ALKALOIDS OF THE AUSTRALIAN RUTACEAE: *ACRONYCHIA BAUERI* SCHOTT.

IV. ALKALOIDS PRESENT IN THE LEAVES

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Summary

The leaves of *Acronychia baueri* Schott. contain the acridine alkaloids melicopine, melicopidine, and melicopicine and the furoquinolines skimmianine, acronycidine, and kokusaginine, the structures of which have all been established previously. In addition two new alkaloids are present. These are 2,4-dimethoxy-10-methylacridone (I) and a dimethoxydimethylpyranofuroquinoline which has been named acronidine. Acronidine has been degraded to a phenol which on methylation gives *iso*kokusaginine (II). The alkaloid must therefore possess structure III or IV, the latter being preferred.

I. ISOLATION OF THE ALKALOIDS

In Part I of this series, dealing with the alkaloids in the bark of *Acronychia baueri* Schott., Lahey and Thomas (1949) also reported a preliminary examination of the basic constituents of the leaves. They identified melicopicine (1,2,3,4-tetramethoxy-10-methylacridone) and indicated that other, more strongly basic, alkaloids are present. Eight alkaloids have now been isolated in a pure condition, six of them having been isolated previously from other sources and their structures established. They are the N-methylacridones melicopicine, melicopidine, and melicopine and the furoquinolines kokusaginine, skimmianine, and acronycidine. Of the two new alkaloids, one has been identified as 2,4-dimethoxy-10-methylacridone, the other is given the name acronidine. Yields and references to structure are listed in Table 1. The values should be regarded only as a general guide to the alkaloid content; the amounts present in the plant are certainly somewhat greater. The separation of the bases was facilitated by the sparing solubility of kokusaginine hydrochloride and by the fact that 2,4-dimethoxy-10-methylacridone separates as a hydrate when a solution in benzene is shaken with water.

2,4-Dimethoxy-10-methylacridone has been identified by comparison of the base and its picrate with specimens synthesized by Drummond and Lahey (1949) and by conversion to 2-methoxy-4-hydroxy-10-methylacridone, which was likewise compared with a synthetic specimen. The ultraviolet absorption spectra of 2,4-dimethoxy- and 2-methoxy-4-hydroxy-10-methylacridone have

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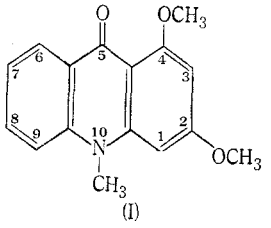
been measured for comparison with the spectrum of the 2,4-dihydroxy- compound reported by Brown and Lahey (1950). In addition, the spectrum of 1-methoxy-

TABLE 1
YIELDS OF PURIFIED ALKALOIDS

Alkaloid	Yield (%)	Reference to Structure
Melicopicine	0·26	Crow and Price (1949)
Melicopidine	0·14	Crow and Price (1949)
Melicopine	0·01	Crow and Price (1949)
2,4-Dimethoxy-10-methyl-acridone	0·05	Present work
Kokusaginine	0·04	Anet, Gilham, Gow, Hughes, and Ritchie (1952)
Skimmianine	0·016	Asahina and Inubuse (1930)
Acronycidine	0·005	Lahey, Lamberton, and Price (1950)
Acronidine	0·06	Present work



(I)

10-methylacridone has been measured in order to complete the series of mono-methoxy-10-methylacridones ; the data are presented in Table 2 and Figure 1. Brown and Lahey state that the intensity of the V_{2f} band* of 10-methylacridone

TABLE 2
ULTRAVIOLET ABSORPTION DATA

Substance	$\lambda_{max.}$ (mμ)	Log $\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	Log $\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	Log $\varepsilon_{max.}$
1 - Methoxy - 10 - methyl-acridone	*410*	3·89	312	3·64	262	4·60
	398	3·91	302	3·63		
2,4 - Dimethoxy - 10 - methylacridone	380	3·94	*~315*	3·75	267	4·67
			289·5	4·15	261	4·66
					~250	4·50
2 - Methoxy - 4 - hydroxy-10-methylacridone	390	3·79	322·5	3·81	269·5	4·67
			293	4·08	262	4·63
					~250	4·45

* Brown and Lahey designate the three band systems as the V_1 (longer wavelength), V_{2f} (middle region), and V_{2p} (shorter wavelength) bands respectively.

is increased by introducing a methoxyl substituent. Such an increase (which, in fact, is not shown by their data in the case of the 3-methoxy-compound) is observed for 1-methoxy-10-methylacridone, but it is not as great as for the 2- and 4-methoxy-compounds. Brown and Lahey also point out that the introduction of a methoxyl group in the 2- or 4-positions leads to a shift of the V_1 band to shorter wavelengths, while a methoxyl group in the 3-position causes a shift of this band to longer wavelengths. Comparison of the spectra of 1,2,3,4-tetramethoxy-, 1,2-methylenedioxy-3,4-dimethoxy-, and 2,3-methylenedioxy-1,4-dimethoxy-10-methylacridones led them to predict that an " unhindered " methoxyl group in the 1-position would cause a greater shift than a methoxyl group in any other position, this shift of course being to longer wavelengths.

