Reaction of Indol-3(2*H*)-one Derivatives With Some Active Methylene Compounds

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The reaction of substituted (*Z*)- and (*E*)-2-arylmethylideneindolin-3(2*H*)-ones with malononitrile gave the Micheal addition products which could be cyclised to the corresponding pyrano[3,2-*b*]indole. Larger molecules such as cyanoacetic acid and ethyl cyanoacetate failed to react.

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During our studies on the synthesis of various indole-3-alkylamine derivatives we decided to investigate indol-3(2*H*)-ones as potential starting materials. These are readily available (1) and routes have already been reported for the synthesis of the corresponding 2-oxo-3-indolylalkylamines (2).

Attempts to condense various active methylene compounds such as malononitrile, cyanoacetic acid and ethyl cyanoacetate with indol-3(2*H*)-ones proved more difficult than expected and gave a variety of products under different conditions. To facilitate condensation at the carbonyl group of indol-3(2*H*)-ones (**1**), which tend to exist mainly in the isomeric enol form (3), derivatives of type **2** were prepared by condensation with the appropriate aldehyde. These 2-arylmethylideneindol-3(2*H*)-ones (**2a-e**) were prepared (4) by condensation under basic conditions in an inert atmosphere at either reflux temperatures (Method A) or at 0° (Method B). Method A gave the (*Z*)-isomer (trans phenyl ring/carbonyl group) for **2d** and **2e** and the (*E*)-isomer for **2a** and **2b**. A mixture of (*Z*)/(*E*)-**2a** and **2b** was obtained by Method B whereas **2c** was isolated only as a (*Z*)/(*E*)-mixture by both methods. (*Z*)- and (*E*)-**2a** and **2b** were separated by preparative chromatography and (*Z*)-**2c** isolated by recrystallisation of the mixed isomers from acetone.

The spectroscopic properties, melting points and analytical data for (*E*)-**2a**, (*Z*)-**2a**, (*E*)-**2b**, (*Z*)-**2b** and (*Z*)-**2d** agreed with literature values (4), the properties for (*Z*)-**2c** and (*Z*)-**2e** are reported in the experimental.

When compounds of type **2** were condensed with active methylene compounds such as malononitrile in the presence of a basic catalyst in ethanol, aqueous ethanol or dimethyl sulphoxide failed to produce the expected Knoevenagel condensation products. Spectroscopic evidence (Table I) showed loss of the π-π^* bond in the uv, a hydroxyl absorption in the ir, two single proton signals for the C_6H_5CH and $CH(CN)_2$ protons in the pmr spectra, and a hydroxyl proton which disappeared on deuteration, suggested that the compounds were the Michael addition products **3a-e**.

These were formed in excellent yield from either the (*Z*)-or (*E*)-isomers of **2**, on a large scale the reaction was carried out with mixed (*Z*)- and (*E*)-isomers.

Acetylation of the hydroxyl group of the dinitriles **3a-e** was readily achieved either by refluxing with acetic anhydride or by stirring at room temperature with acetic anhydride and triethylamine. Both methods converted

