

## Synthesis of Isoacronycine and its Pyranone Analog

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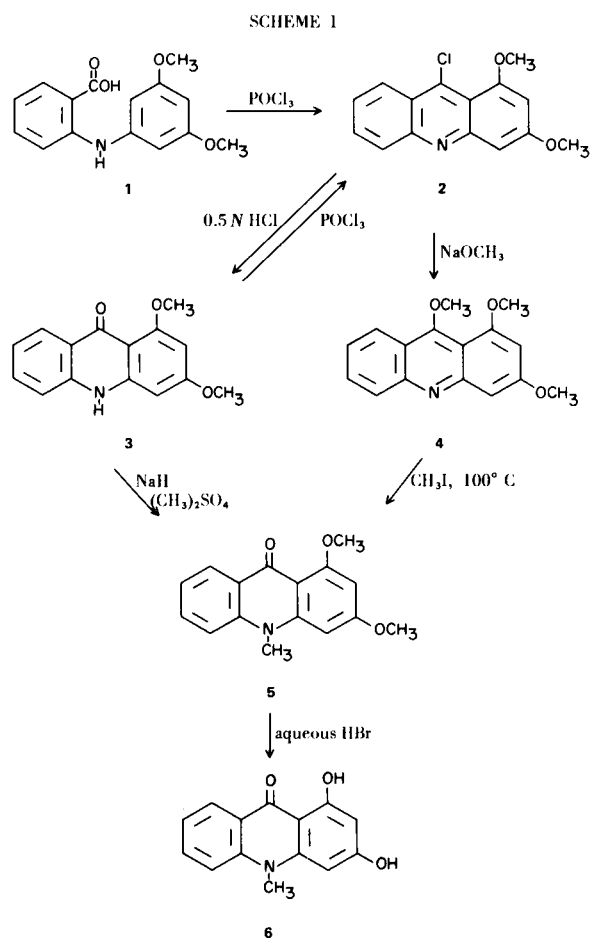
The Pechmann condensation of malic acid with 1,3-dihydroxy-10-methyl-9-acridanone (**6**), performed during the search for a synthetic approach to 5-methoxy-2,2,11-trimethyl-2*H*-pyrano[2,3-*b*]acridan-6-one (isoacronycine, **11a**), afforded 5-hydroxy-11-methyl-2*H*-pyrano[2,3-*b*]acridan-2,6-dione (**7**). This is the first example of a new heterocyclic ring system in which an acridanone and a pyranone ring have been fused. Compound **7** served as the intermediate for the preparation of **11a** and was readily converted into the pyranone analog **9** of isoacronycine by known procedures. Spectral and chemical evidence distinguishing **11a** from acronycine (**12a**) is presented.

Acronycine (**12a**) was isolated from the bark of *Acronychia baueri* Schott, a species of tree indigenous to the tropical rain forests of Queensland. It is related to the alkaloids melicopine, melicopidine and melicopicine, all of which belong to the natural order *Rutacea* (2). Structural degradation studies (3-5) did not distinguish between the linear structure **11a** and the angular structure **12a**. Acheson (6) proposed an unambiguous synthesis of either methyl 1,3-dimethoxy-10-methyl-9-oxoacridan-2-carboxylate (**16**, Scheme III) or its 4-carboxylate isomer would resolve this problem. Macdonald and Robertson (7) synthesized **16** and found discrepancies in physical and spectral properties with those of the methyl ester actually obtained as a degradation product of acronycine. They concluded acronycine should have the angular structure **12a**. Govindachari *et al.*, (8) independently arrived at the same conclusion based on an elegant nmr analysis on a derivative of nor-acronycine (**12b**). The problem was solved by the unambiguous total synthesis of **12a** by Beck and coworkers (9), their product being identical to the natural alkaloid. Among the acridine derivatives found to suppress neoplasms, **12a** possessed the broadest antitumor activity (10).

We wish to report the synthesis of 5-hydroxy-11-methyl-2*H*-pyrano[2,3-*b*]acridan-2,6-dione (**7**) and its conversion into the once controversial linear structure, 5-methoxy-2,2,11-trimethyl-2*H*-pyrano[2,3-*b*]acridan-6-one (isoacronycine, **11a**) and its pyranone analog **9**. Compound **7** and **9** are of interest not only for their potential biological activity but also as the first representatives of a new class of heterocyclic compound containing an acridanone ring fused to a pyranone ring.