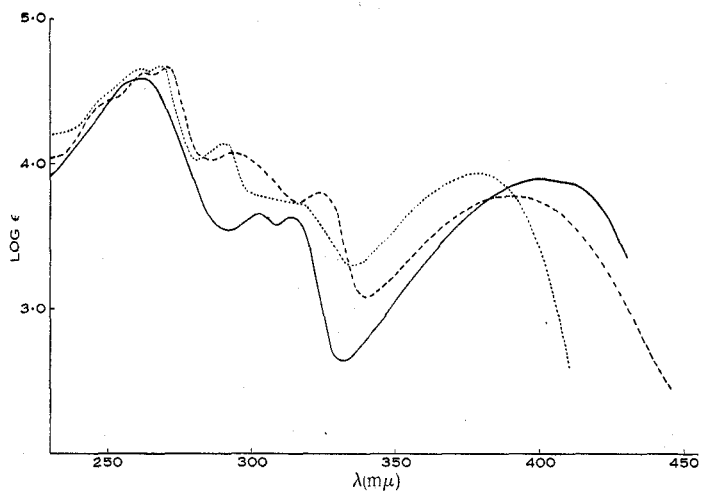


Fig. 1

—— 1-Methoxy-10-Methylacridone.
- - - - 2-Methoxy-4-Hydroxy-10-Methylacridone.
.... 2,4-Dimethoxy-10-Methylacridone.

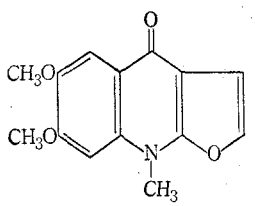
This prediction is not substantiated by measurement ; the V_1 band in 1-methoxy-10-methylacridone *is* located at a longer wavelength than that of 10-methylacridone, but the magnitude of the shift is *less* than for either the 2- or the 3-methoxy-compounds. This discrepancy between prediction and measurement probably arises from the assumption by Brown and Lahey that the methoxyl group in 1-methoxy-10-methylacridone is unhindered, that is, that it can lie in the same plane as the acridone ring. The *peri*N-methyl group may well interfere with this coplanarity and to a greater extent than with a methylenedioxy-substituent. The spectrum of 2,4-dimethoxy-10-methylacridone presents no unexpected features and is very similar to that of acronycinic acid. Demethylation of the 4-methoxyl-group results in a shift of the V_1 band to longer wavelengths, the magnitude of this shift (700 cm.$^{-1}$) being the same as that observed after demethylation of dihydroacronycine.

2,4-Dimethoxy-10-methylacridone hydrochloride resembles the hydrochloride of melicopidine (Crow and Price 1949) in that its solubility in aqueous

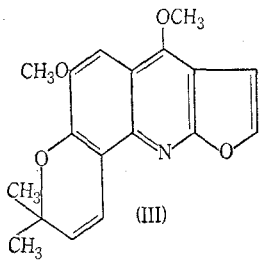
hydrochloric acid increases with increasing acid concentration. It is of interest that acronycine (Drummond and Lahey 1949), an isoprenoid derivative of 2-hydroxy-4-methoxy-10-methylacridone and the major alkaloidal constituent of the bark of *A. baueri* could not be detected in the leaves.

II. The Structure of Acronidine

Acronidine, $C_{18}H_{17}O_4N$, is a weak base containing two methoxyl groups but no methylimino-group.* It is optically inactive and is insoluble in alkali. Heating with methyl iodide brings about isomerization to *iso*acronidine which contains one methoxyl and one methylimino-group. This isomerization is typical of that observed with the furoquinoline alkaloids (see, for example, Lahey, Lamberton, and Price 1950). Demethylation of one of the methoxyl groups, to give noracronidine, takes place on heating the alkaloid with ethanolic hydrochloric acid. The formation under these conditions of noracronycidine from acronycidine, that is, demethylation of the 4-methoxyl group, has been reported previously and norskimmianine has now been prepared from skimmianine by the same procedure.



