Synthesis of Acronycine

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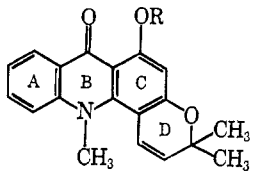
Received March 18, 1968

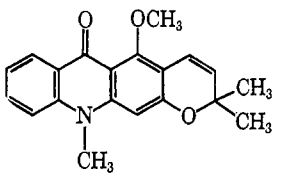
Abstract: Acronycine, an acridone alkaloid with broad-spectrum antitumor activity against experimental neoplasms, has been synthesized by three interrelated routes.

Acronycine,[1-3] one of several acridone alkaloids,[4] has been isolated from the bark of *Acronychia baueri* Schott, an Australian tree commonly called the scrub ash or scrub yellowwood. The related alkaloids, melicopine and melicopidine, have also been isolated from the bark. Svoboda and coworkers[3,5] recently reported that acronycine showed antitumor activity in experimental animals. Significant activity was found against 12 of 17 experimental neoplasms studied, and acronycine possessed the broadest antitumor spectrum of any alkaloid isolated to date in these laboratories.

Initial chemical studies[6,7] indicated either structure **1a** or **2** for acronycine. Later, Brown and Lahey[8] cited evidence favoring structure **2**. In 1965, Macdonald and Robertson[9] reported an unambiguous synthesis of methyl 1,3-dimethoxy-10-methyl-9-oxoacridan-2-carboxylate, a degradation product which would have resulted if structure **2** were correct. Since the product was isomeric with the actual degradation product (presumably the corresponding 4-carboxylate ester), the authors assigned structure **1a** to acronycine. Further evidence for **1a**, based on nmr spin–spin coupling data, was reported by Govindachari and coworkers.[10] Finally, a direct proof of structure, involving three-dimensional single-crystal X-ray diffraction analysis of a brominated derivative (**3**) of dihydroacronycine,[6] was carried out by Gougoutas and Kaski.[11]



1a, R = CH_3
b, R = H



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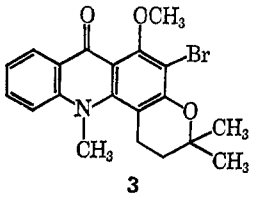

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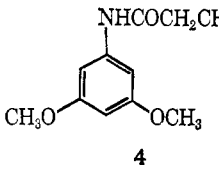
We wish to report three interrelated syntheses of acronycine. A brief account of part of this work was the subject of a previous communication.[12] For the first synthesis to be described, 5,7-dimethoxy-3,4-dihydrocarbostyril (**5a**) was chosen as starting material, since it contained the correct substitution pattern for the C ring of acronycine including the carbon bond involved in the attachment of the D ring. The syntheses of 3,4-dihydrocarbostyrils utilizing aluminum chloride catalyzed cyclizations of the appropriate 3-halopropionanilides have been reported.[13,14] In the synthesis of **5a** from 3′,5′-dimethoxy-3-bromopropionanilide (**4**) it was necessary to utilize milder Lewis acids, such as zinc chloride or antimony trichloride, to catalyze the cyclization. Optimum conditions (25–30% yield) involved fusing **4** with zinc chloride and sodium chloride at 155° for a short period of time.



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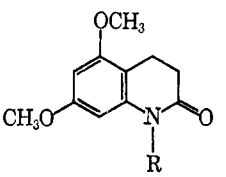
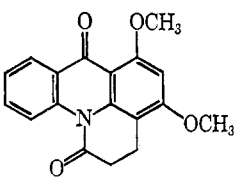


5a, R = H
b, R = 2-$HOOCC_6H_4$



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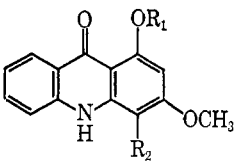


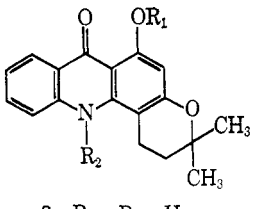
7a, $R_1 = CH_3$; $R_2 = CH_2CH_2COOCH_3$
b, $R_1 = H$; $R_2 = CH_2CH_2COOCH_3$
c, $R_1 = H$; $R_2 = CH_2CH_2C(CH_3)_2OH$

A modification of a procedure originally described by Goldberg[15] was used by allowing **5a** to react with 2-iodobenzoic acid in the presence of cuprous iodide in nitrobenzene. The product obtained, 1-(2-carboxyphenyl)-5,7-dimethoxy-3,4-dihydrocarbostyril (**5b**), was formed in 50–55% yield with some starting material

