A New Route to 4-Substituted and 4,5-Disubstituted Acridans

B. Andes Hess, Jr. and Sebastian Corbino

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

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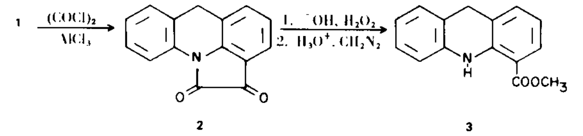
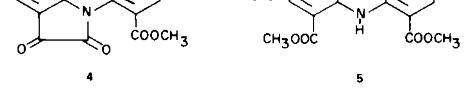
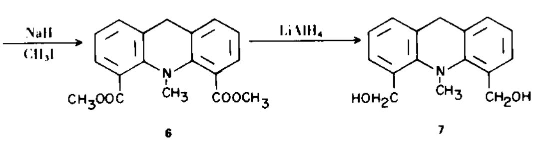
In connection with another study several 4,5-disubstituted acridans were needed. Although a number of substituted acridans had been reported, only one example of a 4,5-disubstituted derivative was known, 4,5-dimethylacridan (1). Since neither this compound nor its method of preparation was of use to us, a new method for the preparation of 4,5-disubstituted acridans was developed. Our synthesis was based on the use of isatin analogs of acridan as intermediates for the introduction of substituents at the positions *ortho* to the nitrogen (2). The stepwise introduction affords 4-substituted as well as 4,5-disubstituted derivatives. A few 4-substituted derivatives of acridan have been reported (3).

Treatment of acridan (**1**) with oxalyl chloride followed by aluminum chloride led to the isatin analog of acridan (**2**) in 88% yield. A basic aqueous solution of **2** was treated with hydrogen peroxide to give a crude acid which, when treated with diazomethane, gave 4-carbomethoxyacridan (**3**) in 78% over-all yield from acridan. Repetition of the above sequence produced the isatin **4** in 52% yield and 4,5-dicarbomethoxy acridan (**5**) in 29% yeild. Methylation of **5** with sodium hydride and methyl iodide gave *N*-methyl-4,5-dicarbomethoxyacridan (**6**) in 76% yield. Reduction of **6** with lithium aluminum hydride gave *N*-methyl-4,5-bishydroxymethylacridan (**7**) in 91% yield.

The above procedure has the potential of producing a number of 4,5-disubstituted derivatives of acridan with either the same two substituents, or different substituents at the four and five positions. The ease of preparation of **3** affords a simple route to a large number of 4-substituted acridans.







EXPERIMENTAL

Isatin Analog of Acridan (**2**).

A solution of 25 g. (0.138 mole) of acridan in 150 ml. of tetrahydrofuran was added over 30 minutes to a refluxing solution of 22 ml. of oxalyl chloride in 100 ml. of tetrahydrofuran. The reaction mixture was refluxed for 3½ hours after addition was completed, then the tetrahydrofuran and oxalyl chloride were removed under reduced pressure. The residue, a dark green oil which solidified on standing overnight, was dissolved in 800 ml. of carbon disulfide and refluxed. To this refluxing solution, 35 g. (0.265 mole) of aluminum chloride was added in 2 g. portions over 5 hours with stirring. Refluxing and stirring were continued for an additional 18 hours. After decantation of the solvent, the residue, cooled by an ice bath, was treated with 150 ml. of concentrated hydrochloric acid followed by 150 ml. of water. To the stirred mixture, 700 ml. of chloroform was added, and the phases were separated. The dark organic layer was washed with 300 ml. of water, dried over sodium sulfate, and evaporated to give 29.6 g. (88%) of crude red isatin analog. A small portion of the compound was chromatographed on silica gel with benzene and recrystallized twice from ethanol to give red crystals, m.p. 220-221°; uv max (absolute ethanol) 261 (17,000), 288 (sh) (9,200); vis. max (absolute ethanol) 419 (583); ir (chloroform) 1749 cm^{-1} (C=O); nmr (deuteriochloroform) τ 2.45-3.08 (m, 7, aromatic), τ 5.95 (s, 2, $-CH_2-$).

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.59; H, 3.85; N, 5.96. Found: C, 76.54; H, 4.04; N, 6.11.

4-Carbomethoxyacridan (**3**).