(II)



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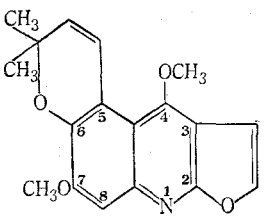


(IV)

The presence of a 2,2-dimethylpyran ring system is implied by the isolation of α-hydroxy*iso*butyric acid after permanganate oxidation. This is in agreement with the result of Kuhn-Roth terminal-methyl group determinations, the *gem*-dimethyl group giving 0·53 mole acetic acid. It is confirmed by the degradation of noracronidine with 30 per cent. potassium hydroxide to a phenol and a mixture of acetone and acetaldehyde which were separated by chromatographing the mixed 2,4-dinitrophenylhydrazones on alumina. Acetone is commonly an alkaline degradation product of 2,2-dimethylpyrano-compounds and its formation excludes the possibility that the α-hydroxy*iso*butyric acid may arise from an *iso*propylfuran ring as it is stated to in the case of oreoselone (see Späth, Klager, and Schlösser 1931).†

* As recorded in Section IV, analyses consistently showed a small positive result in the CH_3N determination, *c.* 20 per cent. of one CH_3N group. The discrepancy is attributed to formation of some volatile iodide by partial breakdown of the pyran ring. The result of the CH_3N determination on *iso*acronidine, which contains one CH_3N group, was also *c.* 16 per cent. high.

† α-Hydroxy*iso*butyric acid was stated to be formed when oreoselone is oxidized with alkaline permanganate. Later, Späth and Klager (1933) obtained α-hydroxy*iso*valeric acid by oxidation with acid permanganate and *iso*butyric acid by oxidation with alkaline hydrogen peroxide.

The phenolic product from the action of potassium hydroxide on noracronidine was not isolated as such. The reaction mixture was methylated directly giving in good yield a colourless weakly basic substance $C_{14}H_{13}O_4N$ containing two methoxyl groups and one methylimino-group. This was identified as *iso*kokusaginine (II) by m.p. and mixed m.p., ultraviolet absorption spectrum (Fig. 2) and R_F value for butanol-acetic acid. Its structure has been established by Anet *et al.* (1952). It follows that acronidine must have structure III or IV, that is, either position 5 or 8 is unsubstituted. In a molecule of this kind, coupling with diazonium salts should occur at position 6 or 8;

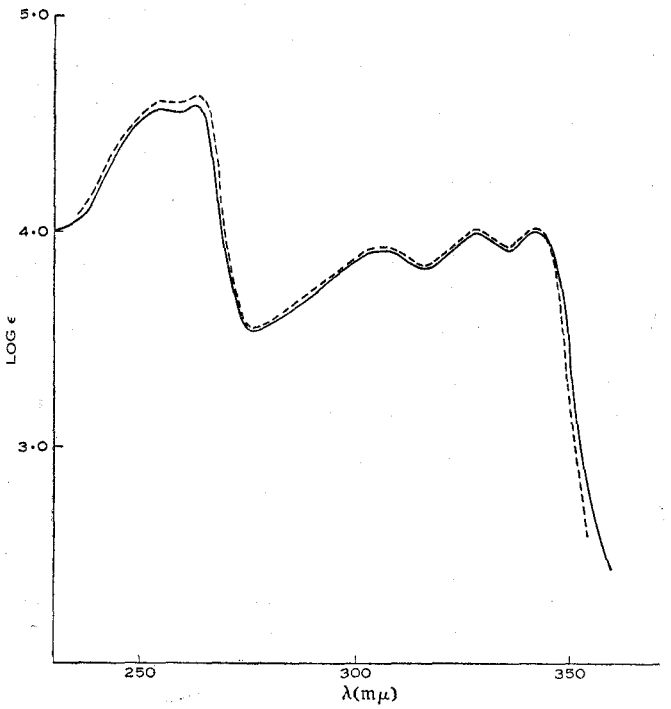


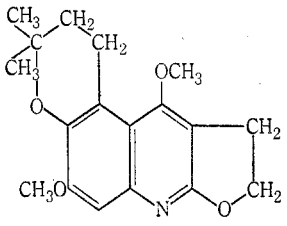
Fig. 2

—— *iso*Kokusaginine from degradation of acronidine.
- - - - *iso*Kokusaginine, authentic.

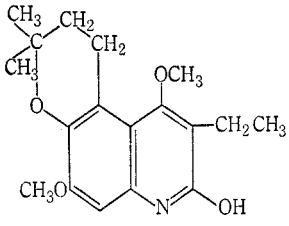
noracronycidine, for instance, with only the 6-position free, couples readily. Noracronidine also couples, and since position 6 is excluded, acronidine evidently possesses structure IV. This conclusion, however, requires confirmation.

Hydrogenation of acronidine over Raney nickel gives a mixture of tetrahydroacronidine (V) and the dihydropyranoquinolone, $C_{18}H_{23}O_4N$ (VI), arising by hydrogenolysis of the furan ring. C-methyl determinations on this substance show 1·85 terminal-methyl groups compared with 0·82 for tetrahydroacronidine. Like carbostyril and unlike tetrahydroacronidine, VI is only sparingly soluble in boiling 1 per cent. hydrochloric acid, but unlike carbostyril it is insoluble in hot aqueous sodium hydroxide. A number of 3-alkylcarbostyrils have been synthesized by Searles and Lindwall (1946) and we are indebted to Dr. A. Langley

Searles, Department of Chemistry, New York University, for the information that these compounds are virtually insoluble in alkali. 3-Ethyl-4-methyl carbostyril, for example, does not give a colour with ferric chloride and is insoluble even in hot 30 per cent. aqueous sodium hydroxide. In agreement with the conclusion of Papa, Schwenk, and Ginsberg (1951) that hydrogenolysis of the furan ring (with Raney nickel and alkali) occurs as a competitive reaction with hydrogenation and must precede hydrogenation, we find tetrahydroacronidine to be unchanged by further treatment with Raney nickel and hydrogen.



