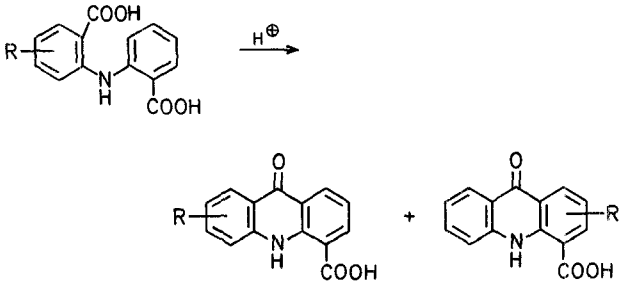
The Synthesis of Substituted 9-Oxoacridan-4-carboxylic Acids; Part 2. The Use of 2-Iodoisophthalic Acid in the Jourdan-Ullmann Reaction

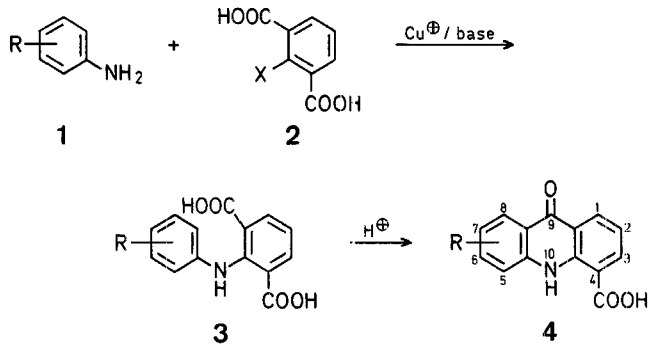
Gordon W. REWCASTLE*, William A. DENNY

Cancer Research Laboratory, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand

Acridones (9-oxoacridans) are important starting materials for the synthesis of a wide range of acridine derivatives. As part of our programme on the study of acridine-based antitumour agents we found a need for a variety of substituted 9-oxoacridan-4-carboxylic acids. The conventional synthesis of acridones involves the initial copper-catalysed coupling of aromatic amines with 2-halobenzoic acids to give an *N*-phenylanthranilic acid (Jourdan-Ullmann reaction), with subsequent acid-catalysed ring closure to the final product. 9-Oxoacridan-4-carboxylic acids can be similarly prepared by use of anthranilic acid as the amine component, but the final ring closure is compromised by the fact that two possible routes are available and thus a mixture of products is often obtained[1].

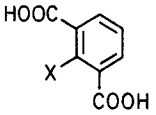


One approach to overcoming the isomer problem is to use a 2-haloisophthalic acid as the acid component.



This approach has received little attention so far[2,3], possibly because of difficulties associated with large-scale synthesis of the halo-diacids. However, the discovery[4] that 2-iodoisophthalic acid (**2c**) is readily available via diazotisation[5] of 2-aminoisophthalic acid prompted us to investigate the use of this particular diacid in the Jourdan-Ullmann reaction.

Initial experiments using aniline with copper(I) chloride as the copper source, potassium carbonate as the proton acceptor, and 2-ethoxyethanol as the solvent gave an appreciable amount of a by-product which was identified by ^{1}H-N.M.R. as 2-(2-ethoxyethoxy)-isophthalic acid[a] (**2e**). Hydrolysis to 2-hydroxyisophthalic acid (**2d**) also occurred, and thus initial yields of 2-(phenylamino)-isophthalic acid (**2f**) were quite low. Replacement of potassium carbonate by anhydrous bases such as *N*-ethylmorpholine reduced the degree of hydrolysis, whilst the use of secondary alcohol solvents eliminated the problem of ether formation. In addition, because of their greater ability to solubilise all of the reactants, dihydroxy solvents such as butane-2,3-diol and hexane-2,5-diol were found to greatly accelerate the rate of the reaction. A direct comparison of the above two diols showed no significant difference in yields and either one could be used successfully as solvent.



2a X = Cl **2d** X = OH
2b X = Br **2e** X = $C_2H_5O-CH_2-CH_2-O-$
2c X = J **2f** X = C_6H_5-NH-

Experiments with the previously used 2-chloro-[2] and 2-bromo-isophthalic[3] acids (**2a** und **2b**) under the same conditions showed no marked differences in the reactivity of these acids, all three giving yields between 84 and 90% for the reaction with aniline. With no real advantage being shown by any particular halo-diacid we chose to use the iodo-acid because of its ready availability in large quantities.