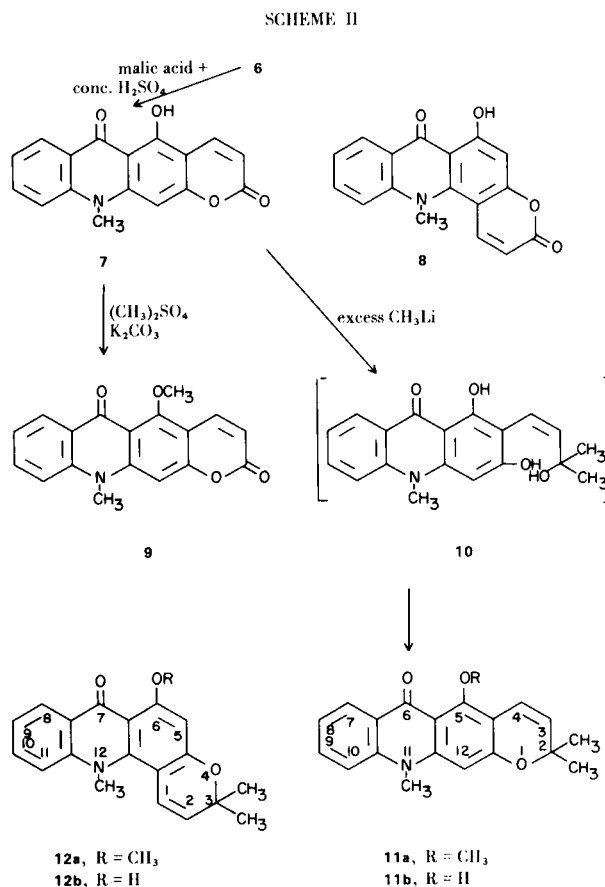
Our synthetic approach involved the use of classical methods to secure coumarin ring systems, selecting appropriately substituted 1,3-dimethoxy-10-methyl-9-acridanone (**5**, Scheme I) and its dihydroxy analog **6** as starting

materials. In the course of preparing these acridanones by conventional methods, a discrepancy was found in the literature concerning the product resulting from cyclization of 3',5'-dimethoxydiphenylamine-2-carboxylic acid (**1**) (**3**). Several sources (3,11,12) report the product to be **3**.



We found the product, m.p. 162°, is actually 9-chloro-1,3-dimethoxyacridine (**2**) which had to be hydrolyzed with dilute hydrochloric acid (**13**) to obtain **3**. The latter compound had completely different physical properties from those reported previously and was reconverted to **2** in nearly quantitative yield (*Cf.* Experimental). Both compounds **2** and **3** were converted to **5** by two different procedures. While the method of Lehmstedt (14) converted **2** into **5** via 1,3,9-trimethoxyacridine (**4**), attempts to methylate the 10-position of **3** with dimethyl sulfate in methanolic potassium hydroxide repeatedly failed. Quantitative conversion into **5** was accomplished by treating **3** with sodium hydride in dry tetrahydrofuran, the resultant anion being readily methylated by dimethyl sulfate. Treatment of **5** with aqueous hydrobromic acid gave 1,3-dihydroxy-10-methyl-9-acridanone (**6**).

Synthesis of **7** by a Perkin reaction with acetic anhydride required formylation of **6** at the 2-position. A Vilsmeier reaction on **5**, known to proceed with ease on phenol ethers (15), or Gatterman and Reimer-Tiemann reactions applied to the more reactive **6** (16) afforded only starting material or intractable tars. Since Pechmann (17) reported the synthesis of Umbelliferone, his condensation reaction has been applied to a variety of phenolic compounds to prepare coumarins (18). However, this condensation has not been applied to hydroxyacridanones. We condensed **6** with malic acid in concentrated sulfuric acid and obtained a product whose structure was either **7** or **8** (Scheme II). Compound **7** (or **8**) was insoluble in aqueous alkali (19), being isolated in 40% yield. An nmr spectral analysis (100 MHz, trifluoroacetic acid) gave inconclusive results for distinguishing between isomers **7** and **8**. Likewise, Macdonald and Robertson (7) stated the chemical



shifts for aromatic protons at 2- and 4-positions of **5** were so close that one could not differentiate between the linear and angular structures proposed for acronycine.

Beck and coworkers (9a) found methylolithium did not

TABLE I

## Nuclear Magnetic Resonance Spectra (a)

Compound <b>11b</b>	Noracronycine( <b>12b</b> ) (b)	Compound <b>11a</b>	Acronycine( <b>12a</b> )	Assignment
1.48 (c)	1.49	1.51	1.50	s(6H) C(CH <sub>3</sub> ) <sub>2</sub> (d)
3.65	3.79	3.77	3.77	s(3H) NCH <sub>3</sub>
—	—	4.11	3.97	s(3H) OCH <sub>3</sub>
5.49(H <sub>3</sub> H <sub>4</sub> ) (e)	5.41(H <sub>1</sub> H <sub>2</sub> )	5.86 (e)	5.46 (e)	d(1H)vinyllic (f)
6.18(H <sub>12</sub> )	6.14(H <sub>5</sub> )	6.83	6.28	s(1H)aromatic
6.75(H <sub>3</sub> H <sub>4</sub> )	6.45(H <sub>1</sub> H <sub>2</sub> )	7.09	6.48	d(1H)vinyllic (f)
7.40(H <sub>10-8</sub> )	7.35(H <sub>11-9</sub> )	7.25-7.90	6.90-7.60	m(3H)aromatic
8.35(H <sub>7</sub> )	8.17(H <sub>8</sub> )	8.75	8.53	m(1H)aromatic

