Steroidal Alkaloids. Part II. Some Observations on the Constitution of Cevine.*

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Treatment of " anhydrocevine " (cevine orthoacetate) with periodic acid affords a crystalline aldehydo-γ-lactone, thus confirming the masked α-ketolic character of cevine.

Acetylation of cevine with hot pyridine–acetic anhydride gives a crystalline triacetate which is stable to chromic acid, thus proving that the α-glycol system of cevine is ditertiary.

The ready interconversion of cevine and " anhydrocevine " tetra-acetates has been demonstrated. The two compounds come to equilibrium with each other at room temperature in solvents containing acetic acid. The " anhydro "-compounds of cevine and its derivatives have been shown to be orthoacetates. The kinetics of orthoacetate formation in the cevine tetra-acetate system have been elucidated and mechanistic proposals have been entertained.

In Part I* of this series the functional groups of the steroidal alkamine, cevine, $C_{27}H_{43}O_8N$, were classified as follows. Three oxygen atoms bound in a masked α-ketol system (I; R = R′ = H); † two oxygen atoms present as a ditertiary or tertiary-(sterically hindered)secondary α-glycol, and one oxygen atom present as an easily esterified primary or secondary hydroxyl group; the remaining two oxygen atoms are classified as tertiary hydroxyl groups. The absence of an ethylenic linkage and the heptacyclic character of the molecule were demonstrated. Our attention has now been turned to a more detailed examination of the complex chemistry of cevine.

Our efforts were first directed to verification of the presence of the grouping (I; R = R′ = H). Reduction of cevine by sodium and alcohol gives, besides dihydrocevine, a deoxydihydrocevine (Jacobs and Craig, *J. Biol. Chem.*, 1938, **125**, 625). The loss of one hydroxyl group is nicely accounted for by the α-ketolic formulation (cf. Macbeth and Robertson, *J.*, 1953, 3512).

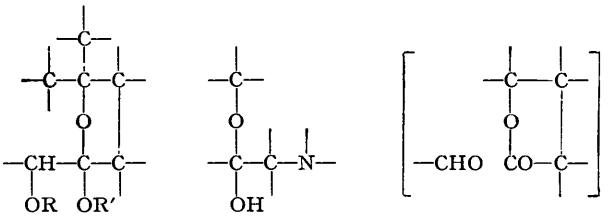
Many of the experimental facts previously discussed are compatible with an alternative masked tertiary α-amino-ketone formulation as in (II). This must be rejected on the following grounds. Whilst the tertiary α-amino-ketone *N*-acetonylpiperidine reduced Fehling's solution and consumed 1 mol. of lead tetra-acetate, its methiodide had no reducing power and consumed no significant amount of lead tetra-acetate. Cevine methiodide, on the other hand, retained intact the reducing power of cevine and, like cevine, consumed 2 mols. of lead tetra-acetate almost instantaneously. Clearly the masking of the nitrogen atom of cevine by quaternisation has no effect on those properties of the molecule which we have ascribed (Barton and Eastham, *loc. cit.*) to the presence of the masked α-ketol system.

The partial structure (I; R = R′ = H) was finally confirmed as follows (see also Barton and Brooks, *Chem. and Ind.*, 1953, 1366). " Anhydrocevine " (cevine ortho-acetate, see below) (Stoll and Seebeck, *Helv. Chim. Acta*, 1953, **36**, 189) in which the ditertiary α-glycol system (see further below) is protected against glycol cleavage, consumed 1 mol. of periodic acid, to give a nicely crystalline compound (III). This was characterised by its infra-red spectrum (in chloroform) as a γ-lactone (band at 1770 $cm.^{-1}$)

* Part I, *J.*, 1953, 424.

