Keten. Part IV.[1] The Addition of Dimethylketen to Some 9-Substituted Acridines

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The reaction of dimethylketen with 9-methylacridine gives open-chain and cyclic adducts composed of one molecule of the heterocyclic base combined with two molecules of dimethylketen. The structures of these compounds have been elucidated. A similar reaction is observed with 9-ethylacridine, but 9-phenylacridine forms only the open-chain adduct. The reactions of these adducts have been investigated, and a mechanism proposed for the migration of an acyl group during reduction with lithium aluminium hydride. The mechanism of formation of keten-*ON*-acetals by methanolysis of the adducts or their dihydro-derivatives is discussed. The n.m.r. spectra of the keten-*ON*-acetals show evidence of restricted rotation about a C–N bond.

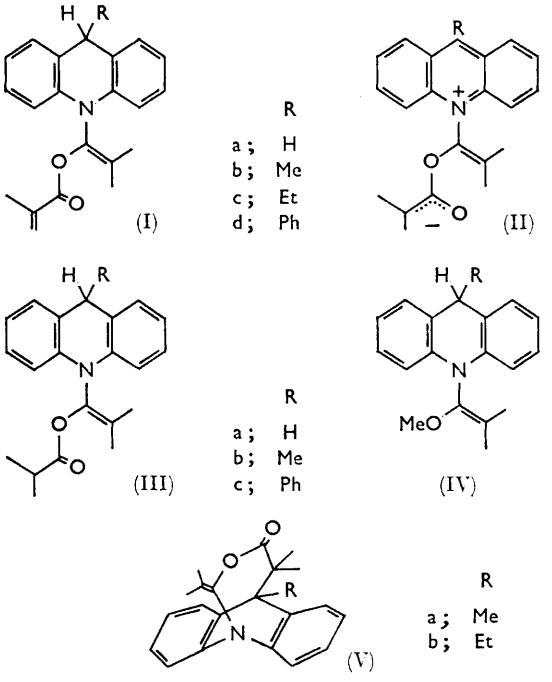
FOLLOWING the elucidation of the structure (Ia)[2] of Strudinger's adduct of dimethylketen and acridine,[3] we investigated the reaction of dimethylketen with some acridines bearing substitutents in the 9-position, in order to examine the effect of substitution upon the intramolecular hydride ion transfer in (IIa), which was proposed as the final stage in the formation of (Ia).

9-Methylacridine reacted with dimethylketen in a variety of aprotic solvents to give two isomeric products $C_{22}H_{23}NO_2$. The first of these, an ether-soluble compound, was readily identified as (Ib) from the similarity of its i.r., u.v., and n.m.r. spectra to those of (Ia).[2] Hydrogenation gave a dihydro-derivative (IIIb) the spectroscopic properties of which closely resembled those

[1] Part III, R. N. Pratt, G. A. Taylor, and S. Procter, *J. Chem. Soc.* (*C*), 1967, 1569.

[2] S. A. Procter and G. A. Taylor, *J. Chem. Soc.*, 1965, 5877.
[3] H. Staudinger and H. W. Klever, *Ber.*, 1907, **40**, 1149.

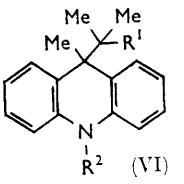
of (IIIa).[2] Hydrolysis of the dihydro-derivative with alkali gave 9,10-dihydro-10-isobutyryl-9-methylacridine and isobutyric acid, whilst reduction with lithium aluminium hydride gave the same amide and isobutyl



alcohol. No reaction was observed on heating (IIIb) with aniline, but treatment with hot benzylamine afforded 9,10-dihydro-10-isobutyryl-9-methylacridine and *N*-benzylisobutyramide. Boiling the dihydro-derivative (IIIb) with acidified methanol gave a compound, $C_{19}H_{21}NO$, identified as (IVb) by comparison of its spectroscopic properties with those of (IVa).[2]

The second adduct from the reaction of dimethylketen with 9-methylacridine had markedly different spectral properties from those of (Ib). The u.v. spectrum showed no absorption maxima, but had broad shoulders at 239 and 273 mμ on an absorption curve which climbed steadily from *ca.* 300 mμ, the i.r. spectrum contained maxima at 1710 and 1754 cm.$^{-1}$, and the n.m.r. spectrum showed the presence of eight aromatic protons and five methyl groups. The u.v. spectrum coupled with the presence of eight aromatic protons strongly suggests that the adduct is an acridan (9,10-dihydroacridine) derivative, and the presence of three singlets in the n.m.r. spectrum corresponding to five methyl groups requires a quaternary centre at the 9-position. The most obvious structure consistent with this information is that arising by ring closure of an intermediate (IIb) giving a structure (Va), an assignment which is fully confirmed by the following degradative evidence.

Treatment of the second (cyclic) adduct with either sodium borohydride in methanol or sodium methoxide gave a compound $C_{23}H_{27}NO_3$ the i.r. spectrum of which contained absorptions at 1721 and 1678 cm.$^{-1}$ with all other spectroscopic properties consistent with the structure (VIa). The same compound could be obtained by alkaline hydrolysis of the adduct (Va), which gave the acid (VIb), followed by esterification with diazomethane. The adduct (Va) was inert to boiling aniline but on heating with benzylamine gave a compound $C_{29}H_{32}N_2O_2$ identified as (VIc) by spectroscopic methods. Pyrolysis of the adduct (Va) gave small amounts of dimethylketen.



