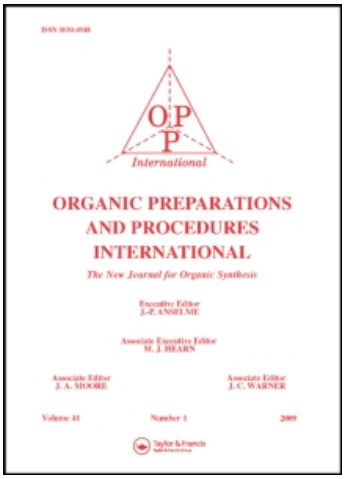

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NEW SPIROPYRAN-4-YLINDOLIDINE DERIVATIVES FROM THE REACTION OF 2-OXO-3-CYANOMETHYLIDENE-2,3-DIHYDROINDOLES WITH CYCLOHEXANEDIONES AND PHENOLS

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NEW SPIROPYRAN-4-YLINDOLIDINE DERIVATIVES FROM THE REACTION OF 2-OXO-3-CYANOMETHYLIDENE-2,3-DIHYDROINDOLES WITH CYCLOHEXANEDIONES AND PHENOLS

Submitted by (10/22/97)

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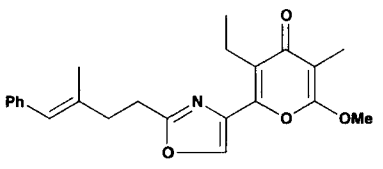
The activity of phenoxan (**1**) and 6-aryl-4-hydroxy-3-methyl-2H-mercapto-2-pyranone (**2**) as anti HIV agent has stimulated recent interest in chemistry of 4-H-pyrans.[1,2] As indolenine **3** has also been reported to possess antibacterial and anti-inflammatory activity,[3-6] the synthesis of compounds having both indolidenene and 4-H-pyran rings seemed of value.



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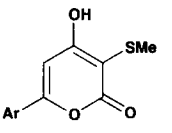

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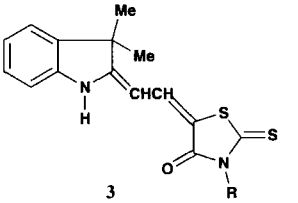

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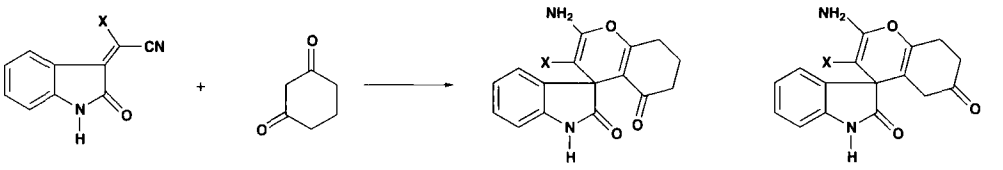
The synthesis of 2-amino-3-substituted-4H-pyrans *via* addition of active methylene ketones, naphthols and phenols to ylidene malononitriles in ethanolic piperidine has been extensively utilized in the literature.[7-9] Attempted addition of **4a,b** to 1,3-cyclohexanedione (**5**) under similar conditions led to self-condensation of the dione.[8] On the other hand, treatment of **4a,b** with **5** in refluxing acetic

acid and in the presence of sodium acetate afforded 1:1 adducts for which the 2-aminospyropyranylidolidinone structure **6** was established based on analytical and spectral data (IR, ^{1}H NMR and ^{13}C NMR). Thus, the IR spectra for compounds **6a,b** showed an NH absorption. Their ^{1}H NMR spectra exhibited a broad signal at δ 10.26 for NH. The ^{13}C NMR spectrum of the product of the reaction of **4a** and **5** revealed signals for a sp^3 spiropyran carbon at δ 52.01 which can be rationalised only in terms of structure **6a**. Similarly, compounds **4a,b** reacted with 1,4-cyclohexanedione in refluxing acetic acid and in the presence of sodium acetate to yield the spiropyrans **7a, b**.