Twenty-nine g. (0.123 mole) of the crude isatin was dissolved in a solution of 40 g. of sodium hydroxide in 400 ml. of water. The solution was stirred for 1 hour. One liter of water was added, and stirring was continued for 1 additional hour. Over 30 minutes 33 ml. of 30% hydrogen peroxide in 330 ml. of water was added to the stirred solution. Stirring was continued for 2 hours while the solution was maintained at room temperature during that time. After acidification with concentrated hydrochloric acid, the resulting slurry was filtered by suction. The solid was washed with a small amount of cold absolute ethanol and dried to give 25.5 g. of crude greenish-yellow acid. The acid was slurried in 1000 ml. of ether, and excess diazomethane was added at 0°. The reaction mixture was stirred for 15 minutes and excess acetic acid added. The ether solution was washed with 100 ml. of water, 1 *N* sodium bicarbonate solution, and finally 100 ml. of water. The ether solution was dried and evaporation gave 27.1 g. (98%) of a red-orange solid. The crude ester was recrystallized from absolute methanol to give 13.4 g. of orange needles. A second crop of 5.1 g. was obtained. The mother liquor was evaporated to dryness and the residue was chromatographed on 150 g. of silica gel with benzene to give 4.5 g. of ester. The total purified yield was 23.0 g. (85%). A small portion of the first crop was recrystallized twice from methanol and sublimed to give yellow crystals, m.p. 129-131°; uv max (absolute ethanol) 218 (sh) (14,100), 284 (9,120), 368 (2,820); ir (chloroform) 3360 cm^{-1} (N–H), 1690 cm^{-1} (C=O); nmr (deuteriochloroform) τ 0.19 (broad s, 1, –N*H*), τ 2.26 (d, 1, proton *ortho* to ester, J = 8), τ 2.72-3.43 (general absorption, 6, aromatic), τ 5.97 (s, 2, –C*H*$_2$–), τ 6.13 (s, 3, OC*H*$_3$).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.10; H, 5.49; N, 6.01.

Isatin Analog of 4-Carbomethoxyacridan (**4**).

Twenty-two g. (0.092 mole) of 4-carbomethoxyacridan in 1000 ml. of ether was added over a 1 hour period with stirring to a refluxing solution of 40 ml. of oxalyl chloride in 200 ml. of ether. The stirred solution was refluxed for an additional 5 hours. The ether and oxalyl chloride were removed by evaporation at 60°/20 mm. The green solid was dissolved in 700 ml. of carbon disulfide and the solution heated to reflux. The reaction mixture was stirred while 32 g. of aluminum chloride was added in small portions over 4 hours. After stirring for an additional 15 hours, the reaction mixture was cooled. The carbon disulfide was decanted through glass wool, and the residue was thoroughly cooled in an ice bath. One-hundred-fifty ml. of concentrated hydrochloric acid at 0° was added, followed by 150 ml. of ice water. To the stirred mixture, 700 ml. of chloroform was added. The layers were separated and the organic phase was washed with 150 ml. of water and dried over sodium sulfate. Evaporation of the chloroform yielded 14 g. of crude isatin derivative (52%). A small portion of the isatin was chromatographed on silica gel with benzene and recrystallized twice from ethanol to give dark red needles, m.p. 212-213°; uv max (absolute ethanol) 255 (14,850), 283 (sh) (4,110), 355 (3,140); vis. max (chloroform) 435 (310); ir (chloroform) 1700 cm^{-1} (C=O), 1735 cm^{-1} (C=O); nmr (deuteriochloroform) τ 2.29-2.89 (general absorption, 6, aromatic), τ 5.74 (broad s, 2, –C*H*$_2$–), τ 6.09 (s, 3, –OC*H*$_3$).

Anal. Calcd. for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78. Found: C, 69.47; H, 3.91; N, 4.82.

4,5-Dicarbomethoxyacridan (**5**).