	R^1	R^2
a;	CO_2Me	$Me_2CH{\cdot}CO$
b;	CO_2H	$Me_2CH{\cdot}CO$
c;	$CO{\cdot}NH{\cdot}CH_2Ph$	$Me_2CH{\cdot}CO$
d;	CH_2OH	$Me_2CH{\cdot}CO$
e;	$CH_2O{\cdot}CO{\cdot}CHMe_2$	H
f;	CH_2OH	H
g;	CH_2O^-	$Me_2C{-}\overset{\vert}{C}{-}O$
h;	CH_2O^-	$Me_2CH{\cdot}CO$
i;	$CH_2O{\cdot}CO{\cdot}CHMe_2$	-ve charge
j;	CO_2H	$Me_2C{=}\overset{\vert}{C}(OMe)$

Reduction of the adduct (Va) by lithium aluminium hydride gave two isomeric products $C_{22}H_{27}NO_2$, both of which had u.v. spectra consistent with the presence of an acridan skeleton. One of these, isomer A, had an absorption in the i.r. at 1659 cm.$^{-1}$ consistent with it being a 10-acylacridan, whilst the second product, isomer B, absorbed at 1705 cm.$^{-1}$ which we attribute to the presence of an ester carbonyl group. Both isomers had i.r. absorption in the region characteristic of NH or OH groups, and prolonged reduction of both isomers with lithium aluminium hydride gave the same product $C_{18}H_{21}NO$, which was identified as (VIf) from the n.m.r. spectrum. We conclude that isomer A is the amide (VId), whilst isomer B is the ester (VIe), an assignment consistent with the relative positions of the methylene group absorptions in the n.m.r. spectra. Attempts to convert (VIf) into either (VId) or (VIe) by reaction with isobutyryl chloride failed, which we attribute to the steric effect of the bulky 9-substituent preventing access to both hydroxy- and amino-groups.

The mechanism by which the two isomers could be formed presented a problem. If the reduction of the adduct (Va) by lithium aluminium hydride is initiated by attack of hydride ion on the carbonyl group, then the dianion (VIg) would be the ultimate product expected in the reaction mixture. It is unlikely that this species would rearrange, as this would involve attack of one anionic group on another negatively charged centre. That such a rearrangement was not the source of (VIe) was in accord with the observation that the ratio of the two products in a series of reductions varied in a random fashion and was not determined by the reaction temperature or by the length of time for which the reaction was conducted. We concluded that during the work-up, which consisted initially of the cautious dropwise addition of water, the species (VIh) is first formed, and that this anion, unless rapidly protonated to form (VId), can rearrange to (VIi). This was confirmed by experiments in which we were able to demonstrate that rapid addition of water to the reaction mixture gave

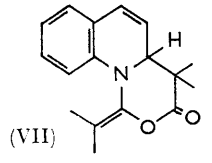
(VId) as the predominant product, whilst protracted addition gave principally (VIe). Furthermore, (VId) is converted rapidly into (VIe) on treatment with sodium methoxide in methanol.

Confirmation of the presence of an isopropylidene group in the adduct (Va), which was suggested by the low-field methyl signals in the n.m.r. spectrum, came from acid-catalysed methanolysis, which gave a compound $C_{23}H_{27}NO_3$ identified by spectroscopic methods as (VIj).

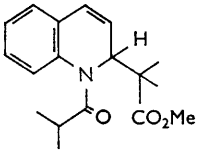
During the course of this work, parallel investigations of the reaction of dimethylketen with 9-ethylacridine and 9-phenylacridine were pursued. A crystalline adduct of one molecule of 9-ethylacridine and two molecules of dimethylketen was isolated, and identified as (Vb) by the n.m.r. spectrum; and the oily residue from this reaction absorbed at τ 3·9 and 4·4 in the n.m.r. spectrum, suggesting the presence of (Ic), which, so far, we have been unable to isolate. Comparison of the n.m.r. spectra of (Va) and (Vb) shows unambiguously that the bridgehead methyl group in (Va) absorbs at τ 8·26, with the isopropylidene methyl groups absorbing at *ca.* τ 7·7 and 8·3, the large difference in chemical shift being attributable to their differing positions relative to the aromatic rings. We tentatively assign the lower-field resonance to the methyl group *cis* with respect to the nitrogen atom, since this lies closer to the peripheral deshielded zone around the aromatic rings.

The reaction of 9-phenylacridine proceeded very much less readily than in the previous cases. Whereas acridine and its 9-methyl and 9-ethyl derivatives reacted rapidly with dimethylketen, 9-phenylacridine could be recovered in high yield when similar proportions of reagents were employed. In the presence of a large excess of the keten, an adduct of 2 : 1 molar proportions was obtained in good yield, but no trace of a second adduct could be detected. The adduct, $C_{27}H_{25}NO_2$, was identified as (Id) by spectroscopic methods and the corresponding dihydro-derivative (IIIc) and keten-*ON*-acetal (IVc) were prepared. The failure of 9-phenylacridine to form a cyclic adduct like (V) is probably due to the steric effects of the phenyl group preventing close approach of the enolate anion in (IId) to the 9-position of the acridine skeleton.