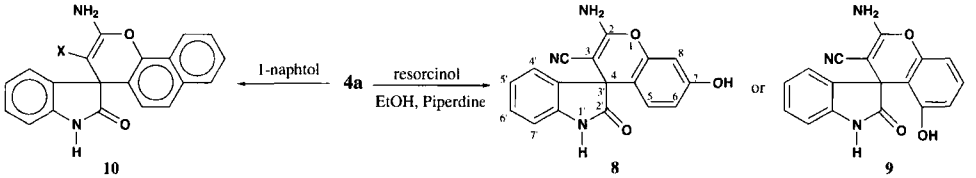
4 5 a) X = CN b) X = CO_2Et 6 7

Treatment of **4a** with resorcinol gave a product which was assigned structure **8** or **9** based on ^{13}C NMR spectra that revealed a sp^3 carbon at 51.52 ppm. Structure **8** is preferred over **9** based on ^{1}H NMR which showed a doublet with J = 9 Hz for both H-5 and H-6 in the spiropyran moiety of the molecule. If the reaction product was **9**, a different coupling value for such proton should have been observed as H-6 would then be part of an ABC system. Compound **4a,b** reacted with 1-naphthol to yield **10a,b**. The ^{13}C NMR of **10a** revealed a signal at δ 51.38 ppm for sp^3 carbon. In addition,^{1}H NMR spectrum of **10b** revealed signals for the ester group.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra (KBr) were recorded on a Shimadzu IR-740 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 80 Hz spectrometer with DMSO-d_6 as solvent and $SiMe_4$ as an internal standard; chemical shifts are reported in δ units. Microanalyses were performed with the general facility apparatus LECO CHNS-932 of Kuwait University. Compounds **4a,b** were prepared following literature procedure.[10]

Reaction of 2-Oxo-2,3-dihydroindole Derivatives 4a,b with 1,3- and 1,4-Cyclohexanediones. General Procedure.- A suspension of **4a,b** (0.01 mol) in acetic acid (100mL) was treated with 1,3- or 1,4-cyclohexadione (0.01 mol) and sodium acetate (0.01 mol). The reaction mixture was refluxed for 1 h then poured into water. The solid, so formed, was then collected and crystallised from an appropriate solvent.



10 a) X = CN b) X = CO_2Et 1-naphtol 4a resorcinol EtOH, Piperdine 8 or 9

TABLE 1. Spectral Data for Compounds **6a,b**, **7a,b**, **8**, and **10a,b** (IR, ^{1}H NMR and ^{13}C NMR)

Cmpd No.	IR (cm^{-1})	^{1}H NMR (δ_H)	^{13}C NMR (δ_C)
6a	3335,3140(NH and NH_2), 2185(CN), 1705(ring CO), 1648 (amide CO).	1.90-1.98 (2H,m, H-7), 2.185 (2H, t, J = 6 Hz, H-8), 2.64 (2H, t, J = 6 Hz, H-6), 6.72-7.15 (6H m, arom-H and NH_2), 10.26 (1H, brs, NH).	194.74 (ring CO), 165.8 (amide CO), 158.82 (C-2), 142.29 (C-8a), 134.6, 130.0, 128.13, 126.0, 123.17, 121.63 (arom. carbons), 119.0 (C-4a), 113.5 (CN), 109.24(C-3), 52.01 (C-4), 36.6 (C-6), 26.8 (C-8), 19.8 (C-7).
6b	3320,3300,3150 (NH and NH_2), 1704 (ester CO), 1695 (ring CO) and 1610 (amide CO).	1.15 (3H, t, J = 6 Hz, CH_3) 1.90-2.10 (2H, m, H-7), 2.30 (2H, t, J = 6 Hz, H-8), 2.80 (2H, t, J = 6 Hz, H-6) 3.90 (q, 2H, J = 6 Hz, -OCH_2), 7.00-7.30 (6H, m, arom-H and NH_2), 10.5 (1H,br, NH).	
7a	3315,3155 (NH and NH_2), 2165 (CN), 1701(ring CO), 1633 (amide CO).	1.60 (2H, t, J = 6 Hz, H-8), 2.41 (2H, t, J = 6 Hz, H-7), 2.65 (2H, s, H-5) 6.81-7.35 (6H, m, arom-H and NH_2), 10.4 (1H, brs, NH).	193.24 (ring CO), 177.59 (amide CO), 160.73 (C-2), 141.93 (C-8a), 133.83, 129.35, 124.67, 122.26, 118.26, 117.37 (arom. carbons), 116.00 (C-4a), 107.99 (CN), 102.58 (C-3), 54.85 (C-4), 33.37 (C-6), 31.07 (C-8), 26.21 (C-7).
7b	3245 (br, NH and NH_2), 1713-1690 (br, ester CO and ring CO), 1610 (amide CO)	1.15 (3H t, J = 6 Hz, CH_3), 2.18 (2H, t, J = 6 Hz, H-8), 2.60 (2H, t, J = 6 Hz, H-7), 2.72 (2H, s, H-5), 3.63 (2H, q, J = 6 Hz, -OCH_2), 6.97-7.07 (6H, m, arom-H and NH_2), 10.4 (1H, brs, NH).	
8[a]	3410-3185 (brs, OH, NH and NH_2), 2175 (CN), 1670 (amide CO).	6.30 (1H, d, J = 9 Hz, H-6), 6.47 (2H,br , NH_2), 6.91 (1H, d, *J* = 9 Hz, H-7`), 6.99 (1H, s, H-8) 7.03-7.39 (4H, m, H-5, H-4`, H-5` and H-6`), 9.92 (1H, br, OH), 10.65 (1H, br, NH).	179.19 (ring CO), 161.71 (C-7), 158.82 (C-2), 149.74 (C-8a), 142.19, 140.21, 134.81, 128.83, 127.40, 124.78, 122.54, 118.50, 112.95, 111.39, (arom. carbons), 109.92 (CN), 102.92 (C-3), 51.82 (C-4).
10a	3450,3275,3150 (NH and NH_2), 2185 (CN), 1690 (amide CO).	6.53-8.37 (12H, m, arom-H and NH_2), 10.59 (1H, br, NH).	179.23 (ring CO), 161.53(C-2), 142.36 (C-10a), 135.11, 133.54, 129.68, 128.11, 127.76, 127.47, 124.23, 121.23, 118.94 (arom.carbons), 115.32 (CN), 110.47 (C-3), 51.38 (C-4).
10b	3370, 3155 (NH and NH_2), 1703 (ester CO), 1670 (amide CO).	1.90 (3H, t, J = 6 Hz , CH_3), 4.15 (2H, q, J = 6 Hz, -OCH_2), 6.80-7.69 (12H, m, arom-H and 2H, NH_2), 10.70 (1H, br,NH).	

