A Convenient Synthesis of Some Phthalazine Derivatives from Azocoupled Homophthalic Anhydride

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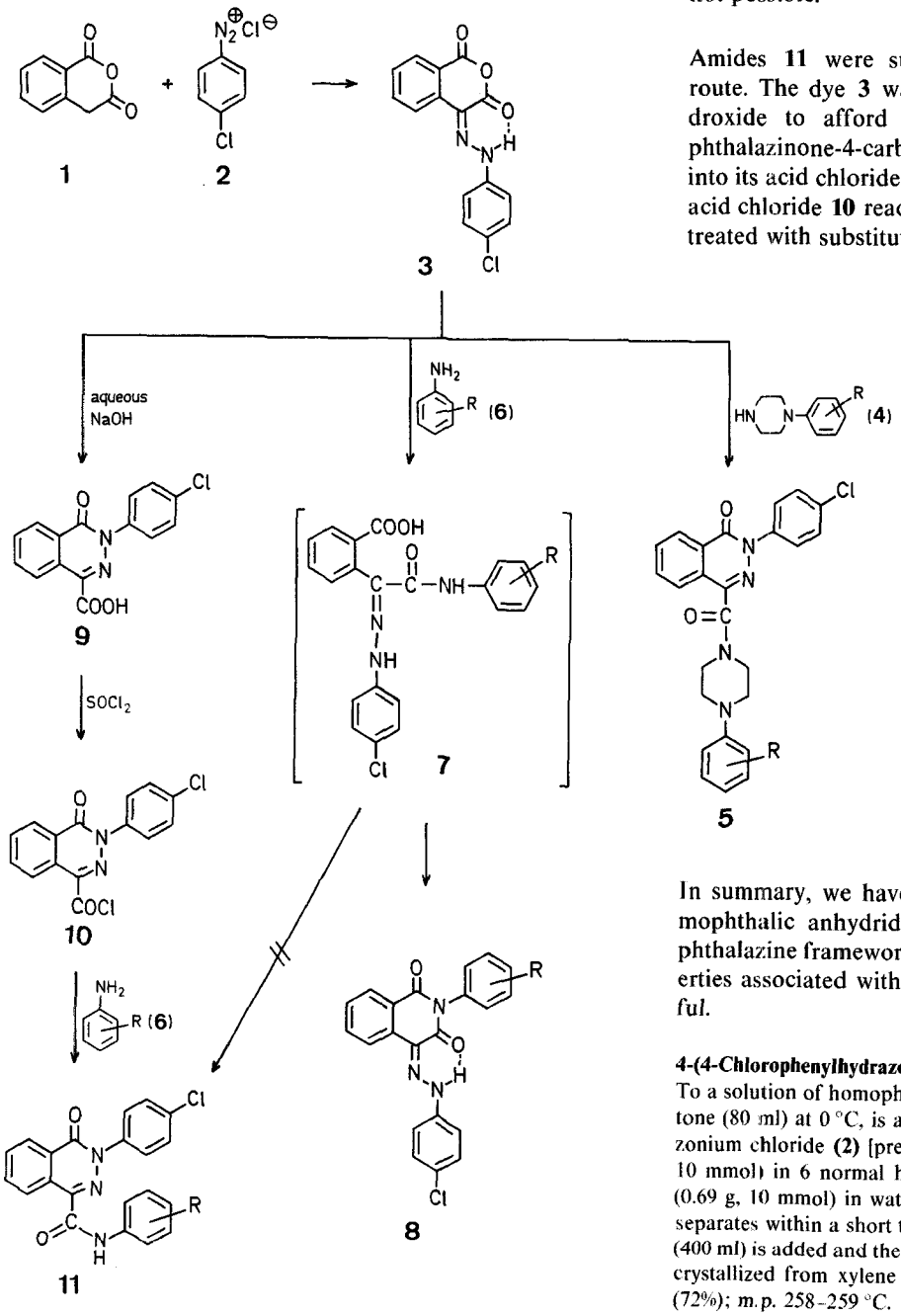
Isomerization of α-hydrazono cyclic anhydrides by aqueous alkali leads to heterocycles incorporating the hydrazo linkage[1-4]. The mechanism of this reaction suggests that the anhydride ring can be opened by nucleophiles and subsequent cyclization gives heterocycles incorporating the hydrazo linkage and the nucleophile. With this idea in view, we reacted 1-arylpiperazines **(4)** and substituted anilines **(6)** with 4-(4-chlorophenylhydrazono)-1*H*-2-benzopyran-1,3(4*H*)-dione **(3)**, to prepare the corresponding phthalazinones **5** and **11**, respectively, as possible anti-hypertensive agents.