(a) Spectra determined in deuteriochloroform with tetramethylsilane as an internal reference at 60 MHz on a Varian A60 spectrophotometer. (b) Taken from reference 8. (c) Chemical shifts are in ppm ( $\delta$ ) downfield from tetramethylsilane. (d) s = singlet, d = doublet and m = multiplet. (e) Symbols (H<sub>n</sub>) refer to protons as shown in formulas **11a**, **11b**, **12a** and **12b**. Proton assignment for **11a** is the same as for **11b**, and for acronycine the same as for noracronycine. (f) J = 9.5 Hz. The vinyl protons could not be separately assigned.

TABLE II

Ultraviolet Spectra (a)

Compound <b>11b</b>	Noracronycine( <b>12b</b> ) (b)	Compound <b>11a</b>	Acronycine( <b>12a</b> ) (b)
$\lambda$ max (log $\epsilon$ )	$\lambda$ max (log $\epsilon$ )	$\lambda$ max (log $\epsilon$ )	$\lambda$ max (log $\epsilon$ )
250 <sup>c</sup> (4.31)	255(4.50)	225(4.31)	225(4.21)
291-3(4.75)	285(4.75)	285-290(4.76)	280(4.58)
302(4.81)	293(4.69)	300(4.71)	293(4.54)
324-330(3.96) ( <i>d</i> )	305-310(4.41)	320(3.99)	3-5-310(4.23)
410(3.64)	410-415(3.79)	400(3.99)	395(3.82)

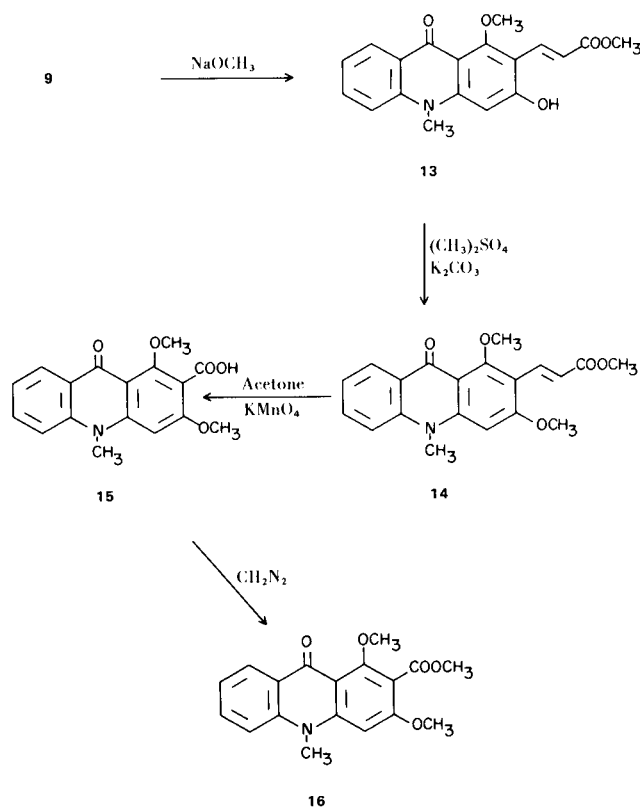
(a) Determined in 95% ethanol on a Bausch and Lomb Spectronic 505. (b) Taken from reference 8. (c)  $\lambda$  max are recorded in nm scale. (d) Inflections are indicated by numerals printed in italics.