a) ^{1}H NMR was recorded on a Shimadzu 250 Hz NMR spectrometer.

TABLE 2 Yields, mps, Color and Elemental Analysis for Compounds **6a,b**, **7a,b**, **8** and **10a,b**

Cmpd No.	yield (%)	mp. (°C)	Color	Elemental Analysis (Found) C	H	N
6a[a]	85	304-305	white	66.44 (66.21)	4.26 (4.52)	13.68 (13.53)
6b[b]	65	>320	brown	64.40 (64.10)	5.11 (4.88)	7.90 (8.11)
7a[c]	60	>320	white	66.44 (66.22)	4.26 (4.11)	13.68 (13.42)
7b[b]	75	274-275	brown	64.40 (64.39)	5.11 (4.88)	7.90 (8.11)
8[b]	70	273-274	yellow	66.88 (66.61)	3.60 (3.81)	13.76 (13.53)
10a[d]	85	317-318	white	74.32 (74.10)	3.86 (4.07)	12.38 (12.22)
10b[b]	65	262-263	white	71.49 (71.60)	4.70 (4.88)	7.25 (6.90)

Solvents for recrystallization: a) acetic acid; b) ethanol; c) benzene; P.E.3:1; d) dioxane

Reaction of 2-Oxo-2,3-dihydroindole Derivatives 4a,b with Resorcinol and Naphthol. General Procedure.- Equimolar amounts of **4a,b** (0.01 mol) and resorcinol or α-naphthol (0.01 mol) in ethanol (50 mL) were treated with a few drops of piperidine. The reaction mixture was refluxed for 1 hour. The solid product was collected and crystallized from the proper solvent.

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A FACILE SYNTHESIS OF 5-BENZOYLCYTOSINE DERIVATIVES

Submitted by R. B. Toche[†], M. N. Jachak[†], T. S. Dalvi[†], R. W. Sabnis[††*],
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Fluorophoric heterocycles such as pyrimidine are exceedingly important in nucleic acid chemistry.[1] Pyrimidines in particular cytosine derivatives, are of special interest because of their potential use as therapeutic agents. Cytosines exhibit promising antiviral,[2] antitumour[3] and antiAIDS[4] activities. We recently reported the synthesis of novel heterocyclic compounds,[5-8] and also described new synthetic routes towards pyrimidines[9] and pyrazoles.[10] Previous papers have demonstrated the activity of fused pyrimidines as potential antineoplastic agents.[11,12] The results of these studies have encouraged us to develop new synthetic routes towards the pyrimidine nucleus. This communication reports a facile and novel synthesis of hitherto unknown 5-benzoylcytosine derivatives (**4**).

3-Dimethylamino-2-benzoylpropenenitrile (**2**), was obtained by condensation of benzoylacetonitrile (**1**) with dimethylformamide dimethyl acetal in 70% yield. Reactions of compound (**2**) with N-substituted ureas or thioureas in acidic medium yielded ureidopropenenitriles (**3a-l**). Cyclization of (**3a-l**) with sodium methoxide in methanol gave 3-substituted-5-benzoylcytosine derivatives (**4a-l**) in 50-65% yield. Compounds (**3a-l**) can also be synthesized in 85-87% yield by stirring benzoylacetonitrile (**1**), the N-substituted urea or thiourea and triethylorthoformate at 60-90°. The alternate procedure is better because it generated a higher product yield.