The Synthesis of Substituted 9-Oxoacridan-4-carboxylic Acids; Part 3. The Reaction of Methyl Anthranilates with Diphenyliodonium-2-carboxylates

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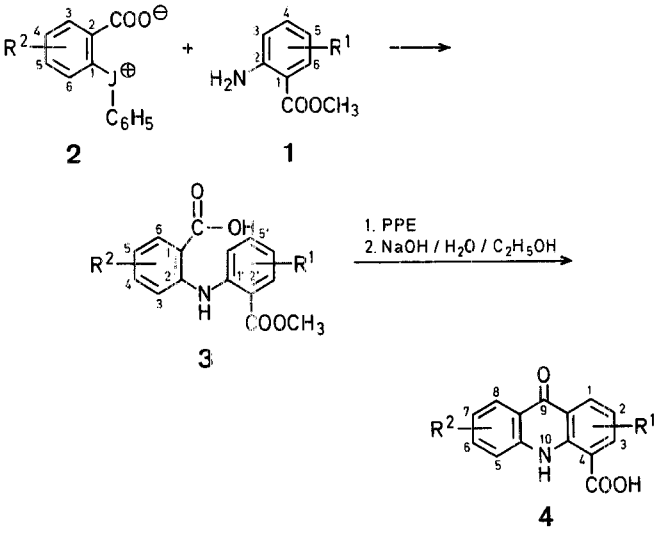
The problem of isomer formation in the ring closure of substituted *N*-(2-carboxyphenyl)-anthranilic acids to 9-oxoacridan-4-carboxylic acids (see Ref.[1,2]) can be overcome by masking one of the two acid groups as its methyl ester[3]. Thus ring closure of substituted 2-(2-methoxycarbonylphenylamino)-benzoic acids (**3**) with polyphosphate ester (PPE)[4] proceeds smoothly to give a single ester product which on either acidic or basic hydrolysis readily furnishes the appropriately substituted 9-oxoacridan-4-carboxylic acid **4**. One route to the diacid monoesters **3** is via a modified anhydrous Jourdan-Ullmann reaction between methyl anthranilate (**1**, R^1 = H) and a substituted 2-chlorobenzoic acid (using an organic base as the proton acceptor)[3]. However, the ester-acids **3** produced by this method are often difficult to obtain pure, and the yields are relatively low (Table 1), so that an improved method was required. A recent report[5] on the synthesis of *o*-substituted benzoic acids by the copper(II)-catalysed reaction of diphenyliodonium-2-carboxylate (**2**, R^2 = H) with anilines and other nucleophiles prompted us to investigate the reactivity of this compound towards methyl anthranilate (**1**, R^1 = H). We found that the reaction proceeds in good yield to a single product (according to T.L.C. and ^{1}H-N.M.R. analysis), and that this product is able to be cyclised directly to the acridone ester without further purification. We also found that the reaction of a variety of substituted methyl anthranilates (**1**) with diphenyliodonium-2-carboxylate (**2**, R^2 = H) affords good yields of the ester-acids **3** in many cases (Table 3). As expected, electron-withdrawing groups (such as nitro) on the benzene ring of the methyl anthranilate retard the reaction whilst electron-donor groups (such as methoxy) accelerate it.

The reaction of a limited number of substituted diphenyliodonium-2-carboxylates (**2**) with methyl anthranilate (**1**, R^1 = H) was also investigated, compounds **2** being prepared from substituted 2-iodobenzoic acids by the standard procedure[5] involving oxidation with potassium persulphate in sulphuric acid and subsequent coupling with benzene (Table 2). The reaction with methyl anthranilate gave reasonable yields of product (Table 3), and it is notable that the presence of a nitro group on the iodonium compound now assists the reaction whereas previously its presence on the anthranilate component reduced it's reactivity.

Ring closure of the ester-diacids **3** is performed using polyphosphoric ethyl ester as previously described[3], to give the methyl esters of the 9-oxoacridan-4-carboxylic acids which are hydrolysed directly to the free acids **4** with a 1 molar solution of sodium hydroxide in 50% aqueous ethanol (Table 4). In two cases involving nitro-containing compounds, however, the product acids are unstable under the basic reaction conditions and different methods of hydrolysis[3,7] are therefore employed (see Table 4, footnotes e and g).



The 9-oxoacridan-4-carboxylic acids (**4**) are obtained as a single isomer, in contrast to the isomeric mixture that is obtained from the cyclisation of the analogous 2-(2-carboxyphenylamino)-benzoic acids[1]. The advantage of this route is that it makes available a variety of 1-, 2-, and 3-substituted 9-oxoacridan-4-carboxylic acids from a single diphenyliodonium-2-carboxylate, thereby complementing our earlier method involving 2-iodoisophthalic acid[2], which is particularly useful for the preparation of 5- and 7-substituted 9-oxoacridan-4-carboxylic acids. The use of substituted diphenyliodonium-2-carboxylates further extends the method to the preparation of 6- and 8-substituted 4-acids, although an obvious limitation is that it is necessary to synthesise each of the derivatives **2** individually.