attack the carbonyl function in acridanones but selectively converted side chain ester carbonyl groups into tertiary carbinols. Treatment of our condensation product (**7** or **8**), suspended in tetrahydrofuran, with excess methyl-lithium yielded a dark tar. Column chromatography gave an eluate containing a single component with a larger  $R_f$  value than the major component in the crude tar. Though we suspected the major component of the crude tar to be a tertiary carbinol, *e.g.* **10**, which dehydrated on the silica gel column to yield **11b**, no further physical or chemical methods were employed to substantiate this intermediate. The product isolated from the eluate, however, was insoluble in aqueous alkali, gave a positive ferric chloride test and melted at 198.5-199.5°. Its infrared spectrum showed bands at 1626, and 1592 and 1563  $\text{cm}^{-1}$ . An nmr analysis showed chemical shifts (Table I) almost identical to those reported for noracronycine (**12b**) (8). Except for differences in the ultraviolet spectrum (Table II) we would have reported a synthesis of **12b** and claimed isomer **8** as the condensation product. Examination of the data in Table I clearly shows the information was inconclusive for distinguishing between **11b** and noracronycine (**12b**). It was a very peculiar result that these isomers **11b** and **12b** should have the same physical constants and spectral properties. Methylation of the dimethylpyran (**11b**) with dimethylsulfate and potassium carbonate in acetone gave pale yellow needles, m.p. 162.5-164°, tlc  $R_f = 0.63$  compared to an authentic sample of acronycine (**20**) m.p. 176-177°, tlc  $R_f = 0.40$ . Spectral comparisons of **11a** and acronycine (**12a**) showed substantial differences (Table I, II). Particularly noticeable was the considerable downfield shift of the aromatic proton at the 12-position of **11a** from the chemical shift for the proton at the 5-position of **12a**. This observation is in direct contrast to the prediction made by Macdonald and Robertson (7) concerning the proximity of such chemical shifts in compounds **11a** and **12a** (*vide supra*). One such downfield absorption of the

4-proton was recently reported (21).

The pyranone analog **9** was obtained from **7** by known methods and employed in the proof of the structure **11a**. The double bond in the dimethylpyran ring in **12a** and **12b** was reported (5) cleaved by neutral permanganate leaving the acridanone ring intact. However, this method did not oxidize **9**, only starting material was recovered. Since  $\alpha$ ,  $\beta$ -unsaturated esters are readily attacked under mild conditions with permanganate (22), the pyranone ring in **9** was

SCHEME III



opened with sodium methoxide to afford the soluble phenol ester **13** (Scheme III) which was prevented from recycling to the lactone on acidification should the ring have opened to the *cis*-carboxylic acid. Compound **13** was soluble in aqueous alkali, gave a positive ferric chloride test and its structure was supported by spectral analysis. The nmr spectrum clearly showed an AX quartet for the *trans* coupling vinylic protons ( $J = 16$  Hz) in good agreement with reported values (23). Etherification of **13** by known methods gave **14** which was oxidized to **15** by neutral permanganate in acetone. Esterification of **15** with diazomethane quantitatively yielded the known compound **16** (7). It was identical with an authentic sample (24) (mixture melting point, nmr, infrared, ultraviolet spectra and tlc).

#### EXPERIMENTAL

All melting points were determined on a Meltemp melting point apparatus and are uncorrected. Combustion analyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, Elbach, Germany and by Schwarzkopf Microanalytical Laboratories, Woodside N. Y. Infrared spectra were measured on a Beckman IR-9 Spectrophotometer. Nuclear magnetic resonance spectral determinations were obtained on a Varian A-60 Spectrophotometer, the results reported in ppm ( $\delta$ ) downfield from a tetramethylsilane internal standard. Ultraviolet spectra were obtained on Bausch and Lomb Spectronic 505.

##### 9-Chloro-1,3-dimethoxyacridine (**2**).

A mixture of 127.7 g. (0.5 mole) of 3',5'-dimethoxydiphenylamine-2-carboxylic acid (**1**) in 950 ml. of phosphorus oxychloride was refluxed two hours with stirring. The excess phosphorus oxychloride was distilled under reduced pressure from the deep scarlet solution and the thick residue diluted with cold chloroform (1 liter). This solution was slowly added with vigorous stirring to cold ammonia water and stirred an additional 3 hours. The chloroform layer was separated and the aqueous alkaline solution further extracted with 1.5 liter of chloroform. The combined chloroform extracts were dried (magnesium sulfate), filtered through a short column of neutral alumina (Woelm) and the resulting green-yellow filtrate evaporated to dryness. Recrystallization from aqueous ethanol afforded 89.6 g. (65.6%) of bright yellow needles, m.p. 161.5-162°; ir (0.5% potassium bromide), 2941, 1626, 1610, 1099, 950  $\text{cm}^{-1}$ ; uv (95% ethanol),  $\lambda$  max nm (log  $\epsilon$ ) 243(5.81), 270(6.22), 358 (4.52), 210(4.47); nmr (deuteriochloroform),  $\delta$  3.87 (s, 6H, OCH<sub>3</sub>), 6.30(d, 1H,  $J_m = 2$  Hz) and 6.84(d, 1H,  $J_m = 2$  Hz) for protons at the 2- and 4-positions, 7.2-8.5 (m, 4H, aromatic protons at 5,6,7 and 8-positions).

*Anal.* Calcd. for C<sub>15</sub>H<sub>12</sub>ClNO<sub>2</sub>: C, 65.81; H, 4.42; Cl, 12.96; N, 5.11. Found: C, 65.71; H, 4.38; Cl, 13.12; N, 4.94.

