o-Aminophenyl Alkyl and Aralkyl Ketones and Their Derivatives; Part II*. A New Synthesis of Substituted 2-Arylisatogens

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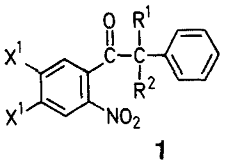
2-Arylisatogens (**2**) may be prepared from o-nitrophenylacetylene derivatives, from o-nitrostilbene derivatives, via 1-(o-nitrophenyl)-2-phenyl-2-pyridinioethanol acetates or ethers, or by oxidation of 2-aryl-1-hydroxyindoles[1,2,3]. There seems to be no report on the synthesis of compounds **2** from benzyl o-nitrophenyl ketones (**1**, $R^1 = R^2 = H$). These nitroketones should readily undergo intramolecular cyclocondensation under basic conditions to give 2-phenylisatogens (**2**).



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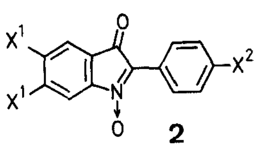

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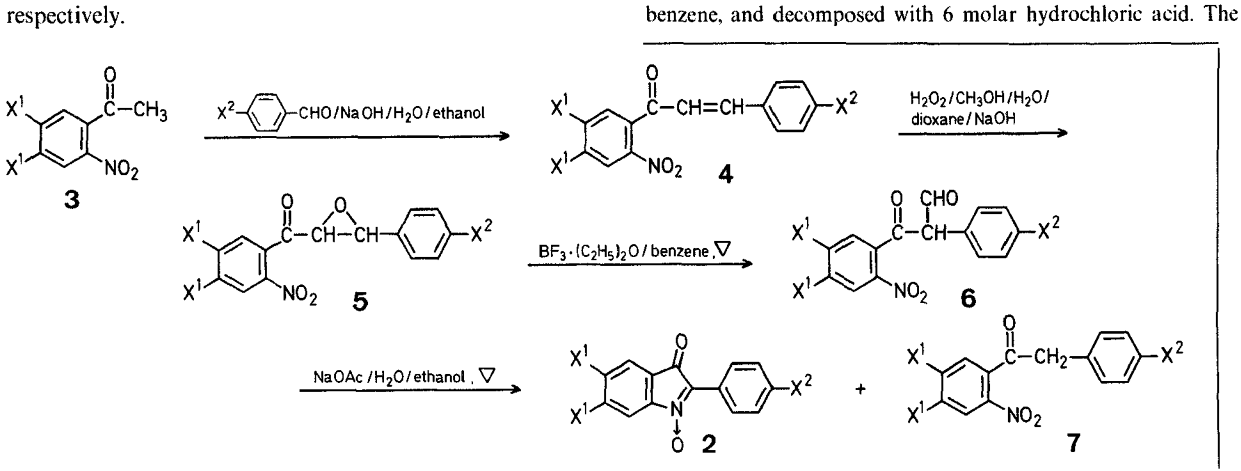
Benzyl 2-nitrophenyl ketones (**1**) have hitherto only been mentioned[4,5] in the literature, their synthesis has not been reported. The preparation of **1** ($R^1 = R^2 = H$; $\equiv$ **7**, $X^2 = H$) has been attempted without success by hydrolysis of diethyl (2-nitrobenzoyl)-phenylmalonate (**1**, $X^1 = H$, $R^1 = R^2 = -COOC_2H_5$)[4] and ethyl (2-nitrobenzoyl)-phenylcyanoacetate (**1**, $X^1 = H$, $R^1 = CN$, $R^2 = COOC_2H_5$)[7] by reaction of 2-nitrobenzoyl chloride with dibenzylcadmium[6]. We present here a four-step reaction sequence which leads from 2-nitroacetophenones (**3**) to 2-phenylisatogens (**2**) and benzyl 2-nitrophenyl ketones (**7**) which are possible intermediates in the reaction. The starting 2-nitroacetophenones (**3**) are condensed with benzaldehydes in alkaline medium to give 2-nitrophenyl styryl ketones (2-nitrochalcones, **4**) which are oxidized to the epoxyketones **5** with hydrogen peroxide. Boron trifluoride-catalyzed rearrangement[8] of **5** affords 3-(2-nitrophenyl)-3-oxo-2-phenylpropanals (**6**) which in boiling aqueous ethanol containing sodium acetate are converted into 2-phenylisatogens and benzyl 2-nitrophenyl ketones, respectively.