Scheme I

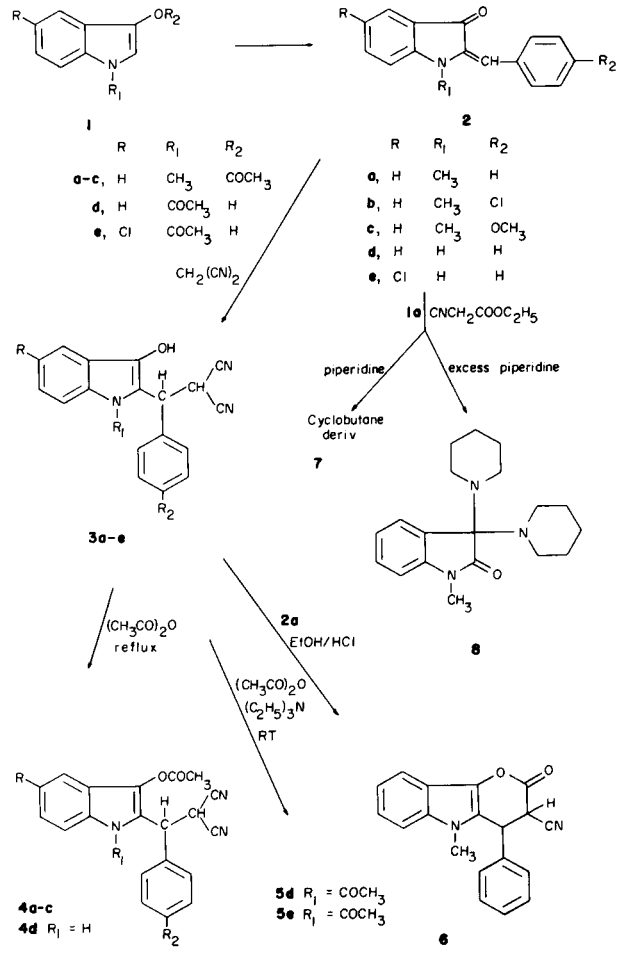


Table 1

Spectroscopic Properties of 2-Aryl-2(3-hydroxyindol-2-yl)-1,1-dicyanoethanes

	λ max (ethanol) nm (log ε)	ν max (potassium chloride) cm^{-1}		δ (deuteriochloroform)			
		-OH	-CN	C_6H_5CH	N-CH_3	OH	$CH(CN)_2$
3a	232 (4.72) 265 (4.13)	3450	2184	3.35	3.46	5.14	6.91
3b	232.5 (4.81) 262.5 (4.28)	3380	2180	3.21	3.36	5.18	6.95
3c	232.5 (4.67) 262.5 (4.27)	3440	2180	3.70	3.30	4.91	6.81
3d	230.0 (4.67) 262.5 (4.32)	3440	2190	3.74	—	5.30	7.15
3e	235.5 (4.67) 267.5 (4.17)	3440	2190	—	—	5.10	7.09

3a-c to **4a-c**, **3d** gave the diacetyl derivatives **5d** at room temperature due to concurrent acetylation of the indole nitrogen, but at reflux with acetic anhydride alone only the 3-OH acetylated to give **4d**.

Diacetylation occurred with both methods for **3e** to give **5e**.

Treatment of the dinitrile **3a** with ethanolic hydrochloric acid resulted in partial hydrolysis and cyclisation to give 3-cyano-2,3-dihydro-2-oxo-4-phenylpyrano[3,2-*b*]-*N*-methylindole (**6**).

Condensation of **2** with molecules larger than malononitrile failed, even under more drastic conditions.

When a mixture of (*Z*)/(*E*)-**2a** was reacted with cyanoacetic acid in a mixture of dioxane and triethylamine at room temperature (2) no reaction occurred. On careful acidification of the reaction mixture with hydrochloric acid (*Z*)-**2a** deposited, dilution of the filtrate with water then resulted in the deposition of (*E*)-**2a**.

Condensation of (*Z*)- or (*E*)-**2a** with ethyl cyanoacetate in ethanol containing a few drops of piperidine at room temperature for five days resulted in the precipitation of a fine yellow solid which was confirmed by elemental analysis and spectroscopic evidence as dispiro-[1-methyl-3-oxoindoline-2,1′-(3,4-diphenylcyclobutane)-2′,2″-(1-methyl-3-oxoindoline)] (**7**) previously reported by Hooper (5).

Attempted condensation of (*Z*)- or (*E*)-**2a** with cyanoacetic acid, cyanoacetamide or ethyl cyanoacetate in ethanol solution in the presence of sodium methoxide similarly gave high yields of the cyclobutane **7**.

When either of these reactions was carried out in the absence of light, the yield of **7** was unaffected, a result at variance with the previous report (5) when the formation of **7** was stated to be photochemical.

When the reaction of (*Z*)- or (*E*)-**2a** with ethyl cyanoacetate in ethanol at room temperature was repeated in the presence of excess piperidine a white solid was isolated after evaporation to half volume. Investigation of this solid revealed it to be 1-methyl-3,3-dipiperidinoindol-2(3*H*)-one (**8**), confirmed by its synthesis from 1-methylisatin and piperidine.

EXPERIMENTAL

Perkin Elmer 157G and R32 spectrophotometers were used to record ir and pmr spectra (TMS 1%, I. S.), respectively. Microanalyses are by Dr. J. A. Baker, Department of Pharmacy, Brighton Polytechnic. Melting points are corrected.

2-Arylmethylideneindol-3(2*H*)-ones (**2a-e**).

Method A.