Homophthalic anhydride **(1)** was reacted with diazotized 4-chloroaniline **(2)** to give the dye **3** which exists in the hydrazone form. The dye **3** was treated with 1-arylpiperazines **4** in boiling xylene to afford directly the desired amides **5.** The piperazines opened the anhydride ring by attacking the carbonyl group adjacent to the hydrazono substituent, followed by cyclization to form the phthalazine ring. A parallel reaction of substituted anilines **6** with **3**, however, did not yield the desired amides **11**; instead the reaction products were 4-(4-chlorophenylhydrazono)-2-aryl-1,3(2*H*,4*H*)-isoquinolinediones **8** probably formed via the intermediate **7**. However, in the case of 1-arylpiperazines **4**, the formation of isoquinoline ring is not possible.

Amides **11** were subsequently synthesized by a different route. The dye **3** was treated with hot aqueous sodium hydroxide to afford the isomeric 2-(4-chlorophenyl)-1(2*H*)-phthalazinone-4-carboxylic acid **(9).** The acid was converted into its acid chloride **10** by the action of thionyl chloride. The acid chloride **10** readily afforded the desired amides **11** when treated with substituted anilines **6.**



In summary, we have shown for the first time that the homophthalic anhydride dye **3** can be used to synthesize a phthalazine framework. In view of the anti-hypertensive properties associated with phthalazines, this method may be useful.

4-(4-Chlorophenylhydrazono)-1*H*-2-benzopyran-1,3(4*H*)-dione (3):
To a solution of homophthalic anhydride (**1**; 1.62 g, 10 mmol) in acetone (80 ml) at 0 °C, is added a cold solution of 4-chlorobenzenediazonium chloride **(2)** [prepared by diazotizing 4-chloroaniline (1.28 g, 10 mmol) in 6 normal hydrochloric acid (6 ml) with sodium nitrite (0.69 g, 10 mmol) in water (10 ml)] with constant stirring. The dye **3** separates within a short time. After stirring for additional 0.5 h, water (400 ml) is added and the dye is filtered, washed with water, dried, and crystallized from xylene to give bright yellow needles; yield: 2.16 g (72%); m.p. 258–259 °C.

$C_{15}H_9ClN_2O_3$	calc.	C 59.90	H 3.00	N 9.32	Cl 11.81
(300.7)	found	59.82	2.93	9.40	11.77

I.R. (KBr): $\nu = 3400, 3140, 1765, 1675, 1525\ cm^{-1}$.

2-(4-Chlorophenyl)-4-[[4-(4-methylphenyl)-1-piperazinyl]carbonyl]-1(2*H*)-phthalazinone (5d); Typical Procedure:

A mixture of homophthalic anhydride dye (**3**; 0.6 g, 2 mmol) and 1-(4-methylphenyl)-piperazine (**4d**; 0.35 g, 2 mmol) in xylene (15 ml) is refluxed for 2 h. The solvent is removed under vacuo and ethanol (5 ml) is added to the residue after cooling. The precipitated **5d** is collected, washed with ethanol, and crystallized from benzene to give needles; yield: 0.54 g (59%); m.p. 201–203 °C.

$C_{26}H_{23}ClN_4O_2$	calc.	C 68.05	H 5.02	N 12.21	Cl 7.74
(458.9)	found	68.08	5.03	12.26	7.80

I.R. (KBr): $\nu = 2900, 1695, 1660\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.3$ (s, 3H); 3.2 (t, $J = 5$ Hz, 4H); 3.75 (t, $J = 5$ Hz, 2H); 4.05 (t, $J = 5$ Hz, 2H); 6.7–7.9 (m, 11H); 8.5 ppm (m, 1H).

4-(4-Chlorophenylhydrazono)-2-(4-methoxyphenyl)-1,3(2*H*,4*H*)-isoquinolinedione (8c); Typical Procedure:

Dye **3** (0.6 g, 2 mmol) is fused with 4-methoxyaniline (0.25 g, 2 mmol) in an oil bath at 180 °C. After heating the mixture for 1.5 h at 180 °C, it is cooled to 50–60 °C and ethanol (25 ml) is added to it. Compound **8c** separates as coloured crystals. It is filtered, washed with ethanol and crystallised from dimethylformamide/ethanol; yield 0.76 g (94%); m.p. 256–257 °C.

$C_{22}H_{16}ClN_3O_3$	calc.	C 65.10	H 3.95	N 10.36	Cl 8.75
(405.8)	found	65.18	3.89	10.41	8.68

I.R. (KBr): $\nu = 3400, 1675, 1620, 1600\ cm^{-1}$.