The reaction of iododiacid **2c** with a variety of substituted aniline derivatives (**1**) proceeds cleanly, yields decreasing with the increased size of *ortho* substituents on the aniline, although they are still reasonable even for bulky groups such as bromo and iodo. Electronic effects are more pronounced, with both nitro and carboxy groups markedly depressing the reactivity of the aniline component. In fact, none of the correct product **3** could be isolated from the reaction with either 2-nitroaniline or methyl anthranilate, although the iododiacid was consumed in both cases. The only exception to this pattern of low reactivity occurred with anthranilic acid but this was not unexpected as this compound is known to form a copper complex that markedly increases its reactivity in the Jourdan-Ullmann reaction[6].

Cyclisation of the 2-(phenylamino)-isophthalic acids **3** to the 9-oxoacridan-4-carboxylic acids **4** is performed in polyphosphoric acid at 140°C (1 h). Diacids **3** substituted in the 2- or 4-position of the anilino ring cyclised unequivocally to give the 5- or 7-substituted 9-oxoacridan-4-carboxylic acids respectively, but with diacids substituted in the 3-position there are two available directions of ring closure, and in practice a mixture of both possible isomers was obtained. Generally it is not possible to separate acridone derivatives by chromatographic methods because of their low solubility in most organic solvents, although often the major component can be obtained pure by repeated fractional crystallisation from solvents such as dimethylformamide. We thus obtained clean samples of 6-methoxy-9-oxoacridan-4-carboxylic acid (*para* ring closure) and of 8-nitro-9-oxoacridan-4-carboxylic acid (*ortho* ring closure), respectively, as the major components from the isomer mixtures produced by PPA ring closure of the corresponding 3-substituted phenylaminoisophthalic acids. The addition of another substituent can be used to direct groups to normally unfavourable positions, and thus it was also possible to prepare 8-methoxy-9-oxoacridan-4-carboxylic acid by use of a chloro blocking group which was removed by hydrogenation subsequent to the ring closure.

Table 1. 2-(Phenylamino)-isophthalic Acids (**3**) prepared[a]

R in **1** (and **3**)	Yield[b] [%]	m.p.[c] [°C]	Molecular Formula[d] or m.p. [°C] reported
H	84	247–248°	252–254°[7] (corrected)
2-CH_3	80	247–249°	$C_{15}H_{13}NO_4$ (271.3)
2-C_2H_5	65	237–239°	$C_{16}H_{15}NO_4$ (285.3)
2-C_6H_5	71	257–259°	$C_{20}H_{15}NO_4$ (333.3)
2-OCH_3	78	219–220°	$C_{15}H_{13}NO_5$ (287.3)
2-F	73	230–233°	$C_{14}H_{10}FNO_4$ (275.2)
2-Cl	73	227–229°	$C_{14}H_{10}ClNO_4$ (289.6)
2-Br	65	229–232°	$C_{14}H_{10}BrNO_4$ (336.1)
2-J	56	235–238°	$C_{14}H_{10}JNO_4$ (383.1)
2-COOH	64	258–259°	$C_{15}H_{11}NO_6$ (301.3)
3-OCH_3	78	310–313°	$C_{15}H_{13}NO_5$ (287.3)
3-NO_2	64	235–237°	$C_{14}H_{10}N_2O_6$ (302.2)
4-CH_3	81	207–208°	214–215°[2] (corrected)
4-OCH_3	78	226–228°	$C_{15}H_{13}NO_5$ (287.3)
4-Cl	78	235–237°	$C_{14}H_{10}ClNO_4$ (289.6)
4-NO_2	55	216–218°	$C_{14}H_{10}N_2O_6$[e] (302.2)
4-COOH	52	>360°	$C_{15}H_{11}NO_6$ (301.3)
2,3-di-CH_3	75	226–228°	233–234°[3] (corrected)
2-Cl, 5-OCH_3	60	235–238°	$C_{15}H_{12}ClNO_5$ (321.7)
2,5-di-OCH_3	71	206–208°	$C_{16}H_{15}NO_6$ (317.3)
2,3-benzo (1-napthylamine)	80	>360°	$C_{18}H_{13}NO_4$ (309.3)

[a] Reaction performed in either butane-2,3-diol or hexane-2,5-diol at 120°C for 1–2h. Ratio **1**/**2c** = 1.5/1.

[b] Yield of isolated product based on iodoisophthalic acid. No unreacted acid was recovered and products gave a single spot on T.L.C. analysis.

[c] Uncorrected.

[d] The new compounds gave satisfactory microanalyses: C ±0.38, H ±0.34, N ±0.35. Exceptions: R = 2-CH_3 (C +0.46), R = 2-C_6H_5 (C +0.48), R = 2,3-benzo (H −0.50).

[e] Compound crystallizes with 0.5 H_2O.