(V)



(VI)

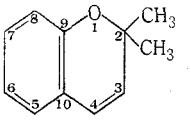
The ultraviolet absorption spectra of acronidine and a number of its derivatives have been measured but will be reported in a later paper.

III. Fission of the Dimethylpyran Ring

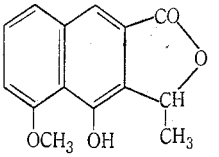
While the formation of acetone by alkaline hydrolysis of noracronidine is in keeping with the behaviour of many 2,2-dimethylpyrans, the co-formation of acetaldehyde is unique. In most other instances all five carbon atoms of the isoprene unit are split off, but only the three represented by the acetone have been identified, and since the conditions of hydrolysis are severe, the fate of carbon atoms 3 and 4 has generally been disregarded. It has been suggested (Wawzonek 1951) that the formation of acetone is good proof for a 2,2-dimethylchromene structure, but it is not a diagnostic test as not all 2,2-dimethylchromenes give acetone under these conditions. 2,2-Dimethylchromene (Shriner and Sharp 1939), 2,2,6-trimethyl-3,4-benzochromene (Cahn 1933), and 2,2-dimethyl-5,7,8-trimethoxy-6-acetylchromene (evodione ; Wright 1948) are not attacked by alkali while the 2,2-dimethylpyranoacridone, acronycine, undergoes ring fission without degradation (Brown *et al.* 1949). On the other hand, from nine coumarins, *iso*flavones, rotenoids, and acetophenones containing the 2,2-dimethylpyran ring, all five carbon atoms are split off, three being recovered as acetone. 2,2-Diphenyl-4-methoxychromene (Heilbron and Hill 1927) behaves likewise giving benzophenone, but replacement of the 4-methoxyl group by methyl leads to a different type of fission, four 2,2-diphenyl-4-methylchromenes (Heilbron and Hill 1927 ; Kartha and Menon 1943) giving benzhydryl phenyl ethers. In the one instance in which a search was made, lactaldehyde was isolated as the second product.

The nine dimethylpyrans which give acetone as the only volatile product all contain a substituent carbonyl or –CH=CH–COOH group in the *p*-position (eight) or an *o*-position (one) to the pyran oxygen atom. The electron-attracting character of these substituent groups renders C_9 (see formula VII) more susceptible to anionic attack and so facilitates opening of the pyran ring by

fission of the C_9–O_1 bond. Following opening of the ring, acetone can split off by a retrograde aldol condensation. Subsequent attack by hydroxyl ion at C_4 would give an intermediate analogous to the naphthalene derivative eleutherol (VIII) from which acetaldehyde is split off almost quantitatively by heating with dilute aqueous potassium hydroxide (Schmid, Meijer, and Ebnöther 1950). Previous workers have isolated and identified the acetone as its 2,4-dinitrophenylhydrazone which usually requires repeated crystallization (see, for

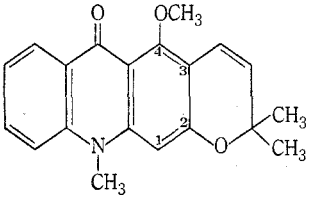


(VII)



(VIII)

example, Wolfrom *et al.* 1946) so it is possible that in some cases a small amount of acetaldehyde is recovered, but has not been detected. The effective absence of acetaldehyde is probably due to the rate of formation being so low that the aldehyde polymerizes before it can be removed by volatilization. A similar situation exists in the alkaline hydrolysis of coumarins. A number of instances are on record where carbon atoms 2,3, and 4 of the α-pyrone ring are eliminated but no acetaldehyde or other volatile carbonyl compound has been detected. On the other hand, 7-hydroxy-3-phenyl-4-methylcoumarin gives benzyl methyl ketone in good yield, together with resorcinol (Baker 1925).