The formation of the keten-*ON*-acetals (IVa)—(IVc) and (VIj) on acid-catalysed methanolysis of the acridine adducts or their derivatives contrasts with the product

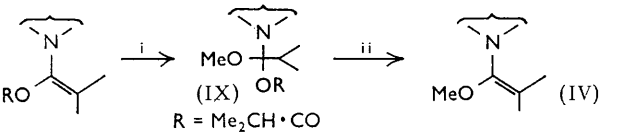


(VII)

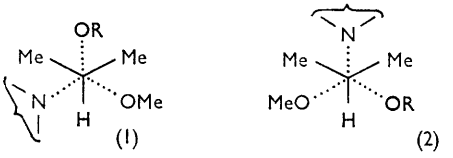


(VIII)

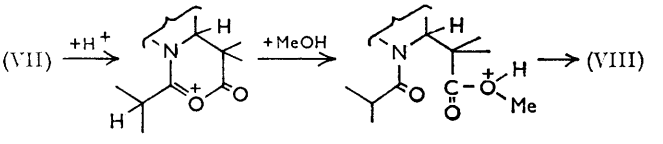
of similar treatment of the quinoline–dimethylketen adduct (VII) which has been shown [1,3] to give the amido-ester (VIII). In a previous Communication,[2] the formation of the keten-*ON*-acetal (IVa) from (IIIa) was suggested to arise by initial addition of methanol across the C=C group, followed by elimination of isobutyric acid, and Newman projections of (IX) support this scheme insofar as they indicate that the conformation (1) of compound (IX), which would lead to formation of the keten-*ON*-acetal (IV) is sterically less crowded than that



Reagents: i, H+—MeOH; ii, —ROH

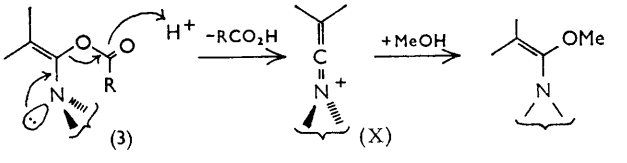


(2) leading to elimination of acridan. However similar projections can be drawn for a hypothetical intermediate arising from addition of methanol to the isopropylidene group of (VII) but methanolysis of the adducts of quinoline, isoquinoline, and their derivatives, with dimethylketen yields exclusively amido-esters akin to (VIII).[1] These presumably arise by a mechanism (Scheme) in which the unusually rapid transesterification of the hindered ester group results from initial protonation of the isopropylidene group. An alternative, more satisfactory explanation of the difference in the products of methanolysis of the two groups of adducts and their derivatives is that both the open-chain and cyclic adducts in the acridine series can adopt a conformation like (3) in which the lone pair on nitrogen and the $(CH_3)_2C_2$–O bond are approximately antiperiplanar about the C–N bond enabling an elimination to occur as shown. The resultant keteniminium ion (X) would add methanol rapidly to give the observed products. The formation

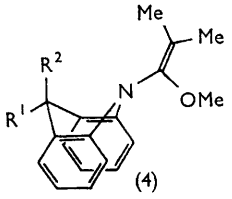


Scheme

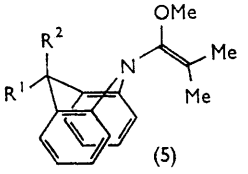
of the keten-*ON*-acetal (VIj) from (Va) is consistent with this scheme, since (Va) has approximately the correct conformation (3) and the sterically hindered carboxylic acid group, once formed, would be esterified extremely slowly. The cyclic adducts of quinoline etc. have the lone pair in an orbital approximately perpendicular to the plane of the relevant C–N and C–O bonds, preventing formation of a similar keteniminium intermediate.



The n.m.r. spectra of the keten-*ON*-acetals (IVb) and (IVc) and (VIj) are more complex than expected at first sight. Whilst the integration shows that some of the peaks correspond to absorption by integral numbers of protons, all these compounds contain peaks which correspond to absorption by fractional numbers of protons. Thus, in the spectrum of (IVb) two peaks at τ 6·59 and 6·73 correspond to 1·8 and 1·2 protons, respectively, whilst in (VIj) similar absorptions at τ 6·46 and 6·93 correspond to 1·6 and 1·4 protons. The n.m.r. spectrum of (IVc) contains two peaks at τ 6·66 and 6·69 of unequal height which are not sufficiently well resolved to give a reliable integration curve at room temperature, but which correspond to 1·6 and 1·4 protons at −30°. In the C–CH_3 region of the spectra of these compounds other pairs of peaks are found which jointly account for three protons, *e.g.*, in the spectrum of (IVc) these occur at τ 8·48 and 8·60 in the ratio 1·4 : 1·6. We conclude that the multiplicity of signals is due to restricted rotation about the N–C bond of keten-*ON*-acetal group, resulting in two preferred conformations corresponding to (4) and (5). The failure to observe



(4)



(5)

multiple signals for (IVa) [2] is presumably due to rapid inversion of the central ring of the acridan system, which would interconvert (4) and (5) ($R^1 = R^2 = H$) without requiring rotation about the C–N bond. In all other cases, inversion of the boat-shaped central ring would not interconvert (4) and (5) if $R^1 \neq R^2$, and such inversion would probably be inhibited if R^1 and R^2 were of widely differing sizes. Examination of models of (4) and (5) suggests that the methoxy-methyl group and the methyl group *cis* to nitrogen change their magnetic environment very greatly on interconverting (4) and (5), whilst the methyl group *trans* to nitrogen changes its magnetic environment very little. It appears from the relative areas under the peaks in the n.m.r. spectrum that, in all cases, the conformation with the less shielded methoxy-group is more highly populated. Although, in these cases, models are more than usually unreliable, owing to the uncertainty about the hybridisation of the nitrogen atom, they suggest that (5) has the less shielded methoxy-group and more shielded C–CH_3 group. Only for (IVc) is the C–CH_3 region of the n.m.r. spectrum sufficiently clear to provide accurate peak : area ratios, and here it is the conformation with the more shielded C–CH_3 group which predominates.