##### 1,3-Dimethoxy-9-acridanone (**3**).

The initially pink solution became pale orange when a mixture of 89.6 g. (0.33 mole) of **2** in 1.5 liter of 0.5 *N* hydrochloric acid was refluxed for 1.5 hours. After cooling to room temperature, the solution was filtered and made alkaline (pH 9) with 2.5 *N* aqueous sodium hydroxide. The resulting yellow mass was recrystallized from aqueous ethanol (water:ethanol, 1:2) to yield 77.2 g. (90.8%) of fine yellow needles, m.p. 258-259.6°; ir (0.5% potassium bromide), 3401, 3125, 1600, 1534sh, 1099, 1055, 952

$\text{cm}^{-1}$ ; uv (95% ethanol),  $\lambda$  max nm(log  $\epsilon$ ) 223(5.28), 256(5.77), 265(5.78), 378(4.84); nmr (DMSO- $d_6$ )  $\delta$  3.80(s, 6H, OCH<sub>3</sub>), 6.16(d, 1H,  $J_m = 2$  Hz) and 6.34(d, 1H,  $J_m = 2$  Hz) for protons at the 2- and 4-positions, 6.83-7.51 (m, 3H, aromatic protons at 5,6 and 7-positions), 8.00 (quartet, 1H,  $J_m = 2$  Hz,  $J_o = 8$  Hz). This resonance is particularly significant since it is *peri* to the carbonyl at the 9-position, appearing downfield coupled to its *ortho* and *meta* protons (25), 11.17 (s, 1H, = NH).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO<sub>3</sub>: C, 70.57; H, 5.13; N, 5.48; OCH<sub>3</sub> 24.31. Found: C, 70.75; H, 5.04; N, 5.61; OCH<sub>3</sub>, 23.83.

Conversion of 1,3-Dimethoxy-9-acridanone into 9-Chloro-1,3-dimethoxyacridine.

A mixture of 0.789 g. (0.0031 mole) of **3** and 35 ml. of phosphorus oxychloride was refluxed for 60 minutes and purified by the same method as described above to obtain 0.840 g. (99%). Infrared, mixture melting point and tlc were identical to those of **2**.

##### 1,3-Dimethoxy-10-methyl-9-acridanone (**5**).

###### Procedure A.

In a 1 liter round bottom flask, 12.0 g. (0.28 mole) of sodium hydride mineral oil dispersion (56%) was stirred into 600 ml. of dry tetrahydrofuran. Finely powdered **3** (40.5 g., 0.16 mole) was then added slowly. When the initial vigorous evolution of hydrogen ceased, the mixture was gently refluxed for 60 minutes. By this time, an intense yellow suspension resulted. After cooling to room temperature, 20 ml. (0.22 mole) of dimethylsulfate, diluted in 100 ml. of tetrahydrofuran, was added with vigorous stirring. The mixture was refluxed for 3.5 hours. The excess tetrahydrofuran was evaporated at reduced pressure, and the resulting residue suspended in 500 ml. of water. The copious light yellow precipitate was collected, washed with water and then dissolved in chloroform. The solution was dried (magnesium sulfate), filtered and evaporated to ca. 150 ml. Addition of petroleum ether (b.p. 30-60°) gave colorless needles (41.5 g., 97%), m.p. 160-161° (lit. (3) 161-163°); ir (nujol) 1634, 1600, 1560, 1550sh, 1497  $\text{cm}^{-1}$  (lit. (26) 1634, 1600, 1561, 1545sh, 1505  $\text{cm}^{-1}$ ); nmr (deuteriochloroform),  $\delta$  3.50, 3.73, 3.81 (each s, 3H, NCH<sub>3</sub>, OCH<sub>3</sub>), 6.07 (two doublets, 2H,  $J_m = 2$  Hz, aromatic protons at 2- and 4-positions), 6.8-7.9 (m, 3H, aromatic protons at 5,6 and 7-positions), 8.25 (d, 1H, aromatic proton at 8-position,  $J_o = 8$  Hz).

*Anal.* Calcd. for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>: C, 71.36; H, 5.58; N, 5.20. Found: C, 71.68; H, 5.60; N, 5.24.

Picrate, m.p. 202-204° (lit. (27) 203-204°).

*Anal.* Calcd. for C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>10</sub>: C, 53.01; H, 3.64; N, 11.24. Found: C, 52.86; H, 3.72; N, 10.98.

###### Procedure B.

A solution of 1.0 g. (0.0039 mole) of **2** in 20 ml. of dry methanol containing 1.5 g. of sodium was refluxed for 90 minutes. After elimination of the solvent, the yellow brown residue was treated with cold water, then extracted with chloroform. The combined extracts were dried (magnesium sulfate), filtered and evaporated to yield yellow solids (**4**), which were treated with 20 ml. of methyl iodide and heated for 2 hours on a steam bath in a pressure bottle. The light yellow solids obtained by elimination of the excess methyl iodide were recrystallized from chloroform and petroleum ether (b.p. 30-60°), to yield colorless needles (0.85 g., 81%), which were identical to the compound obtained in the procedure A.