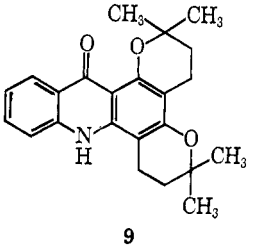
(1) G. K. Hughes, F. N. Lahey, J. R. Price, and L. J. Webb, *Nature*, **162**, 223 (1948).
(2) F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res.*, **A2**, 423 (1949).
(3) G. H. Svoboda, *Lloydia*, **29**, 206 (1966).
(4) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. 2, Academic Press Inc., New York, N. Y., 1952, p 353.
(5) G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Boder, *J. Pharm. Sci.*, **55**, 758 (1966).
(6) R. D. Brown, L. J. Drummond, F. N. Lahey, and W. C. Thomas, *Aust. J. Sci. Res.*, **A2**, 622 (1949).
(7) L. J. Drummond and F. N. Lahey, *ibid.*, **A2**, 630 (1949).
(8) R. D. Brown and F. N. Lahey, *ibid.*, **A3**, 593 (1950).
(9) P. L. Macdonald and A. V. Robertson, *Aust. J. Chem.*, **19**, 275 (1966).
(10) T. R. Govindachari, B. R. Pai, and P. S. Subramaniam, *Tetrahedron*, **22**, 3245 (1966).
(11) J. Z. Gougoutas and B. A. Kaski, private communication.
(12) J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok, and A. Pohland, *J. Amer. Chem. Soc.*, **89**, 3934 (1967).
(13) E. J. Reist, H. P. Hamlow, I. G. Junga, R. M. Silverstein, and B. R. Baker, *J. Org. Chem.*, **25**, 1368 (1960).
(14) F. Mayer, L. van Zutphen, and H. Philipps, *Ber.*, **60**, 858 (1927).
(15) I. Goldberg, *Ber.*, **39**, 1691 (1906); *cf.* P. E. Weston and H. Adkins, *J. Amer. Chem. Soc.*, **50**, 859 (1928).

recovered unchanged. Cyclization to the corresponding acridone was brought about by heating **5b** with polyphosphoric acid at 90°. The product was actually a mixture of the tetracyclic lactam **6** and 1,3-dimethoxy-9-oxoacridan-4-propionic acid, resulting from hydrolysis of **6**. The lactam component of the mixture could be isolated by crystallization techniques after treatment of the mixture with excess diazomethane. The ordinary procedure, however, involved treatment of the crude product with methanolic hydrogen chloride, which converted both components to the same intermediate, namely, methyl 1,3-dimethoxy-9-oxoacridan-4-propionate (**7a**). The over-all yield for the two steps was 80–85%.

In order to introduce the *geminal* methyl groups, conditions were necessary wherein alkylation occurred at the ester carbonyl in **7a**, but not at the acridone carbonyl function. Semon and Craig[16] reported that treatment of acridone with methylmagnesium iodide yielded 9-methylacridine (44%) and 9,9-dimethylacridan (17%). Perrine and Sargent[17] found that the reaction of 2-methoxy-9-acridanone with methylmagnesium iodide yielded 2-methoxy-9-methylacridine, but only in 10–15% yield. The same reaction with methyllithium, however, yielded none of the desired product. Lehmstedt and Dostal[18] reported that treatment of acridone with phenylmagnesium bromide yielded 9-phenylacridine (19%) with most of the acridone recovered unchanged. The same reaction with phenyllithium, however, gave a 92% yield of 9-phenylacridine. When **7a** was treated with an excess of methylmagnesium iodide in ether–pyridine as the solvent, the product obtained in high yield was methyl 1-hydroxy-3-methoxy-9-oxoacridan-4-propionate (**7b**). This product apparently was formed by rapid ether cleavage followed by precipitation of its magnesium chelate salt from the reaction mixture. The same intermediate was formed by treatment of **7a** with boron trichloride[19] in methylene chloride. Attempted treatment of **7a** with methyllithium was frustrated by its insolubility in ethereal solvents at low temperatures. Treatment of **7b** with excess methyllithium in tetrahydrofuran at −18°, however, yielded the desired product, 1-hydroxy-4-(3-hydroxy-3-methyl-*n*-butyl)-3-methoxy-9-acridanone (**7c**, 75–85%).