† In partial formula (I) we have formed the ether bridge of cevine from a tertiary hydroxyl, not from a secondary hydroxyl, group as in the paper by Barton and Eastham (Part I). The reason for the change is that " anhydrocevagenin triacetate " is now recognised as cevagenin orthoacetate diacetate (see below), and we find that it is stable to chromic acid. It cannot therefore retain an unacetylatable secondary hydroxyl group. These experiments, carried out in collaboration with Dr. P. de Mayo, will be published in the near future.

and as an aldehyde (bands at 1724 and 2730 cm.$^{-1}$). The presence of the carbonyl group was substantiated by the preparation of a 2 : 4-dinitrophenylhydrazone. This retained the γ-lactone band (in chloroform) at 1775 cm.$^{-1}$, but had lost the bands indicative of the aldehyde function. Further, the ultra-violet absorption maximum was characteristic of that of an aldehyde derivative (see Braude and Jones, *J.*, 1945, 498). The cleavage



(I) (II) (III)

product showed reducing power towards Fehling's solution in consonance with its aldehydic nature.

Additional evidence for the masked α-ketolic structure of cevine has been provided by Sundt, Jeger, and Prelog (*Chem. and Ind.*, 1953, 1365) and by Stoll, Stauffacher, and Seebeck (*Helv. Chim. Acta*, 1953, **36**, 2027), who oxidised the α-ketol cevagenin (see Barton and Eastham, *loc. cit.*) to the corresponding diosphenol.

Treatment of cevine under mild acetylating conditions affords a diacetate (I; R = Ac, R′ = H) (see Barton and Eastham, *loc. cit.*). We now find that when cevine is heated on the steam-bath with pyridine–acetic anhydride it affords a crystalline triacetate which we formulate as (I; R = R′ = Ac). There is sound analogy (Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252) for the preferential acetylation of the tertiary hydroxyl group attached to the carbon bearing the ethereal oxygen atom (relative to the other tertiary hydroxyl groups). The triacetate retained the α-glycol system of cevine for it consumed 1 mol. of lead tetra-acetate and of periodic acid. It was, however, resistant to chromic acid oxidation and therefore a first proof is provided that the α-glycol system of cevine is indeed ditertiary.

We now turn to a consideration of the nature of " anhydrocevine " (see also Barton and Fawcett, *Chem. and Ind.*, 1953, 615). Treatment of cevadine with acetic anhydride and perchloric acid gives " triacetylanhydrocevadine " (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942; Kupchan, Lavie, Deliwala, and Andoh, *J. Amer. Chem. Soc.*, 1953, **75**, 5519) whilst cevagenin affords " triacetylanhydrocevagenin " under analogous but not identical conditions (Stoll and Seebeck, *loc. cit.*). The last authors showed that the " anhydro "-compounds were produced with disappearance of the (ditertiary) α-glycol system and regarded them as formed by the change

Stoll and Seebeck (*loc. cit.*) also drew attention to the fact that comparable acetylation of cevine itself gave cevine tetra-acetate, and not an " anhydro "-compound. It seemed to us that this difference might be of structural significance and that it justified a further examination of " anhydro "-compound formation. We soon found that " anhydrocevine tetra-acetate " previously obtained by Stoll and Seebeck (*Helv. Chim. Acta*, 1953, **36**, 189) by an indirect route from veracevine * (Pelletier and Jacobs, *J. Amer. Chem. Soc.*, 1953, **75**, 3248; Kupchan *et al.*, *loc. cit.*) is, in fact, the direct product of perchloric acid-catalysed

* We thank cordially Dr. S. M. Kupchan (Harvard) for informing us that he intends to withdraw his name protocevine for this compound and to use instead the name veracevine proposed by Pelletier and Jacobs. Dr. Kupchan has also kindly informed us of experiments on veracevine triacetate which parallel those reported by us on cevine triacetate (see Kupchan and Lavie, *J. Amer. Chem. Soc.*, 1954, **76**, 314).

acetylation, and that cevine tetra-acetate itself is formed by ready hydration during crystallisation from aqueous acetic acid. Further investigation revealed that both cevine tetra-acetate and its " anhydro "-derivative and their respective perchlorates came into equilibrium with each other in aqueous acetic acid at room temperature. In pure acetic acid the equilibrium is 100% on the side of the " anhydro "-compound, in water it is 100% on the side of the cevine tetra-acetate. Illustrative data for the equilibrium of the perchlorates at 28·2° in mixtures of acetic acid and water are summarised in Table 1. Most of the results were, for convenience, obtained by starting with cevine tetra-acetate

TABLE 1.