The methyl anthranilates (**1**) were generally prepared by known procedures:

- esterification of the anthranilic acid with methanol in the presence of 3% sulphuric acid;
- treatment of the corresponding nitroacid sequentially with thionyl chloride and methanol, followed by hydrogenation over 5% palladium on charcoal;

Table 1. 2-(2-Methoxycarbonylphenylamino)-benzoic Acids (**3**, R^1 = H) from Methyl Anthranilate (**1**, R^1 = H) and Substituted 2-Chlorobenzoic Acids[a]

R^2	Yield[b] [%]	m.p.[c] [°C]	Molecular Formula[d] or m.p. [°C] reported
4-NH—CO—CH_3	44	245–248°	$C_{17}H_{16}N_2O_5$ (328.3)
4-Cl	32	221–222°	$C_{15}H_{12}ClNO_4$ (305.7)
4-NO_2	35	243–245°	$C_{15}H_{12}N_2O_6$ (316.3)
5-NO_2	30	228–229°	$C_{15}H_{12}N_2O_6$ (316.3)

[a] For description of the method, see Ref. [3]; ratio 2-chlorobenzoic acid/methyl anthranilate = 1/1.5.
[b] Yield of isolated product based on 2-chlorobenzoic acid.
[c] Uncorrected.
[d] The microanalyses were in satisfactory agreement with the calculated values: C ±0.16, H ±0.19, N ±0.19.

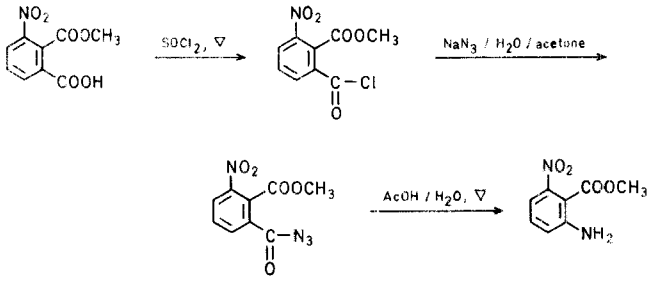
Table 2. Substituted Diphenyliodonium-2-carboxylates (**2**) prepared[a]

R^2	Yield[b] [%]	m.p.[c] [°C]	Molecular Formula[d]
5-NO_2	91	237–238° (dec.)	$C_{13}H_8JNO_4$ (383.1)
3-CH_3	68	199° (dec.)	$C_{14}H_{11}JO_2$ (337.1)
3-Cl	84	187° (dec.)	$C_{13}H_8ClJO_2$ (358.55)

[a] Prepared by oxidation of the 2-iodobenzoic acids with potassium persulphate in sulphuric acid and coupling with benzene (see Ref.[5]).
[b] Yield of isolated product which gave a single spot on T.L.C.
[c] Uncorrected.
[d] The microanalyses were in good agreement with the calculated values: C ±0.19, H ±0.17, J ±0.12.

— reaction of the anthranilic acid with diazomethane in ether.

The only exceptions to the above methods were methyl 6-methoxyanthranilate, which was prepared from methyl 2,6-dinitrobenzoate by the published procedure[6], and methyl 6-nitroanthranilate which was obtained from 2-methoxycarbonyl-3-nitrobenzoic acid via a Curtius rearrangement:



Methyl 2-Amino-6-nitrobenzoate:

A suspension of 2-methoxycarbonyl-3-nitrobenzoic acid[12] (62 g, 0.276 mol) in thionyl chloride (250 ml) is heated under reflux with stirring until all of the solid dissolves, and for a further 15 min. Excess thionyl chloride is removed under vacuum and the residual acid chloride is dissolved in dry acetone (600 ml). The solution is cooled in ice and a solution of sodium azide (70 g, 4 equiv.) in water (250 ml) is added. After a further 15 min, the mixture is diluted with water (800 ml) to precipitate the azide as a white solid which is collected by filtration and washed well with water. The moist solid is dissolved in a mixture of glacial acetic acid (300 ml) and water (100 ml), and the solution is heated to gentle reflux as vigourous gas evolution occurs. After a further 30 min, the orange solution is diluted with water (200 ml) and allowed to cool. The precipitated product is isolated by suction and recrystallised from aqueous methanol; yield: 45.4 g (84%); m.p. 105–107°C (Ref.[13], m.p. 108–110°C, corrected).