8a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = R_2 = CH_3$



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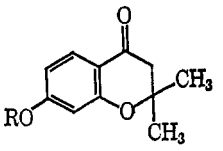
Fusion of **7c** with pyridine hydrochloride at 200° for 2 hr yielded the expected product, 6-hydroxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]acridinone (**8a**). Owing to its insolubility, **8a** was not ordinarily isolated. Instead, the crude product was treated with methyl iodide and potassium carbonate in refluxing acetone, and the resulting intermediate, dihydronoracronycine (**8b**), was purified by column chromatography. The over-all yield for the two steps was 20%. This product was identical by the usual physical comparisons with an authentic sample prepared from the natural product.[8]

Dehydrogenation of **8b** was accomplished by utilizing 2,3-dichloro-5,6-dicyanobenzoquinone in refluxing toluene or dioxane. Optimum conditions were obtained using a slight excess of the quinone and the yields of noracronycine (**1b**) were 40–45% in toluene and 30–35% in dioxane with some starting material recovered in both instances. The same reaction with dihydroacronycine (**8d**) yielded only traces of acronycine, and the brominated derivative **3** yielded none of the corresponding dehydrogenated product. It, therefore, seemed probable that a quinone methide intermediate was involved in the dehydrogenation of **8b**. The product obtained from **8b** was identical with noracronycine prepared from the natural product.[6] Conversion of **1b** to acronycine (**1a**) was carried out using a procedure described in the literature,[6] and the product obtained was identical with the natural acronycine.

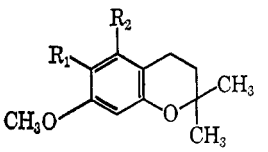
Hughes and Ritchie[20] proposed that the biogenesis of acridone alkaloids probably involved the condensation of 2-aminobenzaldehyde or its equivalent with 1,3,5-trihydroxybenzene to yield 1,3-dihydroxyacridine, which was then oxidized to 1,3-dihydroxy-9-acridanone. The isolation of 1,3-dimethoxy-10-methyl-9-acridanone from the leaves of *Acronychia baueri* by Lamberton and Price[21] further supported this hypothesis. Our second synthesis bears close resemblance to this proposed biogenesis. Although Hughes and Ritchie were able to synthesize 1,3-dihydroxyacridine in excellent yield by the condensation of 2-aminobenzaldehyde with 1,3,5-trihydroxybenzene, they were unable to oxidize the acridine to the corresponding acridone. Baczynski and Niementowski[22] reported the synthesis of 1,3-dihydroxy-9-acridanone by the condensation of anthranilic acid and 1,3,5-trihydroxybenzene, but the yield was quite low. We have found that the same condensation when carried out in *n*-butyl alcohol in the presence of zinc chloride yielded the desired product in 20–25% yield. When 1,3-dihydroxy-9-acridanone was allowed to react with 1-chloro-3-methyl-2-butene in trifluoroacetic acid with zinc chloride as the catalyst, one product, obtained in 15–20% yield, was 6-hydroxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]acridinone (**8a**). This product was identical with **8a** prepared in the first synthesis and was converted into acronycine using the same procedures outlined above. A second product obtained from this reaction was identified as the bischromane **9**.

The third synthesis to be described utilized as starting material 7-hydroxy-2,2-dimethyl-4-chromanone (**10a**), which was prepared by the method of Miyano and Matsui.[23] Methylation of **10a** gave 7-methoxy-2,2-dimethyl-4-chromanone (**10b**) in 75–80% yield. Hydrogenation of **10b** in the presence of copper chromite

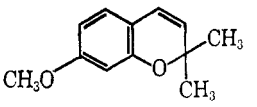
(16) W. L. Semon and D. Craig, *J. Amer. Chem. Soc.*, **58**, 1278 (1936).
(17) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 583 (1949).
(18) K. Lehmstedt and F. Dostal, *Ber.*, **72**, 804 (1939).
(19) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966).
(20) G. K. Hughes and E. Ritchie, *Aust. J. Sci. Res.*, **A4**, 423 (1951).
(21) J. A. Lamberton and J. R. Price, *Aust. J. Chem.*, **6**, 66 (1953).
(22) W. Baczynski and S. von Niementowski, *Ber.*, **38**, 3009 (1905).
(23) M. Miyano and M. Matsui, *Bull. Chem. Soc. Jap.*, **31**, 397 (1958).



10a, R = H
b, R = CH_3



11a, $R_1 = R_2 = H$
b. R_1 = Br; R_2 = H
c, R_1 = H; $R_2 = NH_2$
d, $R_1 = NH_2$; R_2 = H