Acetic acid (%, v/v)	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	" Anhydro " (ortho-acetate) derivative (%) at equil.*	Acetic acid (%, v/v)	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	" Anhydro " (ortho-acetate) derivative (%) at equil.*
100	+118°	1·14	100	60	+54·5	1·21	23·0
95	+ 95·5	1·49	72·5	50	+53	3·27	21·2
90	+ 82	1·10	56·5	30	+49	2·01	16·5
85	+ 73	1·36	45·5	20	+46	0·95	12·7
80	+ 64·5	1·62	35·0	0	+35·5 †	0·20	0
70	+ 61	3·38	31·0				

* The composition of the equilibrium mixture is calculated on the basis of $[\alpha]_D$ +118° for " anhydrocevine tetra-acetate " (cevine orthoacetate triacetate) perchlorate and +35·5° for cevine tetra-acetate perchlorate.

† Determined in 4-dm. tube ; the other rotations were taken in 1-dm. tubes.

perchlorate but appropriate check determinations were run starting with the " anhydro "-compound.

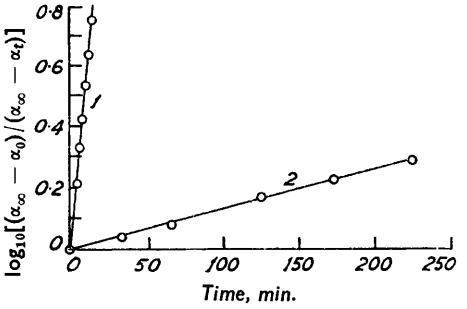
The analytical data of Stoll and Seebeck (*loc. cit.*) disclosed that the " anhydro "-compounds are indeed formed by dehydration. The dependence of the equilibrium data summarised in Table 1 on the water content of the medium confirms this conclusion. It seemed to us, however, that the " anhydro "-compounds were more likely to be tetrahydrofuran or pyran derivatives (see Barton and Fawcett, *loc. cit.*) or even orthoacetates, than epoxides. The possibility of an orthoacetate formulation was strengthened by a comparative study of the infra-red spectra of cevine tetra-acetate and " anhydrocevine tetra-acetate." In chloroform solution it was found that the strength of the acetate band at 1734 cm.$^{-1}$ was only about 75% as intense for the " anhydro "-compound as for cevine tetra-acetate. Further, the infra-red spectrum of " anhydrocevine tetra-acetate " showed a significantly displaced " methyl " band at 1397 cm.$^{-1}$, which band is present for ethyl orthoacetate (at 1392 cm.$^{-1}$ in carbon tetrachloride solution) and other " anhydro "-compounds of cevine, but absent for other cevine derivatives. In addition " anhydrocevine tetra-acetate " has a complex series of ether bands near 1140 cm.$^{-1}$ which is also present in the ethyl orthoacetate spectrum.

The correctness of the orthoacetate formulation was finally proved by a study of " anhydrocevine." In the infra-red spectrum of its carbon tetrachloride solution this compound shows no acetate band, but possesses the displaced " methyl " band at 1404 cm.$^{-1}$ and the complex ether bands near 1140 cm.$^{-1}$. Analytical data disclosed the formula $C_{29}H_{43}O_8N,CH_3{\cdot}OH$ and were not in agreement with earlier findings by Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942) which suggested a formula $C_{27}H_{41}O_7N$. The equivalent weight of " anhydrocevine " was in excellent agreement with the new formula. Finally acetyl determinations revealed the presence of one " acetyl " group, confirmed by the characterisation of the acetic acid as its *p*-bromophenacyl ester—cevine, itself, gave no volatile acid under the conditions of the acetyl determination. In the Kuhn–Roth *C*-methyl determination cevine showed an average of 5·8% of *C*-methyl groups and " anhydro-cevine " an average of 8·2%, again in agreement with the orthoacetate formulation. Our findings require the following nomenclature changes (new name in parentheses) : " anhydrocevine " (cevine orthoacetate) ; " anhydrocevine tetra-acetate " (cevine orthoacetate triacetate) ; " anhydrocevagenin triacetate " (cevagenin orthoacetate diacetate) ; and so on.