Preliminary investigation of the variation of the n.m.r. spectra of the keten-*ON*-acetals between −60 and 80° showed little variation in the relative proportions of (4) and (5) over this range of temperature. For (IVc), coalescence of both methoxy- and C–CH_3 peaks was observed between 80 and 100°, but (IVb) and (VIj) decomposed above 80° in pentachloroethane. The adducts (Ib) and (Id) and their dihydro-derivatives also incorporate the keten-*ON*-acetal group, and might be expected to show multiple peaks in the n.m.r. spectrum, but the only sign of hindered rotation is a broadening of the absorption attributed to one of the isopropylidene methyl groups, suggesting an overwhelming preponderance of one conformer. Further studies of this restricted rotation are currently in progress and will be reported in a separate Communication.

The mass spectra of the adducts have been examined. The mass spectrum of (Ia) shows a fragmentation pattern corresponding to the stepwise degradation of the side chain, prominent peaks occurring at $(M - 69)^+$, $(M - 85)^+$, $(M - 139)^+$, $(M - 140)^+$, 70^+, and 69^+ mass units. The first two of these correspond to the loss of the terminal acyl and acyloxy-groups respectively, the second pair to protonated and unprotonated acridine cation, and the last two to a cation derived from dimethylketen and methacrylium cation, respectively. The other open-chain adducts fragment in a similar fashion and in addition show peaks corresponding to loss of the 9-substituent group. It is noteworthy that no significant $(M - 1)^+$ peak occurs even in the mass spectrum of (Ia).

The cyclic adducts (Va) and (Vb) show a somewhat different fragmentation pattern. Prominent peaks correspond to the loss of the bridgehead substituent followed by two losses of 70 mass units, whilst $(M - 70)^+$ and $(M - 140)^+$ also occur which might arise from pyrolytic decomposition of these adducts in the heated inlet system.

EXPERIMENTAL

Nuclear magnetic resonance spectra were measured in deuteriochloroform (unless otherwise indicated) with a Varian A60 spectrometer, infrared spectra with a Unicam SP 100 spectrometer, and mass spectra with an A.E.I. MS9 mass spectrometer.

9,10-Dihydro-10-(1-methacryloyloxy-2-methylpropenyl)-acridine (Ia).[2]—Mass spectrum: *m/e* 319 (22%), 250 (39%), 234 (8%), 180 (25%), 179 (19%) 70 (11%), and 69 (100%).

The Addition of Dimethylketen to 9-Methylacridine.—Dimethylketen (*ca.* 24 g.) was passed into a solution of 9-methylacridine (12 g.) in dry ether (500 ml.) and the solution was set aside overnight, when crystals of *2-isopropylidene-5,5,6-trimethyldibenzo-3-oxa-1-azabicyclo*[4,2,2]*deca-7,9-dien-4-one* (Va) separated. Evaporation of the ether solution and addition of benzene (10 ml.) gave a further quantity of (Va) (total 6·6 g.). Recrystallisation from benzene gave crystals (3·8 g., 18%), m. p. 183° (decomp.) (Found: C, 79·1; H, 7·1; N, 3·9. $C_{22}H_{23}NO_2$ requires C, 79·3; H, 6·9; N, 4·2%), $\lambda_{max.}$ (ethanol) 239(s) and 273(s) mμ (log ε 3·92 and 3·44); $\nu_{max.}$ (KBr disc) 1754 and 1710 cm.$^{-1}$; τ 2·5—3·0 (8H; multiplet), 7·71 (3H; singlet), 8·26 (6H; singlet), and 8·90 (6H; singlet); mass spectrum: *m/e* 333 (6%), 318 (11%), 264 (7%), 263 (27%), 250 (3%), 248 (9%), 234 (57%), 194 (23%), 193 (100%), 180 (10%), 179 (8%),

70 (39%), and 69 (19%); metastable peaks at *m/e* 304, 193, and 178.

The mother-liquors from the preparation and recrystallisation of (Va) were concentrated and petroleum was added. On standing, crystals of 9,10-*dihydro*-10-(1-*methacryloyloxy*-2-*methylpropenyl*)-9-*methylacridine* (Ib) were deposited. After chromatographic purification on alumina and elution with benzene and petroleum, the adduct was obtained as needles (3·1 g., 15%), m. p. 117° (Found: N, 4·4. $C_{22}H_{23}NO_2$ requires N, 4·2%), $\lambda_{max.}$ (ethanol) 277 mμ (log ε 4·20); $\nu_{max.}$ (KBr disc) 1736 and 1699 cm.$^{-1}$; τ 2·6—3·2 (8H; multiplet), 3·92 (1H; multiplet), 4·50 (1H; multiplet), 5·97 (1H; quartet, J = 7 c./sec.), 8·14 (6H; singlet), 8·43 (3H; singlet), 8·75 (3H; doublet, J = 7 c./sec.); mass spectrum: *m/e* 333 (29%), 318 (100%), 264 (8%), 248 (7%), 194 (7%), 193 (6%), 179 (21%), 180 (13%), 70 (8%), and 69 (96%).