1,3-Dihydroxy-10-methyl-9-acridanone (**6**).

The cleavage of the dimethoxy groups of **5** (100 g., 0.371 mole) with 1175 ml. of hydrobromic acid (48%) according to the procedure of Drummond and Lahey (3) afforded 79.3 g. (100%) of crude **6**, m.p. sinters at 289°, 292.5-295° dec. (lit. (3) m.p. sinters at 270°, 286-289° dec.).

5-Hydroxy-11-methyl-2H-pyrano[2,3-b]acridan-2,6-dione (**7**).

A stirred mixture of 2.5 g. (0.019 mole) of *dl*-malic acid and 3.8 g. (0.018 mole) of **6** in 17 ml. of concentrated sulfuric acid was heated at 115-120° (oil bath temperature) for 20 minutes. After an initial evolution of gas, the mixture gave a crimson colored solution. The cooled solution was poured into 300 ml. of ice water and the green-yellow precipitate formed was filtered and washed with water. The precipitate was suspended in 300 ml. of cold water and aqueous sodium hydroxide added to render a pH of 9. After stirring an additional 15 minutes, the solution was exhaustively extracted with chloroform. The combined extracts were dried (magnesium sulfate) and evaporated to dryness, the residue being redissolved in hot 1,4-dioxane which upon cooling gave fine yellow orange needles (2.1 g., 40%), m.p. 310-317° dec.; ir (0.5% potassium bromide) 1765, 1650, 1629sh, 1616, 1566, 1495, 1453, 1136, 909, 813, 768, 755 cm<sup>-1</sup>; uv (chloroform),  $\lambda$  max nm (log e) 266 (4.56), 317 (4.60), 367 (4.44), 397sh (4.08), 412 inf. (4.05); nmr (F<sub>3</sub>CCO<sub>2</sub>H)  $\delta$  4.05 (s, 3H, NCH<sub>3</sub>), 6.99 (s, 1H, aromatic 12-position), 6.04 (d, 1H, J = 10 Hz) and 8.37 (d, 1H, J = 10 Hz) assigned to protons at 3- and 4-positions with the aromatic proton at 7-position apparently masked by these doublets, 7.4-8.5 (m, 3H, aromatic protons at 8, 9 and 10-positions).

*Anal.* Calcd. for C<sub>17</sub>H<sub>11</sub>NO<sub>4</sub>: C, 69.63; H, 3.78; N, 4.78. Found: C, 69.90; H, 3.90; N, 4.69.

5-Methoxy-11-methyl-2H-pyrano[2,3-b]acridan-2,6-dione (**9**).

A mixture of 2.1 g. (0.072 mole) of **7**, 48 g. of anhydrous potassium carbonate and 24 ml. (0.26 mole) of dimethylsulfate in 500 ml. of acetone was refluxed with stirring for 20 hours. After cooling and filtering, the clear solution was evaporated to dryness and the resultant residue suspended in 200 ml. of water and extracted with chloroform. The combined extracts were washed with water, then saturated sodium chloride solution, dried (sodium sulfate) and filtered. The filtrate was evaporated to about 50 ml. which was then passed through a short column of alumina (Woelm), the column being further washed with 100 ml. of chloroform. The combined chloroform solutions were again reduced in volume to about 100 ml. and the warm solution was treated with petroleum ether (b.p. 30-60°). Upon cooling, fine yellow needles were obtained (1.8 g., 82%) m.p. 227.5-279°; ir (0.5% potassium bromide), 1730, 1642, 1600, 1487, 1354, 1136, 753 cm<sup>-1</sup>; uv (chloroform),  $\lambda$  max nm (log e) 258 (4.47), 272 (4.39), 279sh (4.38), 319 (4.33), 341sh (4.13), 354 (4.26), 392 (4.02), 409 (4.14); nmr (DMSO-d<sub>6</sub>)  $\delta$  3.87; 3.95 (each, s, 3H, OCH<sub>3</sub>, NCH<sub>3</sub>), 6.31 (d, 1H, J = 10 Hz) and 8.12 (d, 1H, J = 10 Hz) assigned for AX quartet of pyranone ring double bond, 7.2-7.8 (m, 4H, aromatic protons at 8, 9, 10 and 12-positions), 8.27 (m, 1H, aromatic 7-position).

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>NO<sub>4</sub>: C, 70.35; H, 4.26; N, 4.59; OCH<sub>3</sub>, 10.99. Found: C, 70.20; H, 4.17; N, 4.70; OCH<sub>3</sub>, 10.78.

5-Hydroxy-2,2,11-trimethyl-2H-pyrano[2,3-b]acridan-6-one (**11b**).