The large rotational shift accompanying orthoacetate formation makes this reaction

well suited to kinetic analysis. In pure acetic acid the dehydration of cevine tetra-acetate to cevine orthoacetate triacetate is quantitative and follows first-order kinetics up to at least 70% conversion. Illustrative data are plotted in the Figure. Reproducibility was satisfactory as shown by appropriate repetitions. Preliminary experiments in aqueous acetic acid indicated that in this medium the two compounds came into equilibrium by reversible first-order reactions, but we have not made an extensive investigation.

The conversion of cevine tetra-acetate perchlorate into the corresponding orthoacetate in acetic acid containing 20% v/v of acetone has also been studied. This change is likewise of the first order (cf. Figure). It was remarkable that the perchlorate reacted about



1, *Cevine tetra-acetate in acetic acid at* 28·2°.
2, *Cevine tetra-acetate perchlorate in* 80% *v/v acetic acid–acetone at* 28·2°.

60 times *slower* than the parent base. This observation stimulated us to examine the effect of perchloric acid and of triethylamine. Both compounds catalysed orthoacetate formation in proportion to the amount added (see Table 2; measurements were at 28·2° in pure acetic acid).

TABLE 2.

Concn. (g./100 ml.)	Concn. (x) of catalyst	$10^3 k$ (min.$^{-1}$)	$10^3(k - k_0)/x$	Concn. (g.100 ml.)	Concn. (x) of catalyst	$10^3 k$ (min.$^{-1}$)	$10^3(k - k_0)/x$
Perchlorates.				*Free bases.*			
1·63	0·0 *	2·95 (k_0)	—	1·63	0·0	122 (k_0)	—
1·34	0·023 †	164	7000	1·54	1·0 ‡	166	44
1·54	0·047	300	6300	1·53	2·0	209	43·5
				1·52	3·0	256	43·5
				1·66	5·0	348	45

* Value for reaction in acetic acid containing 20% of dry acetone: the equilibrium point lies at 97·5% of complete reaction and so does not affect the simple first-order kinetics.
† G./100 ml. ‡ Ml./100 ml. of solution.

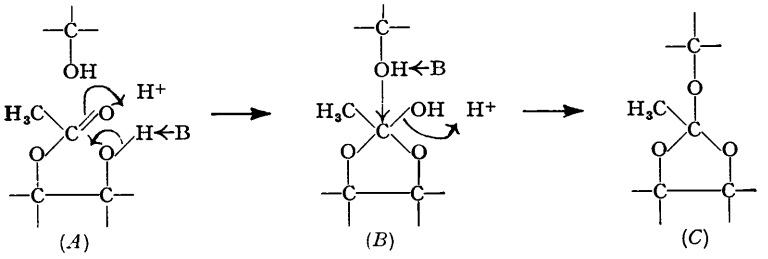
The variation of rate of orthoacetate formation with temperature has been studied for cevine tetra-acetate (Table 3). The results gave a straight-line activation energy plot from which it can be calculated that $k = 9{\cdot}1 \times 10^{10}\, e^{-16{,}400/RT}$ min.$^{-1}$ for the formation of cevine orthoacetate triacetate in pure acetic acid. The results at each temperature were closely duplicated in repetitions.

TABLE 3.

Temp.	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	Orthoacetate (%) at equil.	$10^3 k$ (min.$^{-1}$)
28·2°	+127°	1·63	100	122
33·5	+127	1·45	100	198
39·0	+127·5	1·59	100	314

The catalytic action of acid and base (cf. Swain and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2538) on the rate of orthoacetate formation and the observed kinetic effects can be reconciled with a mechanism such as that annexed (B = base). At the present time we cannot distinguish the rate-determining step. Either (*A*) and (*B*) must be in equilibrium and (*B*) ⟶ (*C*) is rate-determining; or (*A*) ⟶ (*B*) is slow relative to (*B*) ⟶ (*C*). The assignment of a definite mechanistic role to the base explains the otherwise curious fact that

the perchlorate reacts so much more slowly (as there is no free tertiary amine) than the free base.