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yielded 7-methoxy-2,2-dimethylchroman (**11a**) in 60% yield. Alternately, **11a** was synthesized by catalytic hydrogenation of 7-methoxy-2,2-dimethylchromene (**12**), which was obtained by treatment of **10b** with lithium aluminum hydride in ether, followed by treatment with phosphorus oxychloride in refluxing pyridine. The yield of **12** was 80–85% and the yield of **11a** was 85%. Bromination of **11a** yielded 6-bromo-7-methoxy-2,2-dimethylchroman (**11b**, 90% yield). The nmr spectrum of **11b** contained two single proton singlets at δ 6.33 and 7.17 ppm. Treatment of **11b** with 2 mol of sodium amide in liquid ammonia[24] resulted in the formation of 5-amino-7-methoxy-2,2-dimethylchroman (**11c**) in 60% yield. The nmr spectrum of **11c** showed a sharp singlet at δ 5.85 ppm, which integrated for two protons. This product was different from 6-amino-7-methoxy-2,2-dimethylchroman (**11d**), which was obtained by nitration of **11a** followed by catalytic hydrogenation. The nmr spectrum of **11d** showed two single proton singlets at δ 6.33 and 6.44 ppm. Treatment of **11c** with 2-bromobenzoic acid under standard Jourdan–Ullman conditions[25] yielded the corresponding diphenylamine, which was converted without isolation into 6-methoxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]acridinone (**8c**) by treatment with polyphosphoric acid at 90°. The over-all yield for the two steps was 15–20%. Treatment of **8c** with methyl iodide and potassium carbonate in refluxing acetone yielded **8d**, which was identical with dihydroacronycine prepared from the natural product.[6] Utilizing procedures either described in this paper or in the literature,[6] this intermediate could be converted into acronycine.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. All ultraviolet spectra were determined in 95% ethanol. All nmr spectra were determined in deuteriochloroform. All column chromatographic separations were carried out using Merck, Darmstadt silica gel (less than 0.08 mm particle size). The methyllithium used was obtained from Foote Mineral Co.

Bromination of Dihydroacronycine. A mixture containing 3.23 g of dihydroacronycine[6] (0.01 mol) and 1.78 g of N-bromosuccinimide (0.01 mol) in 150 ml of chloroform was heated under reflux for 2.5 hr. The mixture was cooled and filtered. Removal of the solvent and crystallization from ethyl acetate yielded 3.22 g of product, mp 191–194°. An analytical sample, mp 193–195°, was recrystallized from ethyl acetate.

Anal. Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; N, 3.48; Br, 19.87; O, 11.94. Found: C, 59.52; H, 5.15; N, 3.48; Br, 20.33; O, 12.10.

3′,5′-Dimethoxy-3-bromopropionanilide (4). To a stirred, cold solution of 100 g of 3-bromopropionic acid (0.65 mol) in 800 ml of methylene chloride was slowly added 134.6 g of dicyclohexylcarbodiimide (0.65 mol). The mixture was stirred in the cold for 15 min, and then 100 g of 3,5-dimethoxyaniline[26] (0.65 mol) was added portionwise. Stirring was continued for 1.5 hr, and the mixture was allowed to warm to room temperature. It was then filtered into a suction flask containing 800 ml of cold water. The organic layer was washed successively with 3 *N* hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride solutions and was dried with magnesium sulfate. Removal of the solvent and crystallization from ethanol–water yielded 146.5 g of product, mp 108–109.5°. This product was of sufficient purity for use in the next step.

5,7-Dimethoxy-3,4-dihydrocarbostyril (5a). A mixture containing 70 g of zinc chloride and 140 g of sodium chloride was dried at 155° for 2.5 hr. 3′,5′-Dimethoxy-3-bromopropionanilide (**4**, 140 g) was then added rapidly. After gas evolution had begun, heating was continued for 20 min. The mixture was cooled and dissolved in 500 ml of ethyl acetate, which was then washed successively with 3 *N* hydrochloric acid, water, saturated sodium bicarbonate, and saturated sodium chloride solutions. The organic layer was dried with magnesium sulfate and the solvent was removed. Crystallization from methanol yielded 16.9 g of product, mp 192–194°.

The solvent was removed from the mother liquor to yield 100 g of oil. A solution containing this oil and 240 g of potassium carbonate in 300 ml of methyl iodide and 1000 ml of acetone was stirred and heated under reflux for 72 hr. The cooled mixture was filtered and the solvents were removed. The crude material was suspended in ethyl acetate, which was then washed with water. The organic layer was dried with magnesium sulfate and evaporated. Crystallization from methanol yielded 11.7 g of product, mp 195–196°. The combined yield was 28.6 g. An analytical sample was recrystallized from methanol.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 64.07; H, 6.44; N, 6.90.

