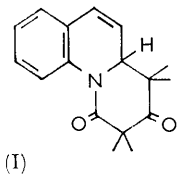
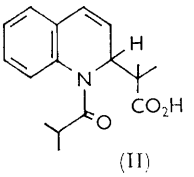
1103. *Keten. Part II.* The Reaction of Dimethylketen with Acridine*

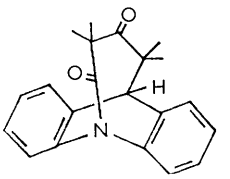
By S. A. Procter and G. A. Taylor

Acridine reacts with two molecules of dimethylketen to form 9,10-dihydro-10-(1-methacryloyloxy-2-methylpropenyl)acridine (IV), not the bridged structure (III) originally proposed.

The reaction of dialkylketens with heterocyclic bases was one of the earliest reactions of ketens described by Staudinger.[1] Quinoline forms an adduct with two molecules of dimethylketen [2] for which the structure (I) was proposed.[3,4] The new ring in (I) could be


(I)


(II)


(III)

cleaved hydrolytically by dilute mineral acid to give the acid (II), or by bases to give derivatives of (II). Adducts of dimethylketen with quinaldine,[3] 6-methylquinaldine,[3] and isoquinoline [4] were also reported, and structures similar to (I) were assigned. In most cases the amido-acid corresponding to (II) was prepared and characterised.

The reaction of dimethylketen with acridine was also investigated, and an adduct of one molecule of acridine with two of dimethylketen was obtained.[3] Unlike the adducts of quinoline, etc., this compound was resistant to acid hydrolysis up to the point where decomposition occurred, and no acid corresponding to (II) was obtained. In the absence of a suitable position for ring-closure adjacent to the nitrogen atom, the structure (III) was proposed,[4] reaction being thought to occur by " breakage of the *para* bond."

In view of the failure of acridine to form bridged adducts with reagents such as dimethyl acetylenedicarboxylate,[5] benzyne,[6] or *o*-xylylene,[7] the structure (III) was of some interest as a possible intermediate in the synthesis of acridan (9,10-dihydroacridine) derivatives with a bridge in the 9,10-position. Accordingly the adduct was investigated with a view to verifying Staudinger's structure.

Dimethylketen reacted smoothly with acridine, giving the reported adduct $C_{21}H_{21}NO_2$ in good yield, and on hydrogenation this compound gave a dihydro-derivative. Neither the adduct nor its dihydro-derivative gave a dinitrophenylhydrazone, and reduction of the adduct with lithium aluminium hydride gave *N*-isobutyrylacridan. Reduction of the dihydro-derivative with lithium aluminium hydride gave *N*-isobutyrylacridan and isobutyl alcohol. Attempted reduction of the adduct or its dihydro-derivative with sodium borohydride gave only *N*-isobutyrylacridan, which might have been produced by alkaline hydrolysis under the reaction conditions.

The dihydro-derivative on treatment with hot alkali gave acridan and isobutyric acid, and reaction with benzylamine gave benzylisobutyramide and *N*-isobutyrylacridan.

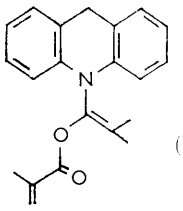
The nuclear magnetic resonance (n.m.r.) spectra of the adduct and its dihydro-derivative conclusively dispose of structure (III). Singlets at τ 5·95 (2 protons) in the adduct and

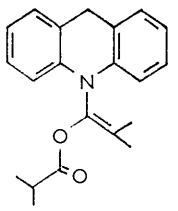
* Part I, G. A. Taylor, *J.*, 1965, 3332.

