCO),7.7-8.2(m,6H,4H indan.+2H o-benzoyl). Anal. Calcd. for $C_{17}H_{10}O_3$: C,77.85; H,3.84. Found: C,78.02; H,3.90.

Preparation of 11-benzoyl-10H-indeno[2,1-b]indolizin-10-one (**5**)

Tosyl chloride (0.40g, 2.1 mmol) was added portionwise to a solution of **1** (0.56g, 2 mmol) in anhydrous pyridine (3ml). The reaction mixture was kept under stirring at room temperature overnight and then poured on ice. The red product so formed (0.58g, 90% yield) was collected and crystallized from acetone. Mp 226-229 °C. UV-Vis(CH_3CN), λ_{max} (log ε):261(4.80),320(4.25),360(4.03),377(4.05), 503(3.38) nm. IR ν_{max}:1710,1620,1600,1575,1500,875,745,720,690 cm^{-1}.MS m/z (relative intensity)[6]: 323(100,M^+),294(8),265(10),246(75),218(6),190(46),163(7),105(5),51(6).^{1}H-NMR spectrum is reported in Table 1.Anal. Calcd. for $C_{22}H_{13}NO_2$: C,81.72; H,4.05; N,4.33. Found: C,81.55; H,3.89; N,4.50.

The above reaction was carried out in d_5-pyridine as solvent and the 1,2,3,4-tetradeutero derivative of **5** was obtained using deuterated solvents in the work-up and crystallization procedures; its analytical and spectroscopic properties were as expected.

ACKNOWLEDGEMENT

We are grateful to Mr. Vincenzo Carta for helpful technical assistance.

REFERENCES

1) For an excellent review on the subject see: "Pharmacochemistry of 1,3-Indanediones", Pharmacochemistry Library vol.3, eds.by W.Th.Nauta and R.F.Rekker, Elsevier, Amsterdam, 1981.
2) A.Carotti,F.Campagna,G.Casini,M.Ferappi and D.Giardinà,Gazz.Chim.Ital., 1979, **109** , 329.
3) F.Campagna,A.Carotti,G.Casini and M.Ferappi, Gazz.Chim.Ital.,1983, **113**, 507.
4) F.Campagna,A.Carotti,G.Casini,M.Ferappi and S.Ottolino, Chim.Ind.(It.), 1983, **65**, 122.
5) A.Carotti,G.Casini,M.Ferappi and G.M.Cingolani, J.Het.Chem., 1980, **17**, 1577.
6) Only the most intense peaks are listed in the Experimental. Peaks of lower intensity resulting from loss of CO molecules from the molecular ion are present at 267 and 295 m/z.

7) P.Crews, R.R.Kintner and H.C.Padgett, J.Org.Chem., 1973, **38**, 4391.

8) The crystals chosen for the crystallographic analysis were taken from the tetradeuterated compound.

9) J.Sam, J.D.England and D.W.Alwani, J.Med.Chem., 1964, **7**, 732.

10) J.Sam, D.W.Alwani and K.A.Parajithan, J.Het.Chem., 1966, **2**, 366.

11) P.Main, S.J.Fiske, S.E.Hull, L.Lessinger, G.Germain, J.P.Declercq and M.M.Woolfson, 1980. MULTAN 80: A system of ccmputer Programs for the automatic solution of Crystal Structure from X-ray Diffraction Data. Univs. of York, England, and Louvain, Belgium.

12) W.Klyne and V.Prelog, Experentia, 1960, **16**, 521.

13) E.Oeser, Chem.Ber., 1972, **105**, 2351.

14) L.A.Aslanov, V.M.Ionov, I.S.Akhired Ferog, V.A.Tafeenko, S.M.Vinogradova, A.N.Kost and P.B. Terent'ev, Zh Strukt.Khim., 1976, **17**, 746 (Chem.Abs.,1977, **86**, 10952).

15) W.Flitsch and E.Gertsmann, Chem.Ber., 1972, **105**, 2344.

16) J.Mirek and K.Bogdanowicz-Szwed, Zasz.Nauk.Uniw.Jagiellon.Pr.Chem., 1973, **18**, 179(Chem.Abs., 1974,**80**, 2723).

17) This compound seems to have been reported in a study of antivitamin-K activity of some un saturated derivatives of 1,3-indanedione by L.V.Moiseeva, V.P.Krivstov and L.I.Trukhacheva, Elektronika i Khimiya V.kardiol, 1976, 108 (Chem.Abs., 1977, **87**, 134776n), but since no data on its preparation and physicochemical properties are easily available, they are provided in the experimental section.

18) Y.Tamura,N.Tsujimoto,Y.Sumida and M.Ikeda, Tetrahedron, 1972, **28**, 21.

19) E.Pohjala, Tetrahedron Letters, 1972, 2585.

Received, 25th February, 1985