1-(2-Carboxyphenyl)-5,7-dimethoxy-3,4-dihydrocarbostyril (5b). A mixture containing 19.8 g of 5,7-dimethoxy-3,4-dihydrocarbostyril (**5a**, 0.096 mol), 45.0 g of 2-iodobenzoic acid (0.181 mol), 70 g of potassium carbonate, and 17 g of cuprous iodide in 300 ml of nitrobenzene was stirred and heated at 165–175° for 6.5 hr. The nitrobenzene was removed by steam distillation. The cooled aqueous solution was filtered and the solid thus obtained was crystallized from methanol to yield 4.4 g of unreacted 5,7-dimethoxy-3,4-dihydrocarbostyril, mp 198–199°. The filtrate was carefully acidified and then extracted with ethyl acetate. The organic layer was extracted with saturated sodium bicarbonate solution. The aqueous layer was then carefully acidified to pH 5 and the crystalline product was collected and washed with cold ethanol. The yield was 12.6 g, mp 222–225°. An analytical sample, mp 224–226°, was crystallized from methanol.

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.83; H, 5.37; N, 4.22.

2,3-Dihydro-4,6-dimethoxy-1H,7H-pyrido[3,2,1-*de*]acridine-1,7-dione (6). A suspension of 603 mg of 1-(2-carboxyphenyl)-5,7-dimethoxy-3,4-dihydrocarbostyril (**5b**) in 40 ml of polyphosphoric acid was heated at steam bath temperature for 12 hr. The mixture was poured into ice–water, and the solid product was collected by filtration. This material was suspended in ether and allowed to react with an excess of diazomethane. The resulting solid (473 mg) was collected and crystallized from methanol. The yield was 186 mg, mp 222–225°. Recrystallization yielded 161 mg of product, mp 226–228°.

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.79; H, 5.07; N, 4.78.

The infrared spectrum in chloroform showed lactam absorption at 1710 cm^{-1}. The ultraviolet spectrum contained maxima at 218 (ϵ 19,200), 240 (32,200), 313 (15,800), and 356 mμ (8040).

Methyl 1,3-Dimethoxy-9-oxoacridan-4-propionate (7a). A suspension of 4.37 g of 1-(2-carboxyphenyl)-5,7-dimethoxy-3,4-dihydrocarbostyril (**5b**) in 160 ml of polyphosphoric acid was heated at steam bath temperature for 1.5 hr. The mixture was poured into ice–water and the solid product was collected. The dried product was dissolved in 100 ml of 1 *N* methanolic hydrogen chloride, and the mixture was heated to reflux for 2.5 hr. The solvent

(24) R. Levine and W. C. Fernelius, *Chem. Rev.*, **54**, 449 (1954).
(25) A. Albert, "The Acridines," St. Martins Press, New York, N. Y., 1966, p 56.
(26) R. A. Benkeser, R. A. Hickner, D. I. Hoke, and O. H. Thomas, *J. Amer. Chem. Soc.*, **80**, 5289 (1958).

was removed by vacuum distillation, and the crude product was triturated in saturated sodium bicarbonate solution. The resulting solid was collected, dried, and crystallized by dissolvin git in ethanol–chloroform and slowly boiling off the chloroform on the steam bath. The yield was 3.74 g, mp 244–245°.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.81; H, 5.64; N, 4.07.

The ultraviolet spectrum showed maxima at 221 (ε 16,750), 258 (53,200), 291 (15,700), and 380 mμ (9040).

Methyl 1-Hydroxy-3-methoxy-9-oxoacridan-4-propionate (7b). **A.** Methylmagnesium iodide was prepared from 2.8 g of magnesium and 4.4 ml of methyl iodide in 75 ml of dry ether. Pyridine (100 ml) was added dropwise to the rapidly stirring cold mixture. A solution containing 2.45 g of methyl 1,3-dimethoxy-9-oxoacridan-4-propionate (**7a**) in 260 ml of pyridine was added dropwise to the cold mixture, which was then heated at 50–60° for 4 hr. The cooled mixture was poured into a cold, saturated solution of ammonium chloride, which was then extracted with chloroform. The organic layer was washed with water and saturated sodium chloride solution and dried with magnesium sulfate. Removal of the solvent and crystallization from methanol yielded 1.95 g of product, mp 193–194°. An analytical sample, mp 194–195°, was recrystallized from methanol.

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.91; H, 5.67; N, 3.94.

B. Boron trichloride was bubbled into a cold solution containing 5.00 g of methyl 1,3-dimethoxy-9-oxoacridan-4-propionate (**7a**) in 350 ml of methylene chloride for several min. The mixture was then allowed to stand at room temperature for 1 hr. It was washed successively with water, saturated sodium bicarbonate, and saturated sodium chloride solutions and dried with magnesium sulfate. Removal of the solvent and crystallization from ethanol–chloroform, as in the preparation of **7a**, yielded 3.53 g of product, mp 190–192°.

The ultraviolet spectrum showed maxima at 220 (ε 16,450), 242 (29,800), 261 (shoulder), 267 (48,500), 295 (13,850), 322 (5500), and 395 mμ (7050).