The appropriate indol-3(2*H*)-one **1** (0.01 mole) was heated in an atmosphere of nitrogen under reflux for one hour with 1.5 *M* sodium hydroxide solution (55 ml). The required benzaldehyde (0.01 mole) in ethanol (2 ml) was then added *via* the condenser and heating was continued for a further two hours. After standing at room temperature overnight the separated solid was collected, washed, dried and if necessary purified.

Method B

The appropriate indol-3(2*H*)-one **1** (0.01 mole) was heated in an atmosphere of nitrogen under reflux for one hour with 1.0 *M* sodium hydroxide solution (55 ml). The reaction mixture was cooled to 0-5°, the required benzaldehyde (0.01 mole) in ethanol (2 ml) was added *via* the condenser and the mixture stirred for two hours. The ice bath was removed and stirring continued at room temperature overnight. The separated material was collected, washed, dried and if necessary purified.

Compound **1a** was converted to a mixture of (*Z*)- and (*E*)-**2a** by Method B, chromatographic separation using B. D. H. silica gel (chromatographic grade) 60-120 mesh with benzene as eluant yielded (*Z*)-**2a**, 78%, mp 132° and (*E*)-**2a**, 18%, mp 105°, (lit (4) mp 131-132° and 109-110°, respectively).

Method A yielded (*E*)-**2a**, 71% (ethanol), mp 105°. Similarly, **1b** was converted to a mixture of (*Z*)-**2b** and (*E*)-**2b**, chromatographic separation as described for (*Z*)- and (*E*)-**2a** yielded (*Z*)-**2b**, 65%, mp 160° and (*E*)-**2b**, 24%, mp 132°, (lit (4) mp 159-160° and 131-132°, respectively). Method A yielded (*E*)-**2b**, 83% (ethanol), mp 132°.

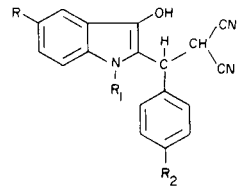
For **2c** both methods gave a mixture of (*Z*)- and (*E*)-isomers as shown by tlc, however, recrystallisation of the mixed isomers of Method B from acetone yielded orange needles of pure (*Z*)-**2c**, 83%, mp 187°; ir: ν max (potassium chloride): 1700, 1610, 1590 cm^{-1}; pmr (deuteriochloroform): δ 3.0 (s, 3H, N-CH_3), 3.78 (s, 3H, OCH_3), 6.5-7.5 (m, 8H, arom), 7.28 (s, 1H, =CH).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70; N, 5.28. Found: C, 76.75; H, 5.83; N, 5.24.

The *N*-acetyl indol-3(2*H*)-ones **1d** and **1e** gave the corresponding (*Z*)-**2d** and (*Z*)-**2e** by Method A. Recrystallisation from methanol gave (*Z*)-**2d** as orange needles 63%, mp 178°, (lit (4) 176-178°. Recrystallisation from ethanol gave (*Z*)-**2e** as orange prisms, 50%, mp 245°; ir: ν max (potassium chloride) 3325, 1680, 1630, 1600; pmr (deuteriochloroform): δ 6.79 (s, 1H, =CH).

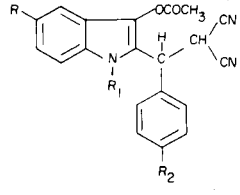
Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.27; H, 3.75; N, 5.46.

Table II



Compound	R	R_1	R_2	Starting material	Recrystallization solvent	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
3a	H	CH_3	H	(*Z*)-**2a**	Benzene	95	234	$C_{19}H_{15}N_3O$	75.50	5.02	13.90	76.10	5.00	13.86
				(*E*)-**2a**	Benzene	92	234					75.92	5.03	13.91
3b	H	CH_3	Cl	(*Z*)-**2b**	Ethanol	75	172	$C_{19}H_{14}ClN_3O$	67.96	4.20	12.52	67.90	4.16	12.51
				(*E*)-**2b**	Ethanol	70	172					67.95	4.22	12.58
3c	H	CH_3	OCH_3	(*Z*)-**2c**	Ethanol/water	83	184.5	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.48	4.99	12.61
3d	H	H	H	(*Z*)-**2d**	Ethanol	93	229	$C_{18}H_{13}N_3O$	75.24	4.56	14.63	75.28	4.41	14.69
3e	Cl	H	H	(*Z*)-**2e**	Ethanol/water	52	206	$C_{18}H_{12}ClN_3O\frac{1}{2}H_2O$	65.30	3.96	12.71	65.36	3.87	12.77