[1] H. Staudinger, " Die Ketene," Ferdinand Enke, Stuttgart, 1912.
[2] H. Staudinger and H. W. Klever, *Ber.*, 1906, **39**, 968.
[3] H. Staudinger and H. W. Klever, *Ber.*, 1907, **40**, 1149.
[4] H. Staudinger, H. W. Klever, and P. Kober, *Annalen*, 1910, **374**, 1.
[5] R. M. Acheson and M. L. Burstall, *J.*, 1954, 3240.
[6] G. Wittig and K. Niethammer, *Chem. Ber.*, 1960, **93**, 944.
[7] K. Sisido, K. Tani, and H. Nozaki, *Tetrahedron*, 1963, **19**, 1323.

τ 5·90 (2 protons) in the dihydro-derivative correspond to the singlet at τ 5·96 (2 protons) in the spectrum of acridan (present work). Singlets at τ 8·17 and 8·40 (3 protons each) in the spectrum of the adduct correspond to singlets at τ 8·17 and 8·42 (3 protons each) in the spectrum of the dihydro-derivative, and an isopropenyl group in the adduct shows as multiplets at τ 8·15 (3 protons, $J = 1$ c./sec.), 4·50 (1 proton), and 3·88 (1 proton), replaced by the peaks of an isopropyl group at τ 8·89 (doublet, 6 protons, $J = 7$ c./sec.) and 7·42 (septet, 1 proton) in the spectrum of the dihydro-derivative. Both the adduct and its dihydro-derivative have a total of eight more protons absorbing in the region τ 2·7—3·3.

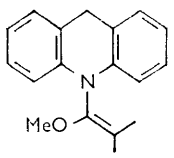
The degradative evidence coupled with the n.m.r. spectra lead to (IV) as the only possible structure for the adduct, and (V) as the structure of its dihydro-derivative.

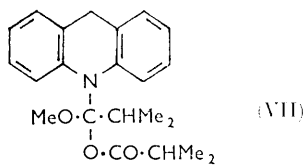

(IV)


(V)

Their ultraviolet spectra are consistent with the presence of an acridan nucleus, and the carbonyl absorptions in the infrared at 1732 and 1751 cm.$^{-1}$, respectively, are consistent with the unsaturated ester groups present in (IV) and (V).

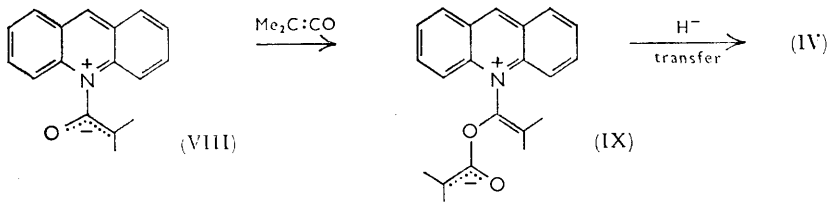
The presence of a keten *ON*-acetal group was confirmed by the reaction of the dihydro-compound (V) with methanol and sulphuric acid. A compound $C_{18}H_{19}NO$ was obtained to which the structure (VI) was assigned on the basis of the n.m.r. spectrum. The acridan moiety was shown by the singlet at τ 5·88 (2 protons) and multiplets at τ 2·7—3·3 (8


(VI)


(VII)

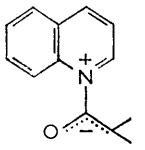
protons), and the rest of the spectrum consisted of three singlets at τ 6·69, 8·12, and 8·57 (3 protons each) corresponding to one OCH_3 and two CCH_3 groups. The conversion of (V) into (VI) probably occurs by addition of methanol to the double bond of (V), followed by elimination of isobutyric acid from the intermediate (VII). Hydrolysis of (VI) under acid conditions gave acridan.