2-(4-Chlorophenyl)-1(2*H*)-phthalazinone-4-carboxylic Acid (9):

Homophthalic anhydride dye **3** (3.0 g, 10 mmol) is boiled with 5% aqueous sodium hydroxide (50 ml) for 15–20 min, when a clear solution is obtained. The solution is cooled and carefully acidified with dilute hydrochloric acid to obtain crude **9**. The crude product is separated, dissolved in 2% sodium hydrogen carbonate (70 ml) solution, and filtered. The filtrate, on acidification with dilute hydrochloric acid, gives pale yellow **9**, which is filtered, washed with water, dried, and crystallized from glacial acetic acid to give fine white needles; yield: 2.8 g (93%); m.p. 219–220 °C.

$C_{15}H_9ClN_2O_3$	calc.	C 59.90	H 3.00	N 9.32	Cl 11.81
(300.7)	found	59.89	2.98	9.32	11.75

I.R. (KBr): $\nu = 3120–2930, 1750, 1645\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): $\delta = 7.4–8.15$ (m, 6H); 8.2–8.6 ppm (m, 2H).

2-(4-Chlorophenyl)-1(2*H*)-phthalazinone-4-carboxylic Acid Chloride (10):

A mixture of acid **9** (3.0 g, 10 mmol) and thionyl chloride (11.9 g, 0.1 mol) is refluxed for 0.5 h. The reaction mixture becomes clear within 10 min. Thionyl chloride is removed completely under vacuo and dry benzene (20 ml) is added. The solid is crushed and benzene is evaporated under vacuo. This treatment is repeated twice. The crude **10** is stirred with aqueous sodium hydrogen carbonate to remove the unreacted acid and crystallised from 80% aqueous dimethylformamide; yield: 2.9 g (92%); m.p. 213–214 °C.

$C_{15}H_8Cl_2N_2O_2$	calc.	C 56.43	H 2.51	N 8.78	Cl 22.26
(319.1)	found	56.34	2.48	8.69	22.14

I.R. (KBr): $\nu = 1820, 1740, 1685\ cm^{-1}$.

2-(4-Chlorophenyl)-4-(4-methylphenylaminocarbonyl)-1(2*H*)-phthalazinone (11d); Typical Procedure:

A mixture of **10** (0.64 g, 2 mmol) and 4-methylaniline (0.5 g, 4 mmol) is refluxed in ethanol (10 ml) for 2 h. The reaction mixture is cooled and the precipitated solid is filtered, washed with ethanol and water. Crude **11d** obtained is crystallized from ethanol; yield: 0.45 g (58%); m.p. 172–173 °C.

$C_{22}H_{16}ClN_3O_2$	calc.	C 67.78	H 4.11	N 10.78	Cl 9.1
(289.8)	found	67.71	4.10	10.78	9.10

I.R. (KBr): $\nu = 3220, 1700, 1655\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.35$ (s, 3H); 7.0–7.8 (m, 11H); 8.4 (m, 1H); 9.1 ppm (m, 1H).

Table. Compounds **5**, **8**, and **11** prepared

Product No.	R	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]
5a	H	72	180–182° (benzene)	$C_{25}H_{21}ClN_4O_2$ (444.9)
5b	2-H_3C	59	184–185° (ethanol)	$C_{26}H_{23}ClN_4O_2$ (458.9)
5c	3-H_3C	54	142–143° (DMF/ethanol)	$C_{26}H_{23}ClN_4O_2$ (458.9)
5d	4-H_3C	see experimental		
5e	2-Cl	69	197–198° (ethanol)	$C_{25}H_{20}Cl_2N_4O_2$ (479.4)
5f	3-Cl	63	130–131° (ethanol)	$C_{25}H_{20}Cl_2N_4O_2$ (479.4)
5g	4-Cl	68	200–201° (DMF/ethanol)	$C_{25}H_{20}Cl_2N_4O_2$ (479.4)
8a	4-H_3C	92	226–228° (DMF)	$C_{22}H_{16}ClN_3O_2$ (389.8)
8b	4-Cl	90	230–231° (DMF)	$C_{21}H_{13}Cl_2N_3O_2$ (410.3)
8c	4-H_3CO	see experimental		
11a	H	66	180–181° (ethanol)	$C_{21}H_{14}ClN_3O_2$ (375.8)
11b	2-H_3C	53	210–212° (DMF/ethanol)	$C_{22}H_{16}ClN_3O_2$ (389.8)
11c	3-H_3C	55	160–161° (DMF/ethanol)	$C_{22}H_{16}ClN_3O_2$ (389.8)
11d	4-H_3C	see experimental		
11e	2-Cl	59	257–258° (DMF)	$C_{21}H_{13}Cl_2N_3O_2$ (410.3)
11f	3-Cl	62	203–204° (ethanol)	$C_{21}H_{13}Cl_2N_3O_2$ (410.3)
11g	4-Cl	54	248–250° (ethanol)	$C_{21}H_{13}Cl_2N_3O_2$ (410.3)

[a] Satisfactory microanalyses obtained: C ±0.32, H ±0.31, N ±0.3, Cl ±0.29.

Received: October 11, 1982

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