[a] ^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 1.13 (t, 3H, J = 9 Hz); 3.49 (q, 2H, J = 9 Hz); 3.68, 4.16 (2t, 2H, J = 7 Hz); 6.75–7.90 ppm (m, 5H).

Table 2. 9-Oxoacridan-4-carboxylic Acids (**4**) prepared

R in **3**	R in **4**	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c] or m.p. [°C] reported
H	H	96	324–325°	325°[6]
2-CH_3	5-CH_3	82	340–342°	315°[e,8], 356–357°[9]
2-C_2H_5	5-C_2H_5	78	338–341°	$C_{16}H_{13}NO_3$ (267.3)
2-C_6H_5	5-C_6H_5	85	341–343°	$C_{20}H_{13}NO_3$ (315.3)
2-OCH_3	5-OCH_3	80	334–336°	335–337°[9]
2-F	5-F	84	300° (sublimes)	$C_{14}H_8FNO_3$ (257.2)
2-Cl	5-Cl	86	352–354°	352°[8]
2-Br	5-Br	88	>360°	$C_{14}H_{18}BrNO_3$ (317.1)
2-J	5-J	82	>360°	$C_{14}H_{18}JNO_3$ (365.1)
2-COOH	5-COOH	77	>360°	$C_{15}H_9NO_5$ (283.2)
3-OCH_3	6-OCH_3	[d]	306–308°	322–324°[10]
3-NO_2	8-NO_2	[d]	330–332°	$C_{14}H_8N_2O_5$ (284.2)
4-CH_3	7-CH_3	85	313–315°	343°[e,8], 325–327°[2] (corrected)
4-OCH_3	7-OCH_3	77	348–350°	$C_{15}H_{11}NO_4$ (269.25)
4-Cl	7-Cl	83	329–330°	$C_{14}H_8ClNO_3$ (273.7)
4-NO_2	7-NO_2	79	350–352°[f]	$C_{14}H_8N_2O_5$ (284.2)
4-COOH	7-COOH	75	>360°	$C_{15}H_9NO_5$ (283.2)
2,3-di-CH_3	5,6-di-CH_3	86	336–339°	342–344°[7] (corrected)
2,5-di-OCH_3	5,8-di-OCH_3	83	313–315°	$C_{16}H_{13}NO_5$[g] (299.3)
2-Cl, 5-OCH_3	5-Cl, 8-OCH_3	77	>360°	$C_{15}H_{10}ClNO_4$[g] (303.7)
2,3-benzo	5,6-benzo	90	357–358°	$C_{18}H_{11}NO_3$[h] (289.3)

[a] Yield of isolated product after recrystallisation from aqueous methanol. Products gave a single spot on T.L.C.
[b] Uncorrected.
[c] The new compounds gave satisfactory microanalyses: C ±0.33, H ±0.22, N ±0.35. Exceptions: R = 7-OCH_3 (C +0.50), R = 5-Cl, 8-OCH_3 (H +0.43).
[d] Isomer mixture obtained. Product shown was isolated after several recrystallisations from methanol.
[e] Melting points from Ref. 8 appear to have been transposed.
[f] This compound is identical in all respects with that obtained in 55% yield by nitration of 9-oxoacridan-4-carboxylic acid with KNO_3 in conc. H_2SO_4.
[g] Compound crystallises with 0.5 H_2O.
[h] Compound crystallises with 0.25 H_2O.

In summary, the reaction of substituted anilines with 2-iodoisophthalic acid proceeds in good yield and provides an excellent unequivocal route to 5- and 7-substituted 9-oxoacridan-4-carboxylic acids. This method is however more restricted as a route to 6- and 8-substituted 9-oxoacridan-4-carboxylic acids; an alternative unequivocal route to these compounds will be published shortly.

2-Iodiosophthalic Acid (2c):
To a solution of 2-aminoisophthalic acid (50 g, 0.28 mol) (prepared by hydrogenation of 2-nitroisophthalic acid[11] with Pd/C) in concentrated sulphuric acid (250 ml) at 0°C is added a solution of sodium nitrite (28.6 g, 0.42 mol) in concentrated sulphuric acid (250 ml) at 0°C. The resulting solution is stirred gently and 85% phosphoric acid (500 ml) is slowly added at a rate designed to maintain the temperature below 10°C. After the addition is complete the mixture is stirred for a further 2 h and urea (30 g) is then added. After being stirred for a further 5 min the mixture is poured into ice (900 g) and the resulting solution is filtered. A solution of potassium iodide (90 g) in water (100 ml) is added and the mixture is heated on a water bath for 30 min before being cooled to 5°C. The solid is collected, washed with sodium disulphite ($Na_2S_2O_5$) solution (200 ml) and water (800 ml), and dried; yield of **2c**: 59 g (73%); m.p. 240–241°C, after recrystallisation from hot water (Ref.[4], m.p. 239–240°C).