The first step in the formation of (IV) is probably the nucleophilic attack of acridine on dimethylketen to give the zwitterion intermediate (VIII). Further reaction of this species with another molecule of dimethylketen to give (IX), followed by transfer of a

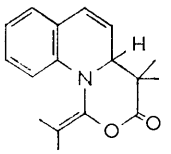


hydride ion from the end of the side-chain to the 9-position of the acridinium moiety, would account for the observed product. A hydride transfer as the final step is unexpected, not only because the positions between which transfer occurs are remote, although models show that the terminal methyl groups of the side-chain can approach the 9-position closely, but also because a similar type of intermediate occurring in the addition of dimethylketen

to quinoline undoubtedly leads to a ring-closed product. A second unexpected feature of this reaction is the formation of the keten *ON*-acetal system as opposed to the β-keto-amide system in the adducts with quinoline, etc. It is difficult to see why the reaction of dimethylketen with (VIII) should proceed in a different way from the reaction with (X), which is presumably the intermediate in the formation of (I) from quinoline and dimethylketen, and the conversion of (VIII) into (IX) is consistent with the well known ability of keten to acylate enols [8] and enolate anions.[9] An alternative possibility is that the adducts of quinoline, etc., with dimethylketen have structures like (XI) rather than (I). Structures such as (XI) would be consistent with the chemistry of these adducts described by Staudinger, and would account for the absence of ketonic properties and the easy cleavage of the new ring by such mild reagents as superheated water or aniline to give the acid (II) and its anilide, respectively.



(X)



(XI)

Experimental

Nuclear magnetic resonance spectra were measured in deuterochloroform with a Varian A60 spectrometer.

9,10-*Dihydro*-10-(1-*methacryloyloxy*-2-*methylpropenyl*)*acridine* (IV.).—Dimethylketen (approx. 18 g.), obtained by pyrolysis of tetramethylcyclobutanedione,[10] was passed into a solution of acridine (18 g.) in dry ether (600 ml.), and the solution was set aside overnight. Evaporation of the ether and recrystallisation of the residue from light petroleum gave the product as prisms (25 g., 78%), m. p. 127—128° (Found: C, 79·2; H, 6·6; N, 4·5. Calc. for $C_{21}H_{21}NO_2$: C, 79·0, H, 6·6; N, 4·4%), $\lambda_{max.}$ 205·5, 278 mμ (log ε 4·69, 4·11), $\nu_{max.}$ (KBr disc) 1732 cm.$^{-1}$.

9,10-*Dihydro*-10-(1-*isobutyryloxy*-2-*methylpropenyl*)*acridine* (V).—A solution of (IV) (7 g.) in ethanol (300 ml.) was shaken with hydrogen (1 atm.) and palladium–charcoal catalyst until absorption ceased. Filtration and evaporation of the solution gave the *product*, crystals (6·0 g.), m. p. 67—68° (from ethanol) (Found: C, 78·6; H, 7·2; N, 4·5. $C_{21}H_{23}NO_2$ requires C, 78·5; H, 7·2; N, 4·4%), $\lambda_{max.}$ 280 mμ (log ε 4·11), $\nu_{max.}$ (KBr disc) 1751 cm.$^{-1}$.

Saponification of (V).—A mixture of (V) (6 g.), ethanol (25 ml.), water (5 ml.), and potassium hydroxide (4 g.) was boiled for ½ hr., after which the ethanol was distilled off. Water (20 ml.) was added to the residue, and the mixture was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving acridan (2·4 g., 71%), m. p. 168° and mixed m. p. (from ethanol). The aqueous layer from the ether extraction was acidified, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. Distillation of the residual liquid gave a fraction, b. p. 146—158° (2·2 g.), containing isobutyric acid, isolated as its *S*-benzylthiouronium salt, m. p. and mixed m. p. 148—150°.

The Reaction of (V) *with Lithium Aluminium Hydride.*—A mixture of (V) (6 g.), ether (150 ml.), and lithium aluminium hydride (2 g.) was boiled under reflux for 6 hr. The excess hydride was decomposed, and the ether solution filtered and evaporated. The oily residue was distilled at 100°/15 mm., giving a colourless distillate (1·0 ml.), b. p. 106°, identified as isobutyl alcohol by mixed m. p. determination of the 3,5-dinitrobenzoate, m. p. 87°.