The isatogens **2** precipitate from the final reaction mixture upon cooling and may be isolated by filtration. The ketones **7** are isolated by evaporation of the filtrate and column chromatography of the residue.

All benzyl 2-nitrophenyl ketones (**7**) obtained are new compounds. Their structures were established by microanalysis, mass spectrum, and ^1H-N.M.R. analysis (singlet of benzyl proton at $\delta = 4.00-4.10$ ppm, 2H). In the case of **7** ($X^1 = X^2 = H$), additional proof of the structure was obtained by reduction (with Fe/HCl) to the known 2-aminophenyl benzyl ketone which was found to be identical (m.p., mixture m.p., 102–103°) with an authentic sample prepared by the literature method[9], having superimposable I.R. spectra.

2-Nitroacetophenone (**3**, $X^1 = H$) and 4,5-dimethoxy-2-nitroacetophenone (**3**, $X^1 = OCH_3$) were prepared according to literature methods.

The T.L.C. analyses were carried out on silica gel using benzene/ethyl acetate (3+1) as solvent. Detection was done by exposure to iodine vapors.

2-Nitrophenyl Styryl Ketones (2-Nitrochalcones, 4); General Procedure:

A solution of sodium hydroxide (4.0 g, 0.1 mol) in water (10 ml) is added in one portion to a stirred solution of the 2-nitroacetophenone **3** (0.1 mol) and the benzaldehyde (0.1 mol) in methanol (150 ml). The mixture is stirred for 2–6 h until the reaction is complete (as indicated by T.L.C. analysis). The precipitated product is isolated by suction, washed several times with water until free from alkali, and recrystallized from ethanol.

2,3-Epoxy-1-(2-nitrophenyl)-3-phenyl-1-propanones (5); General Procedure:

The 2-nitrophenyl styryl ketone **4** (0.01 mol) is dissolved in methanol (50 ml) + dioxan (25 ml) in a 500 ml three-neck flask equipped with dropping funnel, stirrer, and thermometer. To this is added 30% hydrogen peroxide (3 ml, 0.03 mol) with stirring at 15°. Then, 3 molar aqueous sodium hydroxide (3.5 ml, ~0.01 mol) is added dropwise with stirring while the temperature of the mixture is kept at 15–20°. After the addition is complete, stirring is continued for 3–8 h until T.L.C. analysis indicates completion of the reaction. The mixture is poured into water (500 ml), the precipitated product isolated by suction, washed thoroughly with water, and crystallized from ethanol.

Rearrangement of Epoxyketones 5 to 3-(2-Nitrophenyl)-3-oxo-2-phenylpropanals (6); General Procedure[8]:

A solution of the epoxyketone **5** (0.008 mol) in dry benzene (15 ml) containing boron trifluoride etherate (2 ml, 0.016 mol) is refluxed for 2–5 h until T.L.C. analysis indicates complete conversion. The mixture is then thoroughly washed with water (3 × 10 ml) and shaken with saturated aqueous copper(II) acetate solution (50 ml). The copper complex formed is isolated by suction, washed with benzene, and decomposed with 6 molar hydrochloric acid. The resultant mixture is extracted with ether (3 × 50 ml), the extract is dried with Na_2SO_4, the solvent is evaporated, and the residue recrystallized from benzene/petroleum ether.

Conversion of Aldehydes 6 into 2-Phenylisatogens (2) and Benzyl 2-Nitrophenyl Ketones (7), respectively:

A solution of the aldehyde **6** (0.001 mol) and sodium acetate (0.41 g, 0.005 mol) in 3:1 ethanol/water (20 ml) is refluxed for 3–5 h

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Table. Yields and Data of Compounds **2, 4, 5, 6, 7** prepared