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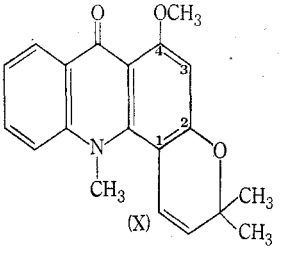

(X)

With the alkaloid acronycine (IX or X) the pyran ring is opened easily as a consequence of activation by the acridone oxygen atom, but the electron availability at C_3 (or C_1 ; IX or X) evidently does not favour breakdown of the carbinol and degradation proceeds no further. In noracronidine, on the other hand, the isoprene chain is attached at a position of low electron availability and when the pyran ring is opened both retrograde aldol condensations should be facilitated, so that the second can give rise to acetaldehyde sufficiently rapidly to permit volatilization of a substantial proportion before polymerization. The difficulty in the case of noracronidine is concerned with the opening of the pyran ring ; nucleophilic substitution at C_6 (formula IV) should be extremely difficult and some other mechanism may be operative. The degradation of 2,2-diphenyl-4-methylchromenes referred to above, which necessarily involves attack by hydroxyl ions at C_3 and C_4, shows the feasibility of ring fission by other than the

" normal " mode of attack at C_9 (formula VII) and it is possible that the O_1–C_2 bond is broken by attack at C_2.* In any event, the formation of acetaldehyde as well as acetone cannot cast doubt on the presence of a 2,2-dimethylpyran ring in acronidine. With regard to the resistance to alkali of 2,2-dimethyl-5,7,8-trimethoxy-6-acetylchromene, there is no evidence to show whether this is due to stability of the carbinol as in acronycine, or to the pyran ring not opening.

IV. Experimental

All melting points are corrected except where otherwise stated. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory.

(*a*) *Extraction and Separation of the Alkaloids.*—Milled air-dried leaves of *A. baueri* (9·6 kg.) were extracted with methanol (Soxhlet), the solution concentrated, and the residue repeatedly extracted with hot 10% hydrochloric acid. Basification with ammonia, extraction with chloroform, and repetition of treatment with hot 10% hydrochloric acid gave 130 g. crude bases. These were dissolved in hot benzene, the solution cooled, filtered, and shaken with a little water. A black tar separated at once and the benzene and water layers were decanted and kept overnight when a quantity of almost colourless crystals separated. A further quantity was obtained from the tar by passing its chloroform solution through a column of alumina, evaporating the eluate, taking up the residue in benzene, and again shaking with water. This crystalline material, identified as *2,4-dimethoxy-10-methylacridone*, is dealt with under (*b*).

The benzene solution after filtration from 2,4-dimethoxy-10-methylacridone, was extracted successively with 1% (*A*), 5% (*B*), and 20% (*C*) hydrochloric acid, six times for each acid concentration. The bases from these fractions were dissolved in benzene and by shaking with water an additional small quantity of 2,4-dimethoxy-10-methylacridone was obtained from fractions *A* and *B*. The benzene solution of fraction *A* was extracted successively with 0·02% (i), 0·05% (ii), 0·1% (iii), and 0·5% (iv) hydrochloric acid, to it was added the benzene solution of fraction *B* and the extraction continued with 1% (v) and 2% (vi) hydrochloric acid. Then was added the benzene solution of fraction *C* and extraction carried on with 5% (vii), 8% (viii), and finally 15% (ix) hydrochloric acid. The crude bases from each of fractions (i-iv) were dissolved in a little warm 2% hydrochloric acid and the acid concentration brought to *c.* 15% by addition of concentrated hydrochloric acid when kokusaginine hydrochloride crystallized, mainly from (iii) and (iv). After removing the bulk of the kokusaginine in this way, the residual bases were fractionally crystallized from ethanol, (i) and (ii) giving acronycidine, (iii) a mixture of acronycidine and skimmianine, and (iv) skimmianine. The mother liquors from each were retreated with hydrochloric acid leading to the separation of a little more kokusaginine hydrochloride after which fractional crystallization gave more skimmianine from (iv). Fractions (i), (ii), and (iii) were combined and chromatographed in benzene solution on alumina giving further quantities of kokusaginine, acronycidine, and 2,4-dimethoxy-10-methylacridone.

Solutions of fractions (v), (vi), and (vii) in benzene were run through alumina to remove dark coloured impurities, the benzene evaporated, and the bases taken up in alcohol and picrates precipitated by addition of alcoholic picric acid. Concentration yielded second crops of picrates after which unprecipitated bases were recovered from the mother liquors. In each case the picrates were separable by crystallization into the more-soluble melicopidine picrate and the less-soluble picrate of the new base *acronidine*. The mother liquors yielded the base melicopine, not precipitated by picric acid, together with further amounts of acronidine and melicopidine. Fraction (viii) dissolved in benzene was chromatographed on alumina giving a little acronidine, melicopine, and melicopidine. The bases recovered from the mother liquors were dissolved in

* The possibility of an alternative mechanism involving initial attack at C_4 and fission of the C_4-C_{10} bond is dependent on the capacity of an aldol aryl ether to split with alkali giving the phenol and two molecules of carbonyl compound—in this case acetone and acetaldehyde. However, β-methoxybutyraldehyde is not broken down to acetaldehyde.

benzene and the solution extracted successively with 5 and 15% hydrochloric acid, the former extract giving melicopidine and the latter melicopicine. Fraction (ix) consisted almost entirely of melicopicine.