Into a liter of freshly distilled (from calcium hydride) tetrahydrofuran, 1.78 g. (0.0061 mole) of **7** was dissolved with gentle warming. Then the solution was cooled to -20° and 18.2 ml. of

methylolithium (1.67 M, 15% hexane solution) was added dropwise with vigorous stirring. The addition took 10 minutes, after which stirring was continued for 60 minutes. Finely powdered ammonium chloride (8 g.) was added and the reaction mixture brought to room temperature. Water (100 ml.) was added slowly, whereupon the solution became quite dark. The excess tetrahydrofuran was distilled at reduced pressure and the remaining aqueous suspension was adjusted to pH 5 by dilute hydrochloric acid. The suspended solids were extracted with 700 ml. of ethyl acetate, and the extract was washed with sodium bicarbonate solution, water and saturated sodium chloride solution. The volume of dried (sodium sulfate) extract was reduced to about 50 ml., 7 g. of silica gel added and the remaining ethyl acetate was driven off by a stream of nitrogen. This mixture of crude product and silica gel was chromatogrammed on a 400 g. silica gel column (diameter 4 cm., height 100 cm.). The yellow orange eluate from 10% ethyl acetate in benzene (singlet spot on tlc, the column must be aged for at least three days before this elution) was evaporated to dryness and recrystallized from ethyl acetate to obtain orange yellow needles (0.837 g., 44.6%), m.p. 198.5-199.5°; ir (0.5% potassium bromide), 1642, 1618sh, 1595, 1558, 1326, 1209, 1136, 752 cm<sup>-1</sup>; For uv and nmr see Table I and II.

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.11; H, 5.60; N, 4.46.

5-Methoxy-2,2,11-trimethyl-2H-pyrano[2,3-b]acridan-6-one (**11a**) (**28**).

Into a solution of compound **11b** (0.458 g., 0.0016 mole) in acetone (31 ml.), 6.3 ml. (0.068 mole) of dimethylsulfate and 12.4 g. of anhydrous potassium carbonate were each added in three equal portions at ca. 12 hour intervals during continuous refluxing of 48 hours. The reaction mixture was poured into 150 ml. of water and stirred for 15 minutes. The acetone was evaporated under reduced pressure and the aqueous suspension extracted with chloroform (3x50 ml.). The combined extracts were washed with 50 ml. of ammonia water, water, and saturated sodium chloride solution. The dried (sodium sulfate) extracts were evaporated to dryness and redissolved in benzene and chromatogrammed on 100 g. neutral alumina (Woelm) column (diameter 2.5 cm., height 25 cm.). A yellow colored eluate from 3% ethyl acetate in benzene was evaporated to dryness and recrystallized from chloroform and petroleum ether (b.p. 30-60°) to yield light yellow needles (0.250 g., 49%), m.p. 162.5-164°; ir (0.5% potassium bromide), 2912, 1636, 1605, 1554, 1494, 1148, 1104, 1046, 776 cm<sup>-1</sup>. For uv and nmr, see Table I and II.

*Anal.* Calcd. for C<sub>20</sub>H<sub>19</sub>NO<sub>3</sub>: C, 74.74; H, 5.96; N, 4.36; OCH<sub>3</sub>, 9.65. Found: C, 74.62; H, 6.12; N, 4.49; OCH<sub>3</sub>, 9.74.

Methyl 3-Hydroxy-1-methoxy-10-methyl-9-oxoacridan-2-propenoate (**13**).

To a solution of **9** (2.13 g., 0.007 mole) in 500 ml. of methanol, 70 ml. of 1M methanolic sodium methoxide was added and the mixture refluxed for 30 hours. The volume of the solution was reduced to about 100 ml. and cooled to 0°. After treatment with water (150 ml.), the solution was acidified (pH 5) by addition of acetic acid. The resultant copious yellow precipitate was collected and washed with water. The precipitate yielded, after recrystallization from hot methanol, light yellowish small needles (2.4 g., 100%), m.p. 244-246° dec. To obtain an analytical sample, the crude crystals were chromatogrammed on a 200 g. silica gel column (diameter 2.5 cm., height 40 cm.). The eluate from 30% ethyl acetate in chloroform was evaporated to dryness and recrystallized from methanol to yield 2.06 g., m.p. 254-255.5° dec.; ir (0.5% potassium bromide), 3352, 1700, 1618, 1600, 1585, 1523, 1489,

1278, 1122, 759  $\text{cm}^{-1}$ ; uv (95% ethanol),  $\lambda$  max nm (log e) 220 (4.14), 247 (4.32), 286 (4.47), 318 (4.69), 343 inf. (4.31), 383 (3.98); nmr (DMSO- $d_6$ )  $\delta$  3.73, 3.80, 3.88 (each s, 3H, OCH<sub>3</sub>, COOCH<sub>3</sub>, NCH<sub>3</sub>), 7.15-7.95 (m, 4H, aromatic protons at 4,5,6 and 7-positions), 7.07 (d, 1H, J = 16 Hz) and 8.15 (d, 1H, J = 16 Hz) assigned to the *trans*-coupled vinylic protons, 8.32 (d, 1H, J<sub>O</sub> = 9 Hz, aromatic proton at 8-position).