Experimental

For general experimental details see *J.*, 1953, 424. Unless specified to the contrary, rotations were determined in chloroform solution at room temperature and light absorption maxima in ethanol (with a Unicam S.P. 500 Spectrophotometer). Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd. in carbon disulphide solution except as otherwise stated. Acetyl determinations were carried out according to H. Roth, Pregl's " Quantitative Organic Microanalysis," J. and A. Churchill Limited, London, 1937.

Deoxydihydrocevine.—Cevine was reduced with sodium and ethanol (instead of *n*-butanol) according to the directions of Jacobs and Craig (*J. Biol. Chem.*, 1938, **125**, 625). Isolation of the product by chloroform extraction (cf. *idem, loc. cit.*) and concentration of the chloroform solution gave deoxydihydrocevine (10—25%), m. p. 276—278°, $[\alpha]_D$ −18° (*c*, 1·98 in MeOH) (Found: C, 65·0; H, 9·25. Calc. for $C_{27}H_{45}O_7N$: C, 65·4; H, 9·15%). Evaporation of the mother-liquors and crystallisation from methanol furnished dihydrocevine (15—20%).

Confirmatory Tests for the α-Ketolic Structure of Cevine.—Cevine, cevine orthoacetate, cevine methiodide, and *N*-acetonylpiperidine (kindly supplied by Dr. R. C. Cookson) all gave strongly positive reducing tests with Fehling's solution. *N*-Acetonylpiperidine methiodide (Stoermer and Burkert, *Ber.*, 1895, **28**, 1250) was non-reducing.

Lead tetra-acetate titrations were carried out according to the procedure described in Part I (*loc. cit.*). The uptake in mols. of oxidant after 5 min. was: cevine, 1·95; cevine methiodide, 1·98; cevine tetra-acetate methiodide, <0·2; *N*-acetonylpiperidine, 0·96; *N*-acetonylpiperidine methiodide, 0·04.

Cevine Tetra-acetate.—The perchlorate (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1270) had (from aqueous acetic acid) $[\alpha]_D$ +38° (*c*, 0·95 in MeOH), +35° (*c*, 1·18 in acetone). The two forms of this compound described in Part I are the true cevine tetra-acetate perchlorate (lower m. p.) and cevine orthoacetate triacetate perchlorate (higher m. p., see below). The derived cevine tetra-acetate had m. p. 295—297° (decomp.), $[\alpha]_D$ +22° (*c*, 2·05), +37° (*c*, 2·10 in MeOH), +35° (*c*, 0·84 in acetone), +36° (*c*, 1·10 in EtOH).

Cevine Orthoacetate Triacetate.—Cevine tetra-acetate perchlorate (500 mg.) in " AnalaR " acetic acid (10 ml.) was heated on the steam-bath for 10 min. Concentration *in vacuo* gave *cevine orthoacetate triacetate perchlorate* (400 mg.), m. p. (from acetic acid) 268—269° (decomp.), $[\alpha]_D$ +109° (*c*, 0·95 in MeOH; unchanged for 24 hr.), +118° (*c*, 0·71 in acetic acid) (Found: C, 53·95, 54·35; H, 6·55, 6·95; N, 1·95; Cl, 3·8; Ac, 26·6. $C_{35}H_{49}O_{11}N,HClO_4,CH_3{\cdot}CO_2H$ requires C, 54·15; H, 6·65; N, 1·7; Cl, 4·35; Ac, 26·2%). Recrystallisation of this perchlorate from 1 : 2 acetic acid–water gave cevine tetra-acetate perchlorate (see above), identified by m. p., mixed m. p., and rotation.

Treatment of cevine orthoacetate triacetate perchlorate (see above) in acetone–ether with cold dilute aqueous ammonia gave the parent base, m. p. [from carbon tetrachloride–light petroleum (b. p. 60—80°)] 282—284° (decomp.), $[\alpha]_D$ +111° (*c*, 0·97), +127° (*c*, 1·14 in acetic acid) (Found: C, 63·9, 64·1; H, 7·75, 7·55; N, 2·65; Ac, 27·2, 24·6. Calc. for $C_{35}H_{49}O_{11}N$: C, 63·7; H, 7·5; N, 2·1; Ac, 26·1%).