1-Hydroxy-4-(3-hydroxy-3-methyl-*n*-butyl)-3-methoxy-9-acridanone (7c). A solution containing 7.35 g of methyl 1-hydroxy-3-methoxy-9-oxoacridan-4-propionate (**7b**) in 600 ml of tetrahydrofuran was stirred and cooled to −18° in an atmosphere of nitrogen. To this was slowly added 125 ml of methyllithium solution (1.7 *M* in ether). Stirring was continued for 1 hr and then 400 ml of 3 *N* hydrochloric acid was added. The mixture was extracted with ethyl acetate, which was then washed with saturated sodium bicarbonate and saturated sodium chloride solutions and dried with magnesium sulfate. Removal of the solvent and crystallization from ethyl acetate yielded 6.08 g of product, mp 213–214°. An analytical sample, mp 215–216°, was recrystallized from ethyl acetate.

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.41; H, 6.44; N, 4.27.

6-Hydroxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]-acridinone (8a). A mixture of 295 mg of 1-hydroxy-4-(3-hydroxy-3-methyl-*n*-butyl)-3-methoxy-9-acridanone (**7c**) and 7 g of pyridine hydrochloride was fused at 190–195° for 3 hr. The mixture was suspended in water, which was then extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with magnesium sulfate. A portion (95 mg) of the crude product was chromatographed utilizing a column containing 60 g of silica gel and benzene–ethyl acetate (5:1) as the eluent. Fractions 15–22 (fraction volume, 15 ml) were combined to yield 45 mg of product (single spot on tlc). Crystallization from benzene–ethyl acetate (2:1) yielded 32 mg of product, mp 275–278° dec.

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.38; H, 5.65; N, 4.56.

Nordihydroacronycine (8b). A mixture of 1.25 g of 1-hydroxy-4-(3-hydroxy-3-methyl-*n*-butyl)-3-methoxy-9-acridanone (**7c**) and 40 g of pyridine hydrochloride was fused at 195–200° for 2 hr. Water was added and the crude product was collected by suction filtration. A solution of the crude product and 10 g of potassium carbonate in 80 ml of acetone and 20 ml of methyl iodide was heated under reflux for 44 hr. The cooled mixture was filtered, water was added, and most of the acetone was removed by vacuum distillation. The mixture was extracted with ethyl acetate and the organic layer was dried with magnesium sulfate and evaporated. The crude product was chromatographed utilizing a column prepared with 150 g of silica gel and benzene–ethyl acetate (100:1) as the eluent. The fractions containing the product were combined to yield 255 mg (one spot on tlc). The product was crystallized from ethanol–chloroform (as in the case of **7a**) to a constant melting point, 212–214°. The product was identical with nordihydroacronycine,[6] which was prepared from the natural product (mixture melting point, nmr, infrared, ultraviolet, and mass spectra, and tlc).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.61; H, 6.11; N, 4.53.

Noracronycine (1b). A solution containing 2.22 g of nordihydroacronycine (**8b**, 7.2 mmol) and 1.89 g of 2,3-dichloro-5,6-dicyanobenzoquinone (8.3 mmol) in 750 ml of toluene was heated under reflux for 2 hr. The toluene was removed by vacuum distillation, and the residue was suspended in ethyl acetate, which was then washed successively with 5% sodium hydroxide and saturated sodium chloride solutions and dried with magnesium sulfate. Removal of the solvent yielded 1.82 g of crude product, which was chromatographed utilizing a column prepared with 180 g of silica gel and benzene–ethyl acetate (30:1) as the eluent. Fractions 32–45 (fraction volume, 20 ml) were combined to yield 824 mg of product (single spot on tlc). Crystallization from ethanol–chloroform (as in the case of **7a**) yielded 782 mg of product, mp 200–201°. The product was identical with noracronycine,[6] which was prepared from the natural product (mixture melting point, nmr, infrared, ultraviolet, and mass spectra, and tlc).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.06; H, 5.44; N, 4.76.

Fractions 48–56 were combined to yield 334 mg of unchanged starting material.

Acronycine (1a). A mixture containing 146 mg of noracronycine (**1b**), 2 g of potassium carbonate, and 1 ml of dimethyl sulfate in 10 ml of acetone was heated under reflux for 16 hr. An additional 1 g of potassium carbonate and 0.5 ml of dimethyl sulfate were added and refluxing was continued for 6 hr. The same quantities were again added and refluxing was continued for 20 hr. The cooled solution was poured into water and most of the acetone was removed by vacuum distillation. The aqueous suspension was extracted with ethyl acetate, which was then washed successively with dilute ammonium hydroxide, water, and saturated sodium chloride solution and dried with magnesium sulfate. The solvent was removed and the crude product was chromatographed utilizing a column prepared with 60 g of silica gel and benzene–ethyl acetate (5:1) as the eluent. Fractions 59–75 (fraction volume, 15 ml) were combined to yield 92 mg of product (single spot on tlc). The product, mp 176–177°, was crystallized from methanol–water. It was identical with the natural product (mixture melting point, nmr, infrared, ultraviolet, and mass spectra, and tlc).