Table III



Compound	R_1	Method	Recrystallization solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	CH_3	A or B	Ethanol	80-85	201	$C_{21}H_{17}N_3O_2\frac{1}{4}H_2O$	72.50	5.07	12.08	72.61	4.97	12.08
4b	CH_3	A or B	Ethanol	75-83	182	$C_{21}H_{16}ClN_3O_2$	66.75	4.27	11.12	66.57	4.17	11.17
4c	CH_3	A or B	Acetic acid/water	89-94	170	$C_{22}H_{19}N_3O_3$	70.76	5.13	11.26	70.59	5.18	11.33
4d	H	A	Ethanol/water	75	184	$C_{20}H_{15}N_3O_2$	72.93	4.59	12.76	72.76	4.44	12.86
5d	$COCH_3$	B	Acetic acid	88	240-242 dec	$C_{22}H_{17}N_3O_3\frac{1}{4}H_2O$	70.29	4.69	11.18	70.19	4.53	11.02
5e	$COCH_3$	A or B	Ethanol/water	88	182	$C_{22}H_{16}ClN_3O_3$	65.11	3.97	10.36	64.88	3.90	10.27

2-Aryl-2(3-hydroxyindol-2-yl)-1,1-dicyanoethanes (**3a-e**).

A solution of malononitrile (0.66 g, 0.01 mole) in ethanol (10 ml) containing piperidine (0.2 ml) was added with stirring to a suspension of the appropriate 2-arylmethylideneindol-3(2*H*)-one (**2a-e**, 0.01 mole) in ethanol (20 ml). Stirring was continued for half an hour and the dark red solution then kept at 0-5° overnight when crystals were deposited, these were collected, washed with ethanol and dried. Dilution of the mother liquor with water (20 ml) gave a further crop of crystals which were collected and dried. The bulked crystals were then recrystallised from a suitable solvent to yield **3a-e** (Table II). Similar yields were obtained if triethylamine was used as the catalyst or if dimethyl sulphoxide was used instead of ethanol. In the latter case the product was isolated by dilution with water, and was slightly more pure than with ethanol as solvent, although the yield was lower.

Acetylation of **3a-e**.

Two methods were used for the acetylation.

Method A.

The appropriate dinitrile (**3a-e**, 0.01 mole) was boiled under reflux with acetic anhydride (15 ml) for one hour, allowed to cool and poured on to ice (50 g) to deposit a cream-white solid. This was collected by filtration, washed with water, dried and recrystallised from a suitable solvent (Table III).

Method B.

The appropriate dinitrile (**3a-e**, 0.01 mole) was stirred at room temperature with acetic anhydride (10 ml) containing triethylamine (3 ml) for one hour and then allowed to stand for two days. The reaction mixture was then poured onto ice (50 g) and the product isolated and purified as described in Method A.

3-Cyano-2,3-dihydro-3-oxo-4-phenylpyrano[3,2-*b*]-*N*-methylindole (**6**).

A mixture of the dinitrile **3a** (1 g) in ethanol (10 ml) and hydrochloric acid (5 ml) was boiled under reflux for 30 minutes. The clear solution was then poured onto ice (40 g) and the precipitated product collected by filtration, washed with water and dried. Recrystallisation from ethanol gave **6** as yellow microcrystals, 52%, mp 210-213°; ir (potassium chloride): ν max 2210, 1700, 1615 cm^{-1}; pmr (TFA): δ 3.54 (s, 3H, N-CH_3), 4.45 (s, 1H, J = 9 Hz, C*H*C_6H_5), 4.85 (s, 1H, J = 9 Hz, C*H*CN), 7.20-7.80 (m, 10H, arom); m/e 302 (M^+).

Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.32; H, 4.55; N, 9.20.

Attempted Condensation of (*Z*)-**2a** and (*E*)-**2a** With Cyanoacetic Acid.

A solution of (*Z*)-**2a** (1.18 g, 0.005 mole) in dioxane (5 ml) was added with stirring to a solution of cyanoacetic acid (0.45 g, 0.005 mole) in dioxane (2 ml) containing triethylamine (1 g). Stirring was continued for one hour and then hydrochloric acid (1.5 ml) was added slowly and with cooling to the dark red solution. After two days at room temperature orange crystals separated which when collected, washed with water, dried and recrystallised from methanol yielded 0.61 g of the starting material (*Z*)-**2a**, mp 131°.