Use of light petroleum (b. p. 60—80) as a solvent for the reaction gave improved yields of (Ia) (32%) and (Va) (26%), but in dimethylacetamide only a trace of (Ia) was formed, though (Va) was isolated in 17% yield.

The Addition of Dimethylketen to 9-Ethylacridine.—Dimethylketen (*ca.* 10 g.) was passed into a solution of 9-ethylacridine (4 g.) in dry ether (120 ml.) and the solution set aside overnight. Evaporation of the solvent left an oil, which was dissolved in light petroleum (b. p. 60—80°) (12 ml.) from which crystals of tetramethylcyclobutanedione were deposited. The light petroleum solution was stored at 0° for several weeks during which time crystals of 6-*ethyl*-2-*isopropylidene*-5,5-*dimethyldibenzo*-3-*oxa*-1-*azabicyclo*-4,2,2]*deca*-7,9-*dien*-4-*one* (Vb) were slowly deposited. Recrystallisation from petroleum and benzene gave colourless needles (1·0 g.), m. p. 154—157° (decomp.) (Found: C, 79·2; H, 7·0; N, 4·0. $C_{23}H_{25}NO_2$ requires C, 79·5; H, 7·2; N, 4·0%), $\lambda_{max.}$ (ethanol) 239(s) and 278(s) mμ (log ε 3·84 and 2·22), $\nu_{max.}$ (KBr disc) 1757 and 1709 cm.$^{-1}$; τ 2·6—3·0 (8H; multiplet), 7·71 (2H; quartet, J = 7 c./sec.), 7·72 (3H; singlet), 8·30 (3H; singlet), 8·89 (6H; singlet), 9·31 (3H; triplet, J = 7 c./sec.); mass spectrum: *m/e* 347 (2%), 346 (4%), 318 (3%), 278 (16%), 277 (73%), 267 (10%), 262 (14%), 248 (3%), 209 (4%), 208 (48%), 207 (38%), 193 (18%), 192 (75%), 180 (6%), 179 (5%), 165 (7%), 70 (100%), and 69 (14%).

Thin-layer chromatography of the mother-liquors revealed the presence of a second product, which was partly purified by chromatography on alumina, and obtained as a pale brown oil the n.m.r. spectrum of which showed strong absorption at τ 3·9 and 4·4.

The Addition of Dimethylketen to 9-Phenylacridine.—Dimethylketen (*ca.* 9 g.) was passed into a solution of 9-phenylacridine (4·5 g.) in ether (350 ml.) and benzene (50 ml.) and the solution set aside overnight. Evaporation of the solution and recrystallisation of the residue from petroleum gave 9,10-*dihydro*-10-(1-*methacryloyloxy*-2-*methylpropenyl*)-9-*phenylacridine* (Id) as needles (3·0 g., 43%), m. p. 115—116° (Found: C, 82·5; H, 6·5; N, 3·2. $C_{27}H_{25}NO_2$ requires C, 82·0; H, 6·3; N, 3·5%) $\lambda_{max.}$ (ethanol) 279 mμ (log ε 4·10); $\nu_{max.}$ (KBr disc) 1736 and 1701 cm.$^{-1}$; τ 2·8—3·5 (13H; multiplet), 3·92 (1H; multiplet), 4·50 (1H; multiplet), 4·80 (1H; singlet), 8·11 (6H; broad singlet), 8·35 (3H; singlet); mass spectrum: *m/e* 395 (18%), 326 (13%), 318 (35%), 310 (3%), 256 (6%), 255 (8%), 248 (12%), 220 (14%), 180 (17%), 179 (18%), 70 (11%), and 69 (100%).

9,10-*Dihydro*-10-(1-*isobutyryloxy*-2-*methylpropenyl*)-9-*methylacridine* (IIIb). A solution of (Ib) (5 g.) in ethanol (500 ml.) was shaken with a palladium–charcoal catalyst in an atmosphere of hydrogen (1 atmos.) until absorption ceased. Filtration and evaporation of the solution gave the *dihydro-derivative* (IIIb) (3·7 g.), m. p. 109—110° (from ethanol) (Found: C, 78·7; H, 7·3; N, 4·1. $C_{22}H_{25}NO_2$ requires C, 78·8; H, 7·5; N, 4·2%), $\lambda_{max.}$ (ethanol) 277 mμ (log ε 4·16), $\nu_{max.}$ (KBr disc) 1760 and 1707 cm.$^{-1}$; τ 2·6—3·2 (8H; multiplet), 5·95 (1H; quartet, J = 7 c./sec.), 7·45 (1H; septet, J = 7 c./sec.), 8·14 (3H; singlet), 8·43 (3H; singlet), 8·73 (3H; doublet, J = 7 c./sec.), 8·90 (6H; doublet, J = 7 c./sec.).