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.64; H, 6.00; N, 4.36.

1,3-Dihydroxy-9-acridanone. A solution containing 68.5 g of anthranilic acid (0.5 mol), 63 g of 1,3,5-trihydroxybenzene (0.5 mol), and 67.5 g of zinc chloride (0.5 mol) in 500 ml of *n*-butyl alcohol was heated to reflux for 8 hr. Water was removed from the reaction mixture by means of a Dean–Stark trap. Benzene (500 ml) and water (500 ml) were added to the cooled solution, which was then filtered. The filtrate was extracted with benzene and the organic layer was dried with magnesium sulfate. The solvent was removed and the crude product (71.5 g) was added to a solution containing 40 g of sodium hydroxide in 2000 ml of water. The resulting mixture was heated at 50° for 45 min and filtered. The filtrate was acidified and the crude product was collected by suction filtration. Crystallization from acetone–benzene yielded 23 g of product, mp 345° dec. The product was of sufficient purity for use in the next step.

6-Hydroxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]acridinone (8a) and 3,4,7,8-Tetrahydro-2,2,6,6-tetramethyl-2H,6H-dipyrano[2,3-*a*:2′,3′-*c*]acridin-14(9H)-one (9). To a solution containing 24.5 g of 1,3-dihydroxy-9-acridanone (0.108 mol) and 14.7 g of zinc chloride (0.108 mol) in 600 ml of trifluoroacetic acid was added dropwise 23.0 g of 1-chloro-3-methyl-2-butene (0.22 mol). The resulting mixture was heated at reflux temperature for 0.5 hr. The solvent was removed by vacuum distillation and the residual solid was suspended in water. The mixture was extracted with ether, which was then washed successively with dilute sodium hydroxide and water solutions and dried with magnesium sulfate. Removal of the solvent and fractional crystallization from benzene–acetone yielded 5.7 g of **8a**, which was identical with that prepared above, and 4.3 g of **9**, mp 288° dec. This product gave a negative ferric chloride test and its nmr spectrum was in agreement with the assigned structure.

Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85; O, 13.21. Found: C, 75.74; H, 7.19; N, 3.82; O, 12.97.

7-Methoxy-2,2-dimethyl-4-chromanone (10b). A mixture containing 100 g of 7-hydroxy-2,2-dimethyl-4-chromanone (**10a**),[23] 150 ml of methyl iodide, and 75 g of potassium carbonate in 1000 ml of acetone was heated to reflux for 4 hr. The mixture was filtered and the solvent was removed under reduced pressure. The residue was extracted with ether, which was then washed successively with dilute sodium hydroxide and water solutions and dried with magnesium sulfate. Removal of the solvent and crystallization from *n*-hexane yielded 80 g of product, mp 81–82°. An analytical sample was recrystallized from *n*-hexane.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.08; H, 6.94.

7-Methoxy-2,2-dimethylchromene (12). To a solution containing 26 g of lithium aluminum hydride in 500 ml of ether was added dropwise with stirring a solution containing 90 g of 7-methoxy-2,2-dimethyl-4-chromanone (**10b**) in 1000 ml of ether. The resulting mixture was heated to reflux for 17 hr. The excess lithium aluminum hydride was decomposed with ethyl acetate and then water was added dropwise until a thick slurry was formed. More ether was added and the ether layer was separated and dried with magnesium sulfate. The solvent was removed and the crude product was dissolved in 500 ml of benzene, which was then added dropwise to a solution containing 42 ml of phosphorus oxychloride, 250 ml of pyridine, and 300 ml of benzene. The resulting solution was heated at 85–90° for 1 hr and then poured into ice–water. The mixture was extracted with ether, which was washed successively with dilute hydrochloric acid, saturated sodium bicarbonate, and water solutions and dried with magnesium sulfate. The product was distilled to yield 66.9 g, bp 85–88° (0.5 mm); $n^{25}D$ 1.5541.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.97; H, 7.37.