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>NO<sub>5</sub>: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.13; H, 5.17; N, 4.26.

#### Methyl 1,3-Dimethoxy-10-methyl-9-oxoacridan-2-propenoate (14).

To a solution of **13** (2.1 g., 0.006 mole) in acetone (500 ml.), 28 g. of anhydrous potassium carbonate and 24 ml. (0.26 mole) of dimethylsulfate were added and the mixture refluxed for 20 hours. The reaction mixture was poured into water (200 ml.), stirred for 15 minutes, and the acetone was distilled under reduced pressure. The aqueous suspension was extracted with chloroform (3 x 250 ml.). The combined extracts were dried (sodium sulfate), reduced to a volume of 150 ml. and passed through a short column of alumina, the first 200 ml. of eluate was collected and evaporated to dryness. The resultant residue was recrystallized from ethyl acetate to yield light yellow small prisms (1.8 g., 90%), m.p. 223-226°; ir (0.5% potassium bromide), 1707, 1695, 1629, 1544, 1492, 1275, 1142, 758  $\text{cm}^{-1}$ ; uv (95% ethanol),  $\lambda$  max nm (log e) 217 (4.26), 249 (4.47), 283 (4.63), 313 (4.68), 347 (4.43), 378 (4.28), 390 inf. (4.27); nmr (deuteriochloroform),  $\delta$  3.76 (s, 3H), 3.99 (s, 6H), 4.01 (s, 3H) for OCH<sub>3</sub>, COOCH<sub>3</sub> and NCH<sub>3</sub>, 6.58 (s, 1H, aromatic proton at 4-position), 7.04 (d, 1H, J = 17.4 Hz) and 8.31 (d, 1H, J = 17.4 Hz) assigned to the *trans*-coupled vinylic protons, 7.30-7.90 (m, 3H, aromatic protons at 5,6 and 7-positions), 8.72 (d, 1H, J<sub>O</sub> = 9.0 Hz, aromatic proton at 8-position).

*Anal.* Calcd. for C<sub>20</sub>H<sub>19</sub>NO<sub>5</sub>: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.00; H, 5.53; N, 4.16.

#### 1,3-Dimethoxy-10-methyl-9-oxoacridan-2-carboxylic Acid (15).

Into a solution of **14** (0.896 g., 0.0025 mole) in acetone (240 ml.), 1.868 g. of finely powdered potassium permanganate was added, and the mixture stirred for 40 minutes, then refluxed for 30 minutes. A dark-brown residue obtained by elimination of the solvent was suspended in water (200 ml.), into which sulfur dioxide was bubbled until no more of the dark colored manganese dioxide was observed. The resultant light yellow precipitate was collected, washed with water and redissolved in sodium bicarbonate (10%). The bicarbonate solution, after filtration and acidification with dilute hydrochloric acid, yielded a light yellow precipitate which was recrystallized from methanol to obtain small needles (0.349 g., 45%), m.p. 201-205°. An analytical sample was obtained by column chromatography (60 g. silica gel, eluant was ethyl acetate, column diameter 2.5 cm.), m.p. 217-218°; ir (0.5% potassium bromide), 3279-2381, 1736, 1598, 1561, 1505, 1477, 1233, 1120, 761  $\text{cm}^{-1}$ ; uv (95% ethanol),  $\lambda$  max nm (log e) 227 (4.18), 270 inf. (4.71), 276 (4.73), 297 inf. (3.89), 373 (3.88), 396 (3.92).

*Anal.* Calcd. for C<sub>17</sub>H<sub>15</sub>NO<sub>5</sub>: C, 65.16; H, 4.83; N, 4.47. Found: C, 65.01; H, 4.82; N, 4.54.

#### Methyl 1,3-Dimethoxy-10-methyl-9-oxoacridan-2-carboxylate (16).

A solution of compound **15** (0.138 g., 0.0004 mole) in methanol (100 ml.) was treated with excess ethereal diazomethane for 1 hour at 0-5°. After evaporating the excess reagent and the solvent, a yellowish residue was obtained, which was dissolved in chloroform, washed with water, dried (sodium sulfate), and passed through a short column of neutral alumina (Woelm). The almost

colorless eluate was evaporated to dryness and recrystallized from ethyl acetate to yield pale yellow prisms (0.098 g., 75%), which were identical to an authentic sample (24).

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