2-(Phenylamino)-isophthalic Acid (2f); Typical Procedure:
A mixture of 2-iodoisophthalic acid (**2c**; 2.92 g, 10 mmol) aniline (1.40 g, 15 mmol), copper(I) chloride (1 g), 2,3-butanediol (12 ml), and benzene (10 ml) is heated and stirred in an oil bath at 120°C with the benzene being allowed to boil off. When the internal temperature reaches 100°C *N*-ethylmorpholine (6 ml) is added, and the mixture is stirred for a further 1 h at 120°C before being diluted with 0.5 molar ammonia solution (50 ml) and treated with charcoal. After filtration through Celite (washing well with water), the dark coloured solution is acidified with 2 normal hydrochloric acid and extracted with ethyl acetate (2 × 100 ml). An insoluble inorganic precipitate is removed by filtration through celite and the organic layer is extracted with 0.5 molar ammonia solution (100 ml). The aqueous extract is acidified with concentrated hydrochloric acid to give an oil which rapidly solidifies. The product is collected by filtration, washed with hot water, and dried; yield: 2.15 g, (84%); m.p. 247–248°C, after recrystallisation from aqueous methanol (Ref.[7], m.p. 252–254°C, corrected).

9-Oxoacridan-4-carboxylic Acid (4, R = H); Typical Procedure:
2-(Phenylamino)-isophthalic acid (**2f**; 2.57 g, 10 mmol) is dissolved in polyphosphoric acid (75 g) at 120°C, and the resulting solution is stirred at that temperature for a further 1–2 h when it is poured into boiling water (250 ml). The yellow precipitate is collected by filtration and dissolved in a mixture of methanol (200 ml) and 1 normal sodium hydroxide solution (200 ml). The hot solution is filtered, acidified with glacial acetic acid, concentrated, and cooled, and the product isolated by suction; yield: 2.30 g (96%); m.p. 324–325°C, after recrystallisation from a large volume of methanol (Ref.[6], m.p. 325°C).

8-Methoxy-9-oxoacridan-4-carboxylic Acid (4, R = 8-OCH_3):
A solution of 5-chloro-8-methoxy-9-oxoacridan-4-carboxylic acid (0.7 g, 2.3 mol) in 0.1 normal sodium hydroxide is hydrogenated over 5% palladium on carbon (0.25 g) for 3 h at room temperature. The catalyst is filtered off and the product isolated by precipitation with conc. hydrochloric acid; yield: 0.59 g (95%); m.p. 284–285°C (methanol).

$C_{15}H_{11}NO_4$	calc.	C 66.92	H 4.12	N 5.20
(269.2)	found	66.60	3.90	5.02

We thank the Auckland Division of the Cancer Society of New Zealand and the Medical Research Council of New Zealand for financial support.

Received: March 21, 1984

* Address for correspondence.

[1] Part 1. G.M. Stewart, G.W. Rewcastle, W.A. Denny, *Aust. J. Chem.* **37**, 1939 (1984).
[2] G. Stapleton, A.I. White, *J. Am. Pharm. Sci.* **43**, 193 (1954).
[3] R.A. Scherrer, *German Patent (DBP)* 1188609 (1965), Parke, Davis & Co.; *C.A.* **63**, 1741 (1965).
[4] W.C. Agosta, *Tetrahedron Lett.* **1965**, 2681.
[5] H.A.J. Schoutissen, *J. Am. Chem. Soc.* **55**, 4531 (1933).
[6] J.M.F. Gagan, in: *Acridines*, Vol. 9 of *The Chemistry of Heterocyclic Compounds*, R.M. Acheson, Ed., John Wiley & Sons, New York, 1973, p.163, 250.
[7] T.R. Westby, C.F. Barfknecht, *J. Med. Chem.* **16**, 40 (1973).
[8] K. Soda, K. Nishiide, *Jap. Patent* 69/27388 (1969), Taisho Pharmaceutical Co.; *C.A.* **72**, 32645 (1970).
[9] W.A. Denny, G.J. Atwell, B.C. Baguley, *J. Med. Chem.* **27**, in press (1984).
[10] W.A. Denny, G.J. Atwell, B.C. Baguley, *J. Med. Chem.* **26**, 1619 (1983).
[11] A. Worl, *Ber. Dtsch. Chem. Ges.* **43**, 3480 (1910).