7-Methoxy-2,2-dimethylchroman (11a). A. A mixture containing 80 g of 7-methoxy-2,2-dimethyl-4-chromanone (**10b**) and 35 g of copper chromite was heated from room temperature to 200° during 2 hr at a hydrogen pressure of 3000 psi. The crude product was dissolved in alcohol and the catalyst was removed by filtration. Removal of the solvent and distillation of the residue yielded 50 g of product, bp 72° (0.3 mm); $n^{25}D$ 1.5312.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.38. Found: C, 75.07; H, 8.40.

B. A mixture containing 48 g of 7-methoxy-2,2-dimethylchromene (**12**) and 10 g of Raney nickel in 150 ml of alcohol was hydrogenated at an initial pressure of 50 psi at room temperature. The mixture was filtered and the solvent was removed at reduced pressure. The residue was distilled to yield 41 g of product, bp 72° (0.3 mm).

6-Bromo-7-methoxy-2,2-dimethylchroman (11b). A solution containing 20.8 g of bromine (0.13 mol) in 100 ml of carbon tetrachloride was added dropwise to a stirred cold solution containing 25 g of 7-methoxy-2,2-dimethylchroman (**11a,** 0.13 mol) in 200 ml of carbon tetrachloride. The resulting solution was stirred at room temperature for 1 hr and then extracted successively with saturated sodium bicarbonate and water solutions and dried with magnesium sulfate. Removal of the solvent and distillation of the residue yielded 33 g of product, bp 104° (0.3 mm). Upon standing, the product, mp 39–41°, solidified.

Anal. Calcd for $C_{12}H_{15}BrO_2$: Br, 29.47. Found: Br, 29.74.

5-Amino-7-methoxy-2,2-dimethylchroman (11c). To a stirred solution containing 25 g of sodium amide (0.64 mol) in 750 ml of liquid ammonia was slowly added 75.4 g of 6-bromo-7-methoxy-2,2-dimethylchroman (**11b**, 0.28 mol). After the resulting mixture had stirred for 4 hr, 34 g of ammonium chloride was added. The ammonia was allowed to evaporate and the residue was diluted with 1000 ml of benzene. The benzene was removed under reduced pressure and the residue was triturated with ether, which was then filtered and dried with magnesium sulfate. Hydrogen chloride was bubbled into the ethereal solution and the solid product was collected by suction filtration. Crystallization from alcohol–ether yielded 40 g of product, mp 245–250°. An analytical sample, mp 255–258°, was recrystallized from alcohol–ether.

Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.45; N, 5.75. Found: C, 59.34; H, 7.49; N, 5.53.

The free base, mp 67–68°, was crystallized from *n*-hexane.

Anal. Calcd for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.98.

6-Methoxy-3,3-dimethyl-2,3-dihydro-7(12H)-1H-pyrano[2,3-*c*]-acridinone (8c). A mixture containing 2.0 g of 5-amino-7-methoxy-2,2-dimethylchromane (**11c,** 0.01 mol), 2.5 g of 2-bromobenzoic acid (0.012 mol), 3.5 g of potassium carbonate, and 0.1 g of copper powder[27] in 40 ml of *n*-amyl alcohol was stirred and heated to reflux for 16 hr. The *n*-amyl alcohol was removed by steam distillation and the aqueous solution was heated with activated charcoal and filtered. The solution was acidified and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate and evaporated to dryness. The crude product was dissolved in 30 ml of polyphosphoric acid and the mixture was heated at 90° for 2 hr. The mixture was poured into ice–water and the resulting yellow precipitate was collected by suction filtration. Crystallization from acetone yielded 500 mg of product, mp 297–299°.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 74.06; H, 6.15; N, 4.57.

This product was methylated by a procedure outlined above and the product obtained was identical with dihydroacronycine[6] obtained from the natural product (mixture melting point and nmr and mass spectra).

6-Amino-7-methoxy-2,2-dimethylchroman (11d). To a solution containing 5.7 g of 7-methoxy-2,2-dimethylchroman (**11a,** 0.03 mol) in 100 ml of glacial acetic acid was added dropwise a solution containing 1.89 g of nitric acid (0.03 mol) in 10 ml of glacial acetic acid. After it had remained at room temperature for 2 hr, the solution was diluted with water and extracted with ether. The organic layer was washed successively with saturated sodium bicarbonate and water solutions and dried with magnesium sulfate. The solvent was removed and the crude product was dissolved in 50 ml of alcohol and hydrogenated (initial pressure of 40 psi) in the presence of 5% palladium–carbon. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was acidified and extracted with ether. The aqueous layer was basified and extracted with ether. Removal of the solvent and crystallization from *n*-hexane yielded 0.9 g of product, mp 89–90°.

Anal. Calcd for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.89.

Acknowledgment. The authors wish to thank Dr. E. Wenkert and Dr. N. Leonard for their stimulating discussions.

(27) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1957, p 446.