The components which have been described previously were identified as follows: values in parentheses are the amounts isolated. Melicopicine (25 g.), yellow prisms from methanol, m.p. and mixed m.p. with an authentic specimen 132–133 °C.; alcoholic hydrochloric acid gave normelicopicine, orange needles from methanol, m.p. and mixed m.p. 128–129 °C. Melicopidine (13·5 g.), pale yellow prisms from methanol, m.p. and mixed m.p. 121–122 °C.; picrate, orange needles from methanol, m.p. and mixed m.p. 134–135 °C. Melicopine (1·1 g.), yellow needles from chloroform-ether, m.p. and mixed m.p. 177–178 °C. Acronycidine (0·5 g.), colourless needles from methanol, m.p. and mixed m.p. 136–137 °C.; picrate, yellow needles from methanol, m.p. and mixed m.p. 181–182 °C. Skimmianine (1·5 g.), colourless needles from methanol, m.p. and mixed m.p. 177–178 °C.; picrate, yellow needles from ethanol, m.p. 196·5–197·5 °C. Kokusaginine (4·1 g.), colourless needles from methanol, m.p. and mixed m.p. 170–171 °C. (Found: C, 65·1; H, 4·9; N, 5·3; CH_3O, 35·5%. Calc. for $C_{14}H_{13}O_4N$: C, 64·9; H, 5·0; N, 5·4; CH_3O, 35·9% (three methoxyls)). Kokusaginine picrate separated from ethanol as yellow needles, m.p. and mixed m.p. 217·5–218·5 °C.; the hydrochloride, colourless needles from 5% aqueous hydrochloric acid melted with decomposition at 225 °C. Small amounts of other basic constituents were present in some mother liquors but in amounts too small to permit of purification.

(*b*) *2,4-Dimethoxy-10-methylacridone.*—After purification through the picrate, the base crystallized from aqueous methanol as colourless needles, m.p. (after drying at 100 °C.) 163–164 °C., which did not depress the m.p. of a synthetic specimen kindly supplied by Mr. L. J. Drummond. Yield 4·5 g. (Found: C, 71·3; H, 5·5; N, 5·0; CH_3O, 22·5; CH_3N, 8·1%. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·6; N, 5·2; CH_3O, 23·0; CH_3N, 10·8%). Colourless needles of a dihydrate were obtained by shaking a benzene solution of the dimethoxyacridone with a little water (Found (on an air-dried specimen): loss of weight at 100 °C., 11·3%. Calc. for $C_{16}H_{15}O_3N.2H_2O$: 11·8%). The picrate separated from methanol as yellow needles, m.p. 205–207 °C., undepressed by admixture with the picrate of the synthetic base. The hydrochloride separated from 5% hydrochloric acid as bright yellow needles, m.p. 135–136 °C. (decomp.); it resembles melicopidine hydrochloride in that its solubility in aqueous acids is anomalous. Though not easily soluble in 1·5N, it dissolves readily in 5N hydrochloric acid. Heated at 170 °C. in an oil-bath for 5 min., the hydrochloride was demethylated giving 2-methoxy-4-hydroxy-10-methylacridone, yellow needles from aqueous ethanol, m.p. 175–176 °C. and not depressed by admixture with a synthetic specimen.

(*c*) *Acronidine.*—The base recovered from its picrate was purified by passage through a column of alumina and crystallized from methanol as large, colourless prisms, m.p. 151–153 °C. Yield 5·8 g. It is insoluble in water, moderately soluble in benzene, and very soluble in chloroform, a chloroform solution being optically inactive (Found: C, 69·5; H, 5·4; N, 4·6; CH_3O, 19·7; CH_3(C), 2·4, 2·7; CH_3N, 1·7, 1·9%; mol. wt. (Rast) 315. Calc. for $C_{18}H_{17}O_4N$: C, 69·5; H, 5·5; N, 4·5; CH_3O, 19·9 (two methoxyls); CH_3(C), 4·8% (one terminal methyl); mol. wt. 311). *Acronidine picrate* separated from *n*-propanol or ethanol as flat yellow needles, m.p. 216–218 °C. (decomp.) (Found: C, 53·6; H, 3·8; N, 10·3%. Calc. for $C_{18}H_{17}O_4N.C_6H_3O_7N_3$: C, 53·3; H, 3·7; N, 10·4%). Acronidine dissolves in 0·5N but is only soluble with difficulty in 0·1N hydrochloric acid. The hydrochloride separated from 2N hydrochloric acid as long cream needles which shrank at *c.* 180 °C. and decomposed gradually without melting as the temperature was raised to 320 °C.; it was not analysed. Acronidine is insoluble in aqueous alkali. It does not give a methylenedioxy test.