Saponification of the Dihydroacridine (IIIb).—A mixture of (IIIb) (3 g.), ethanol (12 ml.), water (2·5 ml.), and potassium hydroxide (2 g.) was boiled under reflux for ½ hr., after which the ethanol was evaporated. Water (20 ml.) was added, and the mixture was extracted with ether, from which was obtained 9,10-dihydro-9-methylacridine (0·8 g.), m. p. 117—120°, identified by a mixed m. p. Isobutyric acid (0·5 ml.) was isolated from the aqueous layer of the ether extraction, and identified by comparison of its *S*-benzylthiuronium salt with an authentic specimen.

Lithium Aluminium Hydride Reduction of the Dihydroacridine (IIIb).—A mixture of (IIIb) (3·5 g.), ether (200 ml.), and lithium aluminium hydride (1·5 g.) was boiled under reflux for 1 hr. After decomposition of the excess hydride, the solution was filtered, dried ($MgSO_4$), and evaporated to small volume. On standing overnight at 0°, crystals (1·75 g.), m. p. 111—114°, were deposited, identified as 9,10-dihydro-10-isobutyryl-9-methylacridine by mixed m. p.

Distillation of the mother-liquor yielded a fraction, b. p. 105—110° (0·5 ml.), identified as isobutyl alcohol by a mixed m. p. of its 3,5-dinitrobenzoate.

The Reaction of the Dihydroacridine (IIIb) *with Benzylamine.*—A mixture of benzylamine (3 ml.) and (IIIb) (1 g.) was heated at 100° for 6 hr., after which the mixture was diluted with ether (30 ml.), extracted several times with dilute sulphuric acid, washed with water, and dried ($CaSO_4$). Evaporation of the ether left an oily residue which crystallised slowly. Fractional recrystallisation from petroleum gave *N*-benzylisobutyramide (0·3 g.), m. p. 89°, and 9,10-dihydro-10-isobutyryl-9-methylacridine (0·4 g.), m. p. 117—119°, both of which were identified by a mixed m. p.

9,10-*Dihydro*-10-*isobutyryl*-9-*methylacridine.*—A mixture of 9,10-dihydro-9-methylacridine (1·3 g.) and isobutyryl chloride (7·5 ml.) was heated at 100° for 2 hr. and then poured into ice-cold dilute ammonia. The oil, which separated, crystallised on standing, and recrystallisation from ethanol gave *the amide* as needles (1·3 g.), m. p. 118—120° (Found: C, 81·3; H, 7·1; N, 5·7. $C_{18}H_{19}NO$ requires C, 81·5; H, 7·2; N, 5·3%), $\lambda_{max.}$ (ethanol) 248 mμ (log ε 3·99), $\nu_{max.}$ 1665 cm.$^{-1}$, τ 2·3—3·0 (8H; multiplet), 6·19 (1H; quartet, J = 7 c./sec.), 6·68 (1H; septet, J = 7 c./sec.), 8·56 (3H; doublet, J = 7 c./sec.), 8·83 (6H; doublet, J = 7 c./sec.).

9,10-*Dihydro*-10-(1-*methoxy*-2-*methylpropenyl*)-9-*methylacridine* (IVb).—A solution of (IIIb) (1·5 g.) in dry methanol (8 ml.) and sulphuric acid (1 drop) was boiled under reflux for ½ hr. The solution was then evaporated to small volume when the product crystallised as needles (1 g.), m. p. 109—110° (from methanol) (Found: C, 81·8; H, 7·4; N, 5·2. $C_{19}H_{21}NO$ requires C, 81·7; H, 7·5; N, 5·0%), $\lambda_{max.}$ (ethanol) 281 mμ (log ε 4·35); $\nu_{max.}$ (KBr disc) 1690 cm.$^{-1}$, τ 2·7—3·3 (8H; multiplet), 5·86 (1H; quartet, J = 7 c./sec.), 6·59,

6·73 (total 3H; singlets), 8·06 and 8·12 (total 3H; singlets), 8·47, 8·65 (total 3H, singlets), 8·61 (3H; doublet, $J = 7$ c./sec.).

9,10-*Dihydro*-10-(1-*isobutyryloxy*-2-*methylpropenyl*)-9-*phenylacridine* (IIIc).—Hydrogenation of (Id), in conditions similar to those described above, gave the *dihydro-derivative* (IIIc) as crystals, m. p. 110—111° (from ethanol) (Found: C, 81·6; H, 6·9; N, 3·7. $C_{27}H_{27}NO_2$ requires C, 81·6; H, 6·8; N, 3·5%), $\lambda_{max.}$ (ethanol) 280 mμ (log ε 4·10), $\nu_{max.}$ (KBr disc) 1752 and 1701 cm.$^{-1}$, τ 2·7—3·3 (13H; multiplet), 4·80 (1H; singlet), 7·50 (1H; septet, $J = 7$ c./sec.), 8·14 (3H; singlet), 8·42 (3H; singlet), 8·94 (6H; doublet, $J = 7$ c./sec.).