Compound Type	X^1	X^2	Yield [%]	m.p.	Molecular formula[a]	I.R. (Nujol) ν_{max} [cm^{-1}]
4	H	H	95	128°[10]	$C_{15}H_{11}NO_3$ (253.2)	1653 ($C{=}O$); 1515, 1333 (NO_2); 966 (*trans*-$CH{=}CH$)
4	H	Cl	87	123–124°[10]	$C_{15}H_{10}ClNO_3$ (287.7)	1665 ($C{=}O$); 1538, 1351 (NO_2); 990 (*trans*-$CH{=}CH$)
4	OCH_3	H	85	159–160°	$C_{17}H_{15}NO_5$ (313.3)	1653 ($C{=}O$); 1515, 1333 (NO_2); 980 (*trans*-$CH{=}CH$)
4	OCH_3	Cl	80	194–195°	$C_{17}H_{14}ClNO_5$ (347.7)	1639 ($C{=}O$); 1515, 1342 (NO_2); 990 (*trans*-$CH{=}CH$)
5	H	H	87	79–80°[10]	$C_{15}H_{11}NO_4$ (269.2)	1709 ($C{=}O$); 1515, 1342 (NO_2)
5	H	Cl	76	94–95°[10]	$C_{15}H_{10}ClNO_4$ (303.7)	1709 ($C{=}O$); 1538, 1351 (NO_2)
5	OCH_3	H	67	124–125°	$C_{17}H_{15}NO_6$ (329.3)	1701 ($C{=}O$); 1515, 1333 (NO_2)
5	OCH_3	Cl	65	165–166°	$C_{17}H_{14}ClNO_6$ (363.7)	1709 ($C{=}O$); 1515, 1325 (NO_2)
6	H	H	67	136°	$C_{15}H_{11}NO_4$ (269.2)	1600 ($C{=}O$); 1520, 1342 (NO_2)
6	H	Cl	70	162°	$C_{15}H_{10}ClNO_4$ (303.7)	1575 ($C{=}O$); 1520, 1333 (NO_2)
6	OCH_3	H	60	169–170°	$C_{17}H_{15}NO_6$ (329.3)	1613 ($C{=}O$); 1511, 1325 (NO_2)
6	OCH_3	Cl	65	171–172°	$C_{17}H_{14}ClNO_6$ (363.7)	1613 ($C{=}O$); 1511, 1325 (NO_2)
7	H	H	31	73–74°	$C_{14}H_{11}NO_3$ (241.2)	1709 ($C{=}O$); 1538, 1351 (NO_2)
7	H	Cl	29	125°	$C_{14}H_{10}ClNO_3$ (275.7)	1715 ($C{=}O$); 1527, 1333 (NO_2)
7	OCH_3	H	15	162–163°	$C_{16}H_{15}NO_5$ (301.3)	1709 ($C{=}O$); 1515, 1333 (NO_2)
7	OCH_3	Cl	15	165–166°	$C_{16}H_{14}ClNO_5$ (335.7)	1709 ($C{=}O$); 1515, 1316 (NO_2)
2	H	H	50	185°[4]	$C_{14}H_9NO_2$ (223.2)	1718 ($C{=}O$); 1176 ($N \rightarrow O$)
2	H	Cl	55	174°[5]	$C_{14}H_8ClNO_2$ (257.7)	1709 ($C{=}O$); 1176 ($N \rightarrow O$)
2	OCH_3	H	75	248°	$C_{16}H_{13}NO_4$ (283.3)	1701 ($C{=}O$); 1190 ($N \rightarrow O$)
2	OCH_3	Cl	70	253°	$C_{16}H_{12}ClNO_4$ (317.7)	1709 ($C{=}O$); 1190 ($N \rightarrow O$)

[a] Molecular weights were confirmed by mass spectral determination on a CEC-2-110B double-focussing spectrometer using a direct-inlet system. All compounds gave satisfactory microanalyses: C, ±0.30; H, ±0.20; N, ±0.30.

until T.L.C. analysis indicates the absence of **6**. The mixture is then cooled to 30°, the colored *2-phenylisatogen* **2** is collected by suction, washed with ethanol, and recrystallized from ethanol. The mother liquors are combined and evaporated. The residue is column-chromatographed on silica gel using benzene/petroleum ether (1:1) as eluent. The first, intensely colored fractions upon evaporation afford the pure *isatogen* **2**; the next fractions contain a mixture of **2** and **7**, and finally, the pure *benzyl 2-nitrophenyl ketone* **7** is obtained.

^1H-N.M.R. ($CDCl_3$) of **7** ($X^1 = OCH_3$; $X^2 = H$): $\delta = 7.3$ (bs, 5H); 7.63 (s, 1H); 6.46 (s, 1H); 4.1 (s, 2H, CH_2); 4.00, 4.83 ppm (2s, 6H, $2OCH_3$).

Cyclocondensation of Benzyl 2-Nitrophenyl Ketones (7) to 2-Phenylisatogens (2):

A solution of the benzyl 2-nitrophenyl ketone **7** (0.001 mol) and sodium acetate (0.41 g, 0.005 mol) in 3:1 ethanol/water (20 ml) is refluxed for 2–3 h until T.L.C. analysis indicates complete conversion. The mixture is cooled to 30°. The precipitated isatogen is isolated by suction, washed with water, and recrystallized from ethanol.

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