(*d*) iso*Acronidine.*—Acronidine (1 g.) heated in a sealed tube at 100 °C. for 4 hr. with methyl iodide (2 ml.) gave iso*acronidine*, colourless needles from ethanol, m.p. 231–232 °C. (Found: C, 69·7; H, 5·4; CH_3O, 10·3; CH_3N, 10·8%. Calc. for $C_{18}H_{17}O_4N$: C, 69·5; H, 5·5; CH_3O, 10·0 (one methoxyl); CH_3N, 9·3%).

(*e*) *Oxidation of Acronidine.*—The alkaloid was oxidized readily by permanganate in acetone but as no tractable product could be isolated the following procedure was adopted. Acronidine

(1·2 g.) was oxidized by potassium permanganate (1·8 g.) in acetone solution and the acetone evaporated under reduced pressure. The residue was stirred with sodium hydroxide solution (5%, 35 ml.) and water (200 ml.) and aqueous permanganate (3%, 180 ml.) added in 20 ml. portions during several hours. Excess permanganate was destroyed by hydrazine and the reaction mixture heated for 1 hr. on the water-bath, filtered, and the filtrate made strongly acid with hydrochloric acid. The manganese dioxide was dissolved in sulphurous acid and the resulting solution combined with the filtrate which was saturated with sodium chloride and continuously extracted with ether. The extracted acids were transferred to aqueous solution by dilute ammonia and oxalic acid removed by precipitation with calcium chloride. The filtrate from the calcium salts was reacidified and again continuously extracted with ether. The ethereal extract was dried, evaporated, and the residue sublimed (*c.* 100 °C., 1–2 mm.). Resublimation and crystallization from light petroleum gave colourless needles, m.p. 78–79 °C., undepressed by admixture with α-hydroxy*iso*butyric acid (Found : C, 46·8 ; H, 7·6%. Calc. for $C_4H_8O_3$: C, 46·2 ; H, 7·7%).

(*f*) *Noracronidine.*—A solution of acronidine (1·0 g.) in ethanol (15 ml.) containing hydrochloric acid (10N ; 4·5 ml.) was refluxed for 20 hr. The sparingly soluble yellow hydrochloride which separated was dissolved in dilute sodium hydroxide and the solution acidified with acetic acid giving noracronidine, colourless needles from ethanol, m.p. 256–257 °C.* Yield 0·5 g. (Found : C, 68·9 ; H, 5·0 ; N, 4·6 ; CH_3O, 10·2%. Calc. for $C_{17}H_{15}O_4N$: C, 68·7 ; H, 5·1 ; N, 4·7 ; CH_3O, 10·4%). Coupling occurred when a solution of benzene diazonium chloride was added to a solution of noracronidine in 10% sodium hydroxide, giving a reddish brown precipitate. Noracronycidine under the same conditions gave a crimson diazo-compound. *Acetyl noracronidine* separated from ethanol as colourless needles, m.p. 212–214 °C. (Found : C, 67·2 ; H, 5·2%. Calc. for $C_{19}H_{17}O_5N$: C, 67·3 ; H, 5·0%).

(*g*) *Action of Alkali on Noracronidine.*—Aqueous potassium hydroxide (30%, 30 ml.) containing noracronidine (0·5 g.) was boiled under reflux, water (20 ml.) being added at 2-hourly intervals and the same volume of liquid distilled off. The earlier distillates smelt strongly of acetaldehyde and to each distillate was added a saturated solution of 2,4-dinitrophenylhydrazine in 10% aqueous sulphuric acid until there was no further precipitation of hydrazone. Refluxing was discontinued after 12 hr. when the amount precipitated was very small. The combined dinitrophenylhydrazones (0·39 g.) were dissolved in benzene and chromatographed on alumina. The eluate was collected in six fractions, each fraction evaporated to dryness and the residues crystallized from ethanol with the following results :

Fraction	Residue	M.p. (°C.)
1	Yellow needles	122–126
2	Deep yellow needles	119–124
3	Orange-yellow needles	104–112
4	Reddish orange flat needles	128–146
5	Reddish orange flat needles	150–158
6	Reddish orange flat needles	156–160

Fraction 2 was recrystallized from the mother liquors from fraction 1, the product, m.p. 121–126 °C. was combined with fraction 1 and recrystallized from ethanol giving acetone 2,4-dinitrophenylhydrazone, m.p. 125–126 °C. undepressed by admixture with an authentic specimen (Found : C, 45·8 ; H, 4·5%. Calc. for $C_9H_{10}O_4N_4$: C, 45·4 ; H, 4·2%). Fractions 5 and 6 were combined and recrystallized first from benzene then from ethanol giving acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 167–168 °C. undepressed by admixture with an authentic specimen (Found : C, 43·4 ; H, 3·6%. Calc. for $C_8H_8O_4N_4$: C, 42·9 ; H, 3·6%). The yield of mixed 2,4-dinitrophenylhydrazones was 50% on the basis of a 1 : 1 molar ratio of acetone : acetaldehyde. The proportion of each 2,4-dinitrophenylhydrazone in the mixture could not be determined but it was estimated that acetone 2,4-dinitrophenylhydrazone constituted not less than 30% and not more than 50% of the mixture. After the sixth distillation the alkaline