9,10-*Dihydro*-10-(1-*methoxy*-2-*methylpropenyl*)-9-*phenylacridine* (IVc).—A solution of (IIIc) (2 g.) in dry methanol (100 ml.) and sulphuric acid (3 drops) was boiled under reflux for 3 hr. and the product isolated as in the preparation of (IIIb) as crystals (1·0 g.), m. p. 160° (from petroleum–benzene) (Found: C, 84·6; H, 6·8; N, 3·8. $C_{24}H_{23}NO$ requires C, 84·4; H, 6·7; N, 4·1%), $\lambda_{max.}$ (ethanol) 284 mμ (log ε 4·19), $\nu_{max.}$ (KBr disc) 1697 cm.$^{-1}$, τ 2·5—3·3 (13H; multiplet), 4·59 (1H; singlet), 6·66 and 6·69 (total 3H; singlets), 8·06 (3H; singlet), 8·48 and 8·60 (total 3H; singlets).

The Reaction of the Oxa-azabicyclodecadienone (Va) *with Sodium Borohydride.* A solution of (Va) (1·5 g.) and sodium borohydride (0·5 g.) in methanol (100 ml.) and aqueous sodium hydroxide (1 ml.; 2M) was stirred for 4 hr., after which the methanol was evaporated. The residue was extracted with a mixture of dilute sulphuric acid and ether, and the ether solution was washed with water and dried (Na_2SO_4). Evaporation of the ether and recrystallisation of the residue from petroleum followed by methanol gave *methyl* 2-(9,10-*dihydro*-10-*isobutyryl*-9-*methyl*-9-*acridinyl*)*isobutyrate* (VIa) (0·6 g.), m. p. 146—147° (Found: C, 75·6; H, 7·2; N, 4·0. $C_{23}H_{27}NO_3$ requires C, 75·5; H, 7·4; N, 3·8%), $\lambda_{max.}$ (ethanol) 250 and 280(s) mμ (log ε 3·90 and 3·24); $\nu_{max.}$ (KBr disc) 1721 and 1678 cm.$^{-1}$, τ 2·3—3·0 (8H; multiplet), 6·48 (3H; singlet), 6·76 (1H; septet, $J = 7$ c./sec.), 8·18 (3H; singlet), 8·74 (6H; doublet, $J = 7$ c./sec.), 8·90 (6H; singlet).

Methyl 2-(9,10-*dihydro*-10-*isobutyryl*-9-*methyl*-9-*acridinyl*)-*isobutyrate* (VIa).—A solution of (Va) (1 g.) in methanol (20 ml.) containing a little sodium methoxide was boiled under reflux for 1½ hr. The solution was cooled, acidified with acetic acid, and evaporated under reduced pressure. Recrystallisation of the residue from methanol gave the ester (0·5 g.) as needles, m. p. 146—147°, identified as the product of the reaction of (Va) with sodium borohydride by a mixed m. p.

2-(9,10-*Dihydro*-10-*isobutyryl*-9-*methyl*-9-*acridinyl*)*isobutyric acid* (VIb).—A mixture of (Va) (0·8 g.), ethanol (9 ml.), water (1 ml.), and potassium hydroxide (0·5 g.) was boiled under reflux for 1 hr. The solution was cooled, poured into water, and acidified with dilute sulphuric acid. The precipitate was collected and recrystallised from ethanol from which plates of the *acid* were obtained (0·4 g.), m. p. 220° (Found: C, 75·6; H, 7·1; N, 3·9. $C_{22}H_{20}NO_3$ requires C, 75·2; H, 7·1; N, 4·0%), $\lambda_{max.}$ (ethanol) 251 and 280(s) mμ (log ε 3·92 and 3·13); $\nu_{max.}$ (KBr disc) 1694 and 1669 cm.$^{-1}$; τ (pyridine) 6·70 (1H; septet, $J = 7$ c./sec.), 7·95 (3H; singlet), 8·67 (6H; singlet), 8·74 (6H; doublet, $J = 7$ c./sec.).

Treatment of a solution of (VIb) in methanol with diazomethane gave the methyl ester (VIa), identified by a mixed m. p.

The Reaction of the Oxa-azabicyclodecadienone (Va) *with Benzylamine.*—A mixture of benzylamine (4 ml.) and (Va) (1·5 g.) was heated at 100° for 10 hr., after which the mixture was diluted with ether, washed with dilute acid and water, and dried. Evaporation of the ether and recrystallisation of the residue from ethanol gave N-*benzyl*-2-(9,10-*dihydro*-10-*isobutyryl*-9-*methyl*-9-*acridinyl*)*isobutyramide* (VIc) as needles (0·9 g.), m. p. 148° (Found: C, 79·1; H, 7·4; N, 6·3. $C_{29}H_{32}N_2O_2$ requires C, 79·1; H, 7·3; N, 6·4%), $\lambda_{max.}$ (ethanol) 251 and 279(s) mμ (log ε 4·05 and 3·38); $\nu_{max.}$ (KBr disc) 1679 and 1625 cm.$^{-1}$; τ 2·3—3·0 (13H; multiplet), 4·55 (1H; broad triplet, $J = 5·5$ c./sec.), 5·73 (2H; doublet, $J = 5·5$ c./sec.), 6·78 (1H; septet, $J = 6·5$ c./sec.), 8·14 (3H; singlet), 8·76 (6H; doublet, $J = 6·5$ c./sec.), 8·88 (6H; singlet).

Pyrolysis of the Oxa-azabicyclodecadienone (Va).—A sample of (Va) was heated in a hard glass test tube in a stream of dry nitrogen and the gases evolved were passed into aniline, from which isobutyranilide was subsequently recovered and identified by comparison with an authentic specimen.