To a solution of 30 g. of sodium hydroxide in 300 ml. of water was added 13.5 g. (0.046 mole) of crude powdered isatin. The mixture was stirred for 30 minutes and diluted to a total volume of 500 ml. To the stirred solution, 16 ml. of 30% hydrogen peroxide in 150 ml. of water was added over 2 hours at 28°. The solution was acidified with concentrated hydrochloric acid and the resultant light green precipitate was collected by suction filtration, washed with 300 ml. of water followed by 25 ml. of cold ethanol, and dried to give 7.2 g. of crude acid. A slurry of the crude acid in 400 ml. ether at 0° was treated with excess diazomethane. After stirring for 15 minutes, the solution was treated with excess acetic acid and washed with water, 1 *N* sodium bicarbonate solution, 1 *N* sodium bisulfite solution, and water. The ether layer was dried over sodium sulfate and the ether evaporated to give 6.1 g. of light green solid. The crude diester was chromatographed on 130 g. of silica gel with benzene to give 4.4 g. of cream colored solid, m.p. 142-145°. Recrystallization from methanol gave 3.4 g. of pale yellow-green needles, m.p. 145-147°; a second crop of 0.6 g. of needles, m.p. 145-148°; The total yield of purified diester was 4.0 g. (29%). A small portion of the diester was recrystallized from methanol giving pale yellow needles, m.p. 147-148°; uv max (absolute ethanol) 221 (27,600), 238 (sh) (12,750), 286 (6,240), 361 (13,050); ir (chloroform) 3385 cm^{-1} (N–H), 1700 cm^{-1} (C=O); nmr (deuteriochloroform) τ -1.94 (broad s, 1, N*H*), τ 2.20 (d of d, 2, protons *ortho* to ester, J = 7.5, J = 1.5), τ 2.87 (d, 2, protons *para* to ester, J = 6.5), τ 3.25 (t, 2, protons *meta* to ester), τ 6.00 (s, 2, –C*H*$_2$–), τ 6.06 (s, 6, OC*H*$_3$), mass spectra (parent, 297).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.04; N, 4.71. Found: C, 68.76; H, 5.02; N, 4.58.

N-Methyl-4,5-dicarbomethoxyacridan (**6**).

To a stirred solution of 3.7 g. (12.4 mmole) of the pure diester in 300 ml. of dry dioxane, 2.5 g. of 50% sodium hydride dispersion was added. Stirring was continued for 30 minutes under positive nitrogen atmosphere. To this mixture 100 ml. of methyl iodide was added, and the reaction mixture was refluxed with stirring for 30 hours. The reaction mixture was cooled to 0° and 250 ml. of water was added. The phases were separated and the aqueous phase extracted with 150 ml. of ether. The organic portions were combined, dried over sodium sulfate, and evaporated to give 3.5 g. of a cream colored solid. The crude product was chromatographed on 100 g. of silica gel with 1:1 benzene-hexane mixture to give 3.08 g. of a cream colored oil. Crystallization from hexane gave 2.93 g. (76%) of light yellow crystals. A small portion of the material was recrystallized once from hexane to give pale yellow crystals, m.p. 136-137°; uv max (absolute ethanol) 226 (sh) (19,310), 284 (7,480), 324 (10,300); ir (chloroform) 1717 cm^{-1} (C=O); nmr (deuteriochloroform) τ 2.35-3.21 (general absorption, 6, aromatic protons), τ 6.01 (s, 6, –OC*H*$_3$), τ 6.10 (s, 2, –C*H*$_2$–), τ 6.75 (s, 3, N–C*H*$_3$).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.28; H, 5.53; N, 4.61.

N-Methyl-4,5-bishydroxymethylacridan (**7**).

A solution of 2.8 g. (11 mmoles) of the above diester and 300 ml. of ether was added dropwise to a slurry of 2 g. of lithium aluminum hydride in 180 ml. of ether over 30 minutes. After the reaction mixture was refluxed for one additional hour, it was cooled and water was added. The ether was decanted, dried over sodium sulfate, and evaporated to give 2.1 g. (91%) of a cream colored oil. A small portion of the oil was crystallized twice from benzene to give colorless rhomboids, m.p. 131-132°; uv max (absolute ethanol) 217 (19,600), 246 (6,000); ir (chloroform) 3461 cm^{-1} (O–H); nmr (deuteriochloroform) τ 2.75-3.09 (m, 6, aromatic), τ 5.38 (ABq, 4, –C*H*$_2$–OH), τ 5.59 (s, 2, –O*H*), τ 6.20 (ABq, 2, –C*H*$_2$–), τ 7.08 (s, 3, N–C*H*$_3$).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.49; H, 6.76; N, 5.29.

REFERENCES

(1) A. Albert and J. B. Willis, *J. Soc. Chem. Ind.*, 65, 26 (1946).

(2) B. A. Hess, Jr. and V. Boekelheide, *J. Am. Chem. Soc.*, 91, 1672 (1969).

(3a) G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1751 (1924); (b) R. A. Reed, *ibid.*, 679 (1944); (c) E. Ziegler and T. Kappe, *Monatsh. Chem.*, 94, 736 (1963).