Cevine Orthoacetate (" *Anhydrocevine* ").—This compound was prepared from cevine orthoacetate triacetate by alkaline hydrolysis essentially according to the procedure of Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942) for the hydrolysis of cevadine orthoacetate diacetate. *Cevine orthoacetate* had m. p. (colourless prisms from methanol) 180—190° and 245—250°, $[\alpha]_D$ +62°, +62°, +62°, +62° (*c*, 1·05, 1·03, 1·08, and 1·04; all in EtOH) [Found, in sample dried *in vacuo* at 95° for 2 days (no change in wt. or crystal form): C, 63·45, 63·5;

H, 8·4, 8·25; Ac, 8·05, 7·25; *C*-Me, 7·9, 8·5%; equiv. (determined potentiometrically), 566. $C_{29}H_{43}O_8N,CH_3{\cdot}OH$ requires C, 63·7; H, 8·4; Ac, 7·6; 3*C*-Me, 8·0; 4*C*-Me, 10·6%; equiv., 566]. On being dried at 160°/0·01 mm. for 5 hr. the crystals sintered and lost 5·5% of their weight (the solvated formula given above requires 5·7%). In one acetyl determination the volatile acid was isolated as the sodium salt and converted into the *p*-bromophenacyl ester, identified as the acetate by m. p. and mixed m. p. When cevine was subjected to an acetyl determination it gave an apparent acetyl content of only 0·26%. Cevine gave 4·8 and 6·75% of *C*-Me (Calc. for $C_{27}H_{43}O_8N,3{\cdot}5H_2O$: 2*C*-Me, 5·25; 3*C*-Me, 7·85%).

In order to confirm that the cevine orthoacetate was solvated with methanol, 50 mg. were oxidised with acidified potassium dichromate and steam-distilled. Formaldehyde was detected in the distillate by the colour reaction with chromotropic acid and by formation of the dimedone derivative (m. p. and mixed m. p.). Similar oxidation of the orthoacetate after drying at 160° (see above) gave no formaldehyde.

Periodic Acid Oxidation of Cevine Orthoacetate.—The orthoacetate (660 mg.) in ethanol (20 ml.) was treated with aqueous periodic acid (30 ml.; M/20), and the solution made up to 50 ml. with ethanol. The uptake (1·00 mol.) of periodic acid was essentially instantaneous (<10 min.). In repeat experiments the amount of periodic acid consumed (10-min. titration; no further uptake after 60 min.) was 0·99 and 0·99 mol. For working up, excess of aqueous sodium arsenite solution and 20 ml. of saturated aqueous sodium hydrogen carbonate were added and the solution was extracted with chloroform (6 × 25 ml.). Evaporation *in vacuo* afforded a colourless oil which crystallised slowly from chloroform–ethyl acetate–light petroleum (b. p. 60—80°) in a flask open to the air, to give prisms of the *aldehydo-γ-lactone* (415 mg.), m. p. 230—233° (decomp.), $[\alpha]_D$ ±0° (*c*, 0·65) (Found : C, 61·75, 61·65, 61·65; H, 7·45, 7·6, 8·2; N, 2·5; Ac, 6·05%; equiv., 575. $C_{29}H_{41}O_8N,2H_2O$ requires C, 61·35; H, 8·0; N, 2·45; Ac, 7·6%; equiv., 568).

The corresponding 2 : 4-*dinitrophenylhydrazone* formed yellow crystals [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 210° after preliminary sintering, $\lambda_{max.}$ 355 mμ (ε 24,000 in $CHCl_3$) (Found : N, 10·6. $C_{35}H_{45}O_{11}N_5$ requires N, 9·85%).

The corresponding *oxime*, prepared with pyridine–hydroxylamine hydrochloride at room temperature, had m. p. 220—225° (decomp.) [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found : N, 4·45. $C_{29}H_{42}O_8N_2$ requires N, 5·1%).