Reduction of the Oxa-azabicyclodecadienone (Va) *with Lithium Aluminium Hydride.*—A mixture of (Va) (1 g.), ether (200 ml.), and lithium aluminium hydride (0·5 g.) was boiled under reflux for 1 hr. After cooling, a portion (*ca.*, 40 ml.) of the mixture was removed and the excess of hydride decomposed by rapid addition of water. The ether solution was filtered, dried ($MgSO_4$), and evaporated, leaving an oily residue, which crystallised slowly. Recrystallisation from methanol gave 9,10-*dihydro*-9-(2-*hydroxymethyl*-2-*propyl*)-10-*isobutyryl*-9-*methylacridine* (VId) as prisms, m. p. 169—170° (Found: C, 78·2; H, 8·1; N, 4·2. $C_{22}H_{27}NO_2$ requires C, 78·3; H, 8·0; N, 4·2%), $\lambda_{max.}$ (ethanol) 249 and 280(s) mμ (log ε 4·12 and 3·2); $\nu_{max.}$ ($CHCl_3$) 3460 (KBr disc) and 1659 cm.$^{-1}$; τ 2·3—2·9 (8H; multiplet), 6·63 (2H; singlet), 6·70 (1H; septet, $J = 7$ c./sec.), 8·24 (3H; singlet), 8·42 (1H; broad singlet, OH gp.), 8·77 (6H; doublet, $J = 7$ c./sec.), 9·11 (6H; singlet).

The remainder of the reaction mixture was stirred and water was added very slowly from a micro-burette during several hours. The ether solution was then worked-up to give 9,10-*dihydro*-9-(2-*isobutyryloxymethyl*-2-*propyl*)-9-*methylacridine* (VIe) as needles, m. p. 125—126° (from ethanol) (Found: C, 78·4; H, 8·2; N, 3·9. $C_{22}H_{27}NO_2$ requires C, 78·3; H, 8·0; N, 4·2%), $\lambda_{max.}$ (ethanol) 279 mμ (log ε 4·24); $\nu_{max.}$ (KBr disc) 3357 and 1705 cm.$^{-1}$, τ 2·5—3·5 (8H; multiplet), 3·73 (1H; broad singlet, NH gp.), 6·19 (2H; singlet), 7·57 (1H; septet, $J = 7$ c./sec.), 8·17 (3H; singlet), 8·92 (6H; doublet, $J = 7$ c./sec.), 9·18 (6H; singlet).

Conversion of (VId) *into* (VIe).—A mixture of (VId) (0·16 g.), ether (20 ml.), and methanol (0·5 ml.) containing a trace of sodium methoxide was stirred for 5 min. The ether solution was washed with water, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue gave (VIe) (0·07 g.) m. p. 115—120° identified by a mixed m. p.

9,10-*Dihydro*-9-(2-*hydroxymethyl*-2-*propyl*)-9-*methylacridine* (VIf).—A solution of (VIe) (0·8 g.), ether (100 ml.), and lithium aluminium hydride (0·4 g.) was boiled under reflux for 4 hr. After decomposition of the excess of hydride the ether solution was filtered, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from light petroleum and benzene gave the *crystalline acridan* (0·2 g.), m. p. 139—140° (Found: C, 80·7; H, 8·0; N, 5·2. $C_{18}H_{21}NO$ requires C, 80·9; H, 7·9; N, 5·2%), $\lambda_{max.}$ (ethanol) 285 mμ

(log ε 4·19), $\nu_{max.}$ (KBr disc) **3474** and **3371** cm.$^{-1}$, τ 2·5—3·5 (8H; multiplet), 3·82 (1H; broad singlet), 6·72 (2H; singlet), 8·19 (3H; singlet), 8·63 (1H; singlet), 9·20 (6H; singlet).

Reduction of (VId) in similar conditions gave an identical product.

Attempted Conversion of (VIf) *into* (VId).—A mixture of (VIf) (0·8 g.) and isobutyryl chloride (7·5 ml.) was heated at 100° for 2 hr. and then poured on ice. The precipitated oil crystallised on standing and was identified as unchanged (VIf) by a mixed m. p.

9-(2-*Carboxy*-2-*propyl*)-9,10-*dihydro*-10-(1-*methoxy*-2-*methylpropenyl*)-9-*methylacridine* (VIj).—A solution of (Va) (2 g.) in dry methanol (120 ml.) and sulphuric acid (1 drop) was boiled under reflux for 3 hr. The solution was evaporated under reduced pressure, and the residue recrystallised from methanol, and then light petroleum–benzene, giving *prisms* of (VIj) (1·3 g.), m. p. 169—170° (Found: C, 75·9; H, 7·4; N, 4·0. $C_{23}H_{27}NO_3$ requires C, 75·6; H, 7·4; N, 3·8%), $\lambda_{max.}$ (ethanol) 282 mμ (log ε 4·47); $\nu_{max.}$ ($CHCl_3$) 3515, 1719, and 1669 cm.$^{-1}$, τ −1·62 (1H, broad singlet, OH gp.), 2·4—3·3 (8H; multiplet), 6·46, 6·93 (total 3H; singlets), 7·85 (3H; singlet), 8·07 (3H, singlet), 8·39, 8·81 (total 3H; singlets), 8·92 (6H; singlet).

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