Dilution of the filtrate with water (15 ml) precipitated a dark red solid which when collected, washed with water, dried and recrystallised from ethanol yielded 0.35 g of the (*E*)-isomer of the starting material (*E*)-**2a**, mp 95-96°.

Repetition of the experiment using (*E*)-**2a** gave virtually identical results.

Attempted Condensation of (*Z*)-**2a** With Ethyl Cyanoacetate.

Method A.

A solution of (*Z*)-**2a** (1.18 g, 0.005 mole) in ethanol (20 ml) containing ethyl cyanoacetate (2.26 g, 0.02 mole) and piperidine (0.1 ml) was allowed to stand at room temperature for five days. The deposited solid was collected, washed with ethanol and recrystallised from benzene to yield yellow microcrystals 0.98 g, mp 198°; ir (potassium chloride): ν max 1710, 1620 cm^{-1}; pmr (DMSO-d_6): δ 2.97, 3.11 (2s, 6H, 2 × N-CH_3), 3.61 (d, 1H, CH), 5.06 (d, 1H, CH), 6.4-7.52 (m, 18H, arom); m/e 470 (M^+); whose physical characteristics were identical to those reported (5) for **7**, yield 83%.

Anal. Calcd. for $C_{32}H_{26}N_2O_2$: C, 81.67; H, 5.57; N, 5.95. Found: C, 81.62; H, 5.53; N, 5.78.

Repetition of the experiment using (*E*)-**2a** gave a 72% yield of **7**.

Method B.

A solution of (*Z*)-**2a** (1.18 g, 0.005 mole) in ethanol (20 ml) containing sodium methoxide (0.54 g, 0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole) was boiled under reflux for one hour. On cooling a yellow solid separated which when isolated and recrystallised as described in Method A gave the same cyclobutane product **7**, yield 81%.

Repetition of the experiment with (*E*)-**2a** and cyanoacetic acid or cyanoacetamide in place of ethyl cyanoacetate all resulted in high yields of the cyclobutane **7**.

Similar results were obtained when the reactions were carried out in the absence of light.

Method C.

A mixture of (*Z*)-**2a** (1.18 g, 0.005 mole) in methanol (100 ml) containing ethyl cyanoacetate (0.66 g, 0.006 mole) and piperidine (10 ml) was stirred at room temperature for twelve hours. The solution was evaporated to half volume under vaccum and allowed to stand for a further twelve hours. The deposited white solid was then collected, dried and recrystallised from ethanol, 1.32 g, mp 140-142° dec. Microanalytical and spectroscopic data showed this to be 1-methyl-3,3-dipiperidinoindol-2(3*H*)-one (**8**); ir (potassium chloride): ν max 2920, 2818, 2800, 2720, 1720, 1610 cm^{-1}; pmr (deuteriochloroform) δ 1.43 (m, 12H, 3, 4, 5H's of piperidine rings), 2.55 (d, 8H, 2, 6H's of piperidine rings), 3.13 (s, 3H, N-CH_3), 6.77-7.40 (m, 4H, arom); m/e 313 (M^+).

Anal. Calcd. for $C_{19}H_{27}N_3O$: C, 72.80; H, 8.68; N, 13.41. Found: C, 72.68; H, 8.72; N, 13.34.

1-Methyl-3,3-dipiperidinoindol-2(3*H*)-one (**8**).

A suspension of 1-methylindol-2,3-dione (1.47 g, 0.01 mole) in dry benzene containing piperidine (3.4 g, 0.04 mole), was boiled under reflux for four hours in a Dean and Stark apparatus. The reaction mixture was filtered and the filtrate evaporated under vacuum to leave a semi solid mass. Recrystallisation from ethanol gave **8** as small white cubic crystals, 1.78 g, 57%, mp 144° dec (colour change to light blue at 124°) whose properties were identical to those reported previously.

REFERENCES AND NOTES

(1) S. J. Holt, A. E. Kellie, D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 1217 (1958).

(2) R. W. Daisley and J. Walker, *Eur. J. Med. Chem.*, **14**, 47 (1979).

(3) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York & London, 1970, p 364.

(4) M. Hooper and W. N. Pitkethly, *J. Chem. Soc., Perkin Trans. I*, 1607 (1972).

(5) M. Hooper and W. N. Pitkethly, *ibid.*, 2804 (1973).