* This is not a good melting point, the substance melts to a thick brown gum but does not flow freely even at 300 °C.

reaction mixture was diluted with an equal volume of water and shaken with dimethyl sulphate (4 ml. in three portions). Extraction with chloroform, and evaporation of the solvent gave a crystalline solid (0·30 g.) which was redissolved in chloroform and the solution filtered through alumina. The recovered solid was crystallized first from benzene, then from water, and obtained as rosettes of short needles, m.p. 247–248 °C. (uncorr.) undepressed by admixture with *iso*-kokusaginine kindly supplied by Mr. G. K. Hughes (Found : C, 64·9 ; H, 5·0 ; N, 5·5 ; CH_3O, 23·6%. Calc. for $C_{14}H_{13}O_4N$: C, 64·9 ; H, 5·0 ; N, 5·4 ; CH_3O, 23·9% (two methoxyls)).

In a blank experiment, 0·45 g. noracronycidine, a typical methoxylated furoquinoline lacking a dimethylpyran ring, was refluxed with potassium hydroxide (30%, 30 ml.) for 2 hr., water (20 ml.) added, and then distilled off. The distillate was odourless and gave no precipitate with a solution of 2,4-dinitrophenylhydrazine in 10% aqueous sulphuric acid. From β-methoxybutyraldehyde (Heyse 1930) under the same conditions only a very small amount of 2,4-dinitrophenylhydrazones was precipitated. No acetaldehyde 2,4-dinitrophenylhydrazone was detected when the mixed dinitrophenylhydrazones were chromatographed on alumina.

(*h*) *Hydrogenation of Acronidine.*—Acronidine (1·0 g.) in ethanol (250 ml.), hydrogenated over Raney nickel, absorbed 152 ml. hydrogen at 21 °C. and 761 mm. ; calculated for 2 moles, 155 ml. The solution was filtered, evaporated, and the residue dissolved in benzene and chromatographed on alumina giving two products. The first was eluted by benzene in *c.* 75% yield and crystallized from methanol as colourless needles, m.p. 192·5–194·5 °C. (Found : C, 68·5 ; H, 6·7 ; CH_3(C), 4·0, 3·8%. Calc. for $C_{18}H_{21}O_4N$: C, 68·6 ; H, 6·7 ; CH_3(C), 4·8% (one CH_3(C) group)). *Tetrahydroacronidine* (V) is insoluble in hot 4% aqueous sodium hydroxide and gives no colour with ferric chloride. It dissolves easily in cold 1% hydrochloric acid.

The second product, the *dihydropyranoquinolone* VII, was eluted by chloroform in *c.* 20% yield and crystallized from methanol as colourless, equidimensional prisms, m.p. 255–257 °C. (Found : C, 68·1 ; H, 7·4 ; N, 4·5 ; CH_3O, 19·3 ; CH_3(C), 8·6, 8·9%. Calc. for $C_{18}H_{23}O_4N$: C, 68·1 ; H, 7·3 ; N, 4·4 ; CH_3O, 19·6 (two methoxyls) ; CH_3(C), 4·7% (one CH_3(C) group)). The substance is insoluble in hot 4% aqueous sodium hydroxide and gives no colour with ferric chloride. It is only sparingly soluble in boiling 1% hydrochloric acid. The yields quoted were not reproduced. In a second experiment, there was obtained *c.* 40% tetrahydroacronidine and *c.* 57% of the higher melting substance. Tetrahydroacronidine was recovered unchanged (m.p. and mixed m.p.) after attempted hydrogenation over Raney nickel in ethanol.

(*i*) *Norskimmianine.*—Skimmianine (0·5 g.) in ethanol (20 ml.) was refluxed for 10 hr. with hydrochloric acid (10N ; 4 ml.). The solid which separated on cooling was dissolved in dilute sodium hydroxide and the filtered solution acidified with acetic acid precipitating norskimmianine which crystallized from benzene or from aqueous ethanol as colourless needles, m.p. 235–236 °C. (Found : N, 5·6 ; CH_3O, 24·9%. Calc. for $C_{13}H_{11}O_4N$: N, 5·7 ; CH_3O, 25·3% (two methoxyls)). Norskimmianine couples with diazonium salts in alkaline solution to give a red precipitate.

(*j*) The ultraviolet absorption spectra were measured in ethanol solution by means of a Beckmann DU spectrophotometer. The specimen of 1-methoxy-10-methylacridone was supplied by Mr. G. K. Hughes.

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