The residue from the distillation, on recrystallisation from light petroleum, gave pale yellow crystals (3·9 g.) identified (mixed m. p.) as 9,10-*dihydro*-10-*isobutyrylacridine*. After recrystallisation from light petroleum it was obtained as colourless prisms, m. p. 84° (Found: C, 81·0; H, 6·8; N, 6·1. $C_{17}H_{17}NO$ requires C, 81·3; H, 6·8; N, 5·9%).

The Reaction of (IV) *with Lithium Aluminium Hydride.*—Under conditions similar to those reported above, 9,10-dihydro-10-isobutyrylacridine was the only identifiable product.

The Reaction of Sodium Borohydride with (IV) *and* (V).—Under the usual conditions, in both cases 9,10-dihydro-10-isobutyrylacridine was the only identified product.

[8] E. F. Degering and B. H. Gwynn, *J. Amer. Chem. Soc.*, 1942, **64**, 2216.
[9] E. F. Degering and J. A. Spence, U.S.P. 2,472,628 (1949).
[10] J. R. Johnson and J. M. Witzel, *Org. Reactions*, 1946, **3**, 136.

9,10-*Dihydro*-10-*isobutyrylacridine*.—A mixture of acridan (1 g.) and isobutyryl chloride (5 ml.) was boiled for 40 min., cooled, and poured into ice and dilute ammonia solution. An oil which separated crystallised on standing. Recrystallisation from light petroleum followed by methanol gave colourless crystals of 9,10-dihydro-10-isobutyrylacridine, m. p. 84° (Found: C, 81·0; H, 6·7%), $\lambda_{max.}$ 237·5sh, 245 mμ (log ε 3·95, 3·97), $\nu_{max.}$ (KBr disc) 1685 cm.$^{-1}$.

The Reaction of (V) *with Benzylamine*.—A mixture of benzylamine (4 ml.) and (V) (2 g.) was heated at 100° for 6 hr., after which the mixture was diluted with ether (30 ml.). The ether solution was extracted several times with dilute sulphuric acid, washed with water, dried ($CaSO_4$), and evaporated, to leave a yellow oil which crystallised slowly. Fractional recrystallisation of the residue from light petroleum gave *N*-benzylisobutyramide (0·7 g.), m. p. 89°, and *N*-isobutyrylacridan (0·3 g.), m. p. 80°, both of which were identified by mixed m. p.

Attempted Reaction of (V) *with Aniline*.—A mixture of (V) (1·8 g.) and aniline (10 ml.) was boiled for 2 hr., after which it was cooled, diluted with ether, and extracted with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The ether solution was dried ($MgSO_4$) and evaporated, leaving an oily residue which solidified on standing. Recrystallisation of the residue from ethanol gave only the starting material (V), m. p. 66—68°, identified by mixed m. p.

9,10-*Dihydro*-10-(1-*methoxy*-2-*methylpropenyl*)*acridine* (VI).—A solution of (V) (5 g.), in dry methanol (16 ml.), and sulphuric acid (1 drop) was boiled under reflux for ½ hr. The mixture was evaporated to small volume and cooled, and the *product* separated (3·5 g.), colourless crystals, m. p. 107—108° (from methanol) (Found: C, 81·4; H, 7·1; N, 5·1. $C_{18}H_{19}NO$ requires C, 81·5; H, 7·2; N, 5·3%), $\lambda_{max.}$ 287 mμ (log ε 4·16).

Hydrolysis of (VI).—A solution of (VI) (0·35 g.) in acetic acid (4·0 ml.), water (1·5 ml.), and sulphuric acid (1 ml.) was heated to 100° for 1 min. After cooling, the solution was made alkaline and extracted with ether. When the ether solution was worked up in the normal way, acridan (0·1 g.) was obtained (identified by mixed m. p.).

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