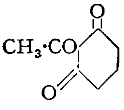
165. *2-Acetyl*cyclo*hexane-1 : 3-dione.*

By Herchel Smith.

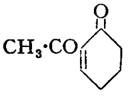
The synthesis and properties of 2-acetyl*cyclo*hexane-1 : 3-dione (I) are described. The ultra-violet absorption spectra of β-triketones are discussed. Catalytic hydrogenation of (I) over palladium–charcoal gives 2-acetyl*cyclo*hexanone together with a small quantity of 2-ethyl*cyclo*hexane-1 : 3-dione, and in the presence of alkali the yield of the latter is increased. (I) gives with aniline 1-(2 : 6-diketo*cyclo*hexyl)ethylideneaniline (VIII), converted by a standard cyclisation procedure into 5 : 6 : 7 : 8-tetrahydro-8-keto-9-methylphenanthridine, reduction of which with lithium aluminium hydride affords 5 : 6 : 7 : 8-tetrahydro-8-hydroxy-9-methylphenanthridine converted by heating with palladium–charcoal into 9-methylphenanthridine. Sodium borohydride hydrogenolyses (VIII) into 2-ethyl*cyclo*hexane-1 : 3-dione in high yield.

2-Acetyl*cyclo*hexane-1 : 3-dione (I) belongs to the general class of tricarbonylmethane compounds containing members of a wide range of physiological interest exhibiting anthelmintic, antibiotic, and insecticidal properties. *C*-Acetyldimedone, the 5 : 5-dimethyl homologue of (I), and certain closely related compounds exhibit weak activity *in vitro* against *Staph. aureus* and *Mycobacterium tuberculosis* (avian type) (Ukita, Tamura, Matsuda, and Kashiwabara, *Japan. J. Exptl. Med.*, 1949, **20**, 109; *Chem. Abs.*, 1950, **44**, 3087), and hence (I) has interest as a potential source of similar, and perhaps more active, compounds. However, its synthesis and chemistry have been investigated chiefly in order to assess its possible use as a starting material for the preparation of intermediates required in steroid synthesis, particularly of the as yet unknown 2-acetyl*cyclo*hex-2-en-1-one (II). Reduction of one of the annular carbonyl groups of (I) to a secondary alcoholic group followed by dehydration of the resulting β-hydroxy-diketone should give (II), and the principal aim of the present investigation was to determine whether the side chain and one annular carbonyl group of (I) could be suitably protected against reduction.

It has long been known that acetic anhydride reacts with 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione at reflux temperature in the presence of sodium acetate to give 2-acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, **101**, 1524), conveniently purified *via* the copper derivative. This method has been extended to *cyclo*hexane-1 : 3-dione (III; R = H) to give the desired (I), but the yield is somewhat lower owing no doubt to the increased tendency of (III; R = H) to give self-condensation products at high temperatures in the presence of catalysts (Thomson, *Org. Synth.*, 1947, **27**, 21). Spassow (*Ber.*, 1937, **70**, 2381) has described the *C*-acetylation in high yield of ethyl acetoacetate by treatment with acetyl chloride in benzene in the presence of magnesium, but application of this procedure to (III; R = H) gave none of (I) despite the report by Ukita *et al.* (*loc. cit.*) that dimedone was successfully *C*-cinnamoylated by this method. Treatment of 2-methyl*cyclo*hexane-1 : 3-dione (III; R = Me) with acetic anhydride in the presence of sodium acetate under conditions where (III; R = H) gave (I) resulted in the formation of only the enol acetate (IV). This is hardly surprising, for in the mesomeric anion derived by proton loss from (III; R = Me) the electron-repelling methyl group, apart from purely steric effects, destabilises a negative charge at the 2-position and thereby increases the energy of activation for the addition of an acetyl cation at this point.



(I)



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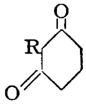

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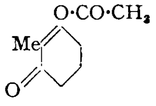
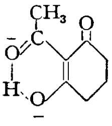
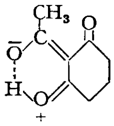


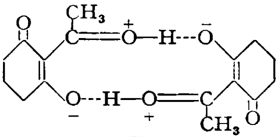
(IV)

2-Acetyl*cyclo*hexane-1 : 3-dione is unattacked by diazomethane in ethereal solution, being in this respect similar to certain chelate *o*-hydroxy-ketones such as alizarin 2-methyl ether (Herzig and Klimosch, *Monatsh.*, 1909, **30**, 535) and *o*-hydroxyacetophenone (Schönberg and Ismail, *J.*, 1944, 367). Schönberg and Mustafa (*J.*, 1946, 746) have used diazomethane in methanol to methylate such compounds in unstated yields, but this reagent leaves (I) substantially unchanged.