Cevine Triacetate.—Cevine (200 mg.) in pyridine (2 ml.) and acetic anhydride (4 ml.) was heated on the steam-bath for 2 hr. The excess of reagents was removed *in vacuo* and the residue dissolved in a little water, made basic with ammonia, and extracted with chloroform. Evaporation of the chloroform *in vacuo* and crystallisation from ether–light petroleum (b. p. 60—80°) gave *cevine triacetate* (needles; 124 mg.), m. p. 307—308° (decomp.), $[\alpha]_D$ +19°, +19° (*c*, 1·74, 1·70 in acetone) (Found : C, 62·2; H, 7·8; N, 2·1, 2·3; Ac, 20·8. $C_{33}H_{49}O_{11}N$ requires C, 62·35; H, 7·75; N, 2·2; Ac, 20·3%). The triacetate (9·8 mg.) in acetic acid (10 ml.) containing lead tetra-acetate (4 mols.) was left at room temperature for 10 min. The uptake of oxidant was 0·95 mol., unchanged for a further 18 hr. The same result (0·97 mol. uptake) was observed in 80% aqueous acetic acid. The triacetate (100 mg.) in ethanol (10 ml.) was treated with excess of periodic acid solution (10 ml.) and saturated sodium hydrogen carbonate solution (5 ml.) for 10 min. The periodic acid uptake corresponded to 1·00 mol. and was unchanged on further standing (experiment by Dr. P. de Mayo).

Cevine triacetate (138 mg.) treated with acetic anhydride–perchloric acid as in the acetylation of cevine itself (see above) gave, after crystallisation from aqueous acetic acid, cevine tetra-acetate perchlorate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +32° (*c*, 1·16 in acetone)}.

Cevine triacetate (94 mg.) was hydrolysed with 20% ethanolic potassium hydroxide as in the preparation of cevine (Macbeth and Robinson, *J.*, 1922, **121**, 1571). The product (62 mg.), crystallised from aqueous ethanol, was identified as cevine by m. p., mixed m. p., and rotation {$[\alpha]_D$ −17° (*c*, 1·04 in EtOH)}.

The triacetate (39·6 mg.) in 95% aqueous acetic acid (10 ml.) containing 125% of the theoretical amount of chromic acid for the oxidation of 1 secondary hydroxyl group was left overnight at room temperature. There was no consumption of oxidant (titration) and pure triacetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +20° (*c*, 1·07 in acetone)}, was recovered unchanged in 70% yield.

Tests for Orthoacetate Formation and its Reversal.—The following compounds, under the conditions stated below, did not afford orthoacetates at room temperature, as shown by the constancy of their rotations after 20 hr. Initial and final rotations are given sequentially. All

rotations are in acetic acid unless specified otherwise. Cevine: $-18°$, $-17°$ (*c*, 1·22); cevine diacetate, $+8°$, $+6°$ (*c*, 1·01); cevine triacetate, $+27°$, $+27°$ (*c*, 1·72); cevine tetra-acetate (see text), also $+22°$ (*c*, 2·05 in $CHCl_3$), $+35°$, $+36°$ (*c*, 0·84 in acetone), $+46°$, $+45°$ (*c*, 0·76 in acetone containing 10·1% w/v of triethylamine and 6·0% w/v of acetic acid, thus giving a molecular ratio of triethylamine : acetic acid of 1 : 1).

Kinetics of Orthoacetate Formation.—The course of the reaction was followed by using a 2-dm. polarimeter tube fitted with a water jacket, which was connected to a circulating pump supplying water from a thermostatically controlled water-tank. The polarimeter tube, placed in a Hilger Standard Polarimeter, soon attained constant temperature, which was measured in a trial experiment for each temperature setting and checked at the end of each experiment. In this way the temperature could be controlled within $\pm 0·05°$.

The determinations were carried out by rapidly dissolving 50—100 mg. of compound in 5 ml. of solvent (previously warmed to the appropriate temperature) and measuring rotations at suitable time intervals.

Reaction rates were calculated from straight line plots of $\log_{10}[(\alpha_\infty - \alpha_0)/(\alpha_\infty - \alpha_t)]$ against t where the final rotation, α_∞, was taken after a period corresponding to 10 times the half-life.

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