Table 3. 2-(2-Methoxycarbonylphenylamino)-benzoic Acids (**3**) from Methyl Anthranilates (**1**) and Diphenyliodonium-2-carboxylates (**2**)[a]

R^1	R^2	Ratio **1/2**	Yield[b] [%]	m.p.[c] [°C]	Molecular Formula[d] or m.p. [°C] reported
H	H	1/1	65	196–198°	$C_{15}H_{13}NO_4$ (271.3)
		1/1.5	81		
5'-CH_3	H	1/1.4	75	173–174°	$C_{16}H_{15}NO_4$ (285.4)
5'-OCH_3	H	1/1.4	84	175–178°	$C_{16}H_{15}NO_5$ (301.3)
5'-Cl	H	1/2.0	59	186–190°	$C_{15}H_{12}ClNO_4$ (305.7)
5'-NO_2	H	1/2.0	61[e]	227–229°	$C_{15}H_{12}N_2O_6$ (316.3)
5'-$COOCH_3$	H	1/1.5	90	198–200°	$C_{17}H_{15}NO_6$ (329.3)
4'-CH_3	H	1/1.3	86	177–178°	$C_{16}H_{15}NO_4$ (258.4)
4'-OCH_3	H	1/1.4	94	211–213°	$C_{16}H_{15}NO_5$ (301.3)
4'-Cl	H	1/2.0	68	200–201°	$C_{15}H_{12}ClNO_4$ (305.7)
4'-NO_2	H	1/2.0	63[e]	234–235°	$C_{15}H_{12}N_2O_6$ (316.3)
4'-$COOCH_3$	H	1/1.5	68	238–239°	$C_{17}H_{15}NO_6$ (329.3)
3'-CH_3	H	1/1.5	91	172–173°	$C_{16}H_{15}NO_4$ (258.4)
3'-OCH	H	1/1.5	95	194–195°	$C_{16}H_{15}NO_5$ (301.3)
3'-Cl	H	1/1.5	86	192–193°	$C_{15}H_{12}ClNO_4$ (305.7)
3'-NO_2	H	1/2.0	82	207–208.5°	$C_{15}H_{12}N_2O_6$ (316.3)
3'-$COOCH_3$	H	1/1.5	97	188–190°	$C_{17}H_{15}NO_6$ (329.3)
H	6-CH_3	1.5/1	55[f]	[g]	$C_{16}H_{18}N_2O_4$ (302.3)
H	6-Cl	1.5/1	54	120–121.5°	$C_{15}H_{12}ClNO_4$ (305.7)
H	4-NO_2	1.5/1	86	243–245°	$C_{15}H_{12}N_2O_6$ (316.3)

[a] Reactions performed in dimethylformamide at 100°C with copper(II) acetate as catalyst.
[b] Yield of isolated product, based on **1**. The crude products **3** gave a single spot on T.L.C.
[c] Uncorrected. The products were recrystallised from benzene/acetone.
[d] The microanalyses showed the following maximum deviations from the calculated values: C ±0.38, H ±0.30, N ±0.35, Cl ±0.15.
[e] Crude product impure. Yield of recrystallised product given.
[f] Oil, compound isolated as relatively insoluble ammonium salt.
[g] Ammonium salt recrystallised from methanol/ethyl acetate, m.p. 154–156°C.

Table 4. 9-Oxoacridan-4-carboxylic Acids (**4**) prepared[a]

Educt **3**		Product **4**		Yield[b] [%]	m.p.[c] [°C]	Molecular Formula[d] or m.p. [°C] reported
R^1	R^2	R^1	R^2			
H	H	H	H	87	324–325°	325°[8]
5'-CH_3	H	1-CH_3	H	100	315–317°	$C_{15}H_{11}NO_3$ (253.25)
5'-OCH_3	H	1-OCH_3	H	92	266–268°	$C_{15}H_{11}NO_4$ (269.25)
5'-Cl	H	1-Cl	H	90	321–323°	>300°[10]
5'-NO_2	H	1-NO_2	H	84	dec. 315°	333°[9]
5'-$COOCH_3$	H	1-COOH	H	87	314–315°	318–320°[1]
4'-CH_3	H	2-CH_3	H	100	334–337°	$C_{15}H_{11}NO_3$ (253.25)
4'-OCH_3	H	2-OCH_3	H	80	335–338°	$C_{15}H_{11}NO_4$ (269.25)
4'-Cl	H	2-Cl	H	87	>360°	$C_{14}H_8ClNO_3$ (273.7)
4'-NO_2	H	2-NO_2	H	83	>360°	$C_{14}H_8N_2O_5$ (284.2)
4'-COOH	H	2-COOH	H	86	>360°	$C_{15}H_9NO_5$ (283.2)
3'-CH_3	H	3-CH_3	H	90	280–283°	$C_{15}H_{11}NO_3$ (253.25)
3'-OCH_3	H	3-OCH_3	H	87	258–260°	$C_{15}H_{11}NO_4$ (269.25)
3'-Cl	H	3-Cl	H	82	280–282°	$C_{14}H_8ClNO_3$ (273.7)
3'-NO_2	H	3-NO_2	H	79[e]	>360°	$C_{14}H_8N_2O_5$ (284.2)
3'-$COOCH_3$	H	3-COOH	H	74	315–316°	$C_{15}H_9NO_5$ (283.2)
H	4-NH—CO—CH_3	H	6-NH_2	91[f]	>360°	$C_{14}H_{10}N_2O_3$ (254.2)
H	4-Cl	H	6-Cl	90	>360°	>360°[9]
H	4-NO_2	H	6-NO_2	98[g]	>360°	>360°[3]
H	5-NO_2	H	7-NO_2	95	>360°	>360°[2]
H	6-CH_3	H	8-CH_3	92	325–330°	$C_{15}H_{11}NO_3$ (253.25)
H	6-Cl	H	8-Cl	92	335–336°	336°[11]

[a] Cyclization performed in PPE. With the exception of the 3-NO_2 and 6-NO_2 compounds, all hydrolyses were performed with a 1 molar solution of sodium hydroxide in ethanol/water (50/50).
[b] Yield after recrystallisation from aqueous ethanol.
[c] Uncorrected.
[d] The microanalyses were in satisfactory agreement with the calculated values: C ±0.27, H ±0.20, N ±0.22.
[e] Cleavage of ester performed with pyridine hydrochloride in boiling pyridine[7].
[f] Crystallises with 1 H_2O.
[g] Cleavage of ester performed with 92% sulphuric acid.

2-(2-Methoxycarbonylphenylamino)-benzoic Acid (3, $R^1 = R^2 = H$); Typical Procedure:

A mixture of methyl anthranilate (**1**, R^1 = H; 1.51 g, 10 mmol), diphenyliodonium-2-carboxylate[5] (**2**, R^2 = H; 3.25 g, 10 mmol), and copper(II) acetate (65 mg) is suspended in dimethylformamide and this suspension is heated in a water bath at 90 °C for 12 h. The solvent is removed under vacuum and the oily green residue is dissolved in ethyl acetate (100 ml). This solution is washed with 0.1 normal hydrochloric acid (100 ml). The organic layer is extracted with 0.1 normal ammonia solution (2 × 50 ml) and the aqueous extract is poured slowly into 0.1 normal hydrochloric acid (200 ml). The precipitated product is isolated by suction and washed well with hot water; yield: 1.72 g (65%); m.p. 196–198 °C (benzene/acetone).

$C_{15}H_{13}NO_3$ (271.3) calc. C 66.40 H 4.83 N 5.16
found 66.47 4.76 5.22

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 3.87 (s, 3H, OCH_3); 5.30–6.20 (m, 2H, NH + OH); 6.90, 7.43, 7.91 ppm (m, $6H_{arom}$).

Reaction of methyl anthranilate with 1.5 equiv. of diphenyliodonium-2-carboxylate gives a product yield of 81% based upon the ester, whilst use of 1.5 equiv. of methyl anthranilate gives a 73% yield based upon the iodonium betain **2**.

9-Oxoacridan-4-carboxylic Acid (4, $R^1 = R^2 = H$); Typical Procedure:

2-(2-Methoxycarbonylphenylamino)-benzoic acid (**3**, $R^1 = R^2$ = H; 1.10 g, 4 mmol) is suspended in a solution of polyphosphoric ethyl ester (PPE; 38 g) in chloroform (50 ml) and the mixture is heated under reflux until all of the solid is dissolved. The reflux condenser is removed and the chloroform is allowed to evaporate to give a red oil which is heated for 1 h in a water bath at 100 °C. The oil is diluted with methanol (5 ml) and water (10 ml) is slowly added to precipitate the *methyl 9-oxoacridan-4-carboxylate* as a yellow solid which is collected and washed with 50% aqueous methanol containing 1% triethylamine (yield of crude product: 0.99 g, 96%). The crude product is suspended in a mixture of ethanol (100 ml) and 2 normal sodium hydroxide solution (100 ml) and heated under reflux for 10 min to give a clear yellow solution which is filtered and acidified with glacial acetic acid. Concentration and cooling gives yellow needles of *9-oxoacridan-4-carboxylic acid*; yield: 0.83 g (87%), m.p. 324–325 °C (Ref.[8]: 325 °C).

Samples for analytical analysis may be further purified by recrystallisation from a large volume of methanol.

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