The infra-red absorption spectrum of (I) in the solid state closely resembles the spectra of the highly enolisable β-diketones investigated by Rasmussen, Tunnicliffe, and Brattain (*J. Amer. Chem. Soc.*, 1949, **71**, 1068) and is notable for the lack of absorption near 3 μ where simple hydrogen-bonded hydroxyl absorption occurs, and for the absence of an unconjugated carbonyl band in the 5·8 μ region. There is, however, general absorption on both sides of the C–H band, a strong conjugated carbonyl band at 5·96 μ (attributable to the normal enol form), and, from its width, a much more intense conjugated carbonyl band at 6·39 μ. Rasmussen *et al.* (*loc. cit.*) have attributed the high intensity and extreme displacement to longer wave-lengths of the latter type of band to enhanced contributions to the resonance hybrid of zwitterionic enol forms. In the case of (I) such forms could be written as in (V) and (VI) but it seems possible (in the solid state at least) that (I) is associated in a manner analogous to that of the fatty acids, so that one zwitterionic form (vinylogous to a fatty acid dimer) could be written as in (VII).


(V)


(VI)


(VII)

The ultra-violet absorption spectrum of (I) in methanol shows two bands—at 235 (ε 14,700) and 275 mμ (ε 11,600)—characteristic of the enolised β-triketone system (Birch and Todd, *J.*, 1952, 3102). Braude (*Ann. Reports*, 1945, **42**, 129) has indicated the empirical rule that heterocyclic compounds containing nitrogen linked by a double bond absorb very similarly to the corresponding systems having an ethylenic instead of an azomethine grouping, so that the absorptions of, *e.g.*, thiazole and thiophen, of benzene and pyridine, are closely similar. If this rule is extended to include oxygen linked by a double bond as in (V) and (VI), then the ultra-violet absorption spectrum characteristic of β-triketones such as (I) can be understood, since the chelate ring in the latter then contains a conjugated diene-type system which is cross-conjugated with the carbonyl group of the carbocyclic ring. Accordingly, the ultra-violet absorption spectrum of (I) should exhibit two principal bands : (*a*) in the region 230—250 mμ, associated with the αβ-unsaturated carbonyl group (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1122), and (*b*) in the region 255—290 mμ, associated with the conjugated diene chromophere contained in one ring (*idem, ibid.*, 1942, **64**, 72), and these bands are, in fact, found. According to the theory, the spectra of the chelated β-diketones acetylacetone and 2-acetyl*cyclo*hexanone, possessing a homoannular conjugated diene-type system, but lacking a carbonyl cross-conjugated with it, should exhibit only one absorption band in the region 255—290 mμ, and indeed the former has a maximum at 270 mμ (ε 10,000) (Rasmussen *et al.*, *loc. cit.*) and the latter one at 290 mμ (ε 5,100). The longer wave-length and decreased intensity of the absorption band in the latter would indicate increased strain in the chromophoric system (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 253). Enolisable β-triketones are weak acids, and as such their degree of ionisation in ionising solvents increases with increasing dilution, and would be expected to be appreciable at dilutions normally employed in the determination of ultra-violet spectra. Hence if the absorption spectra of the anions differ from those of the undissociated forms then it is to be expected that the nature of the spectrum obtained for any one compound may vary with varying dilution. Such concentration-dependent absorption has been observed for various cyclic β-diketones (Bastron, Davis, and Butz, *J. Org. Chem.*, 1943, **8**, 515 ; Blout, Eager, and Silverman, *J. Amer. Chem. Soc.*, 1946, **68**, 566), and so in order to ensure reproducible results it is advisable to determine the spectra of these and similar weakly acidic compounds in the presence of excess of acid so that ionisation may be completely repressed—always providing that the compounds investigated are stable under such conditions. In the presence of excess of mineral acid (I) had maxima at 230 mμ (ε 12,800) and 270 mμ (ε 11,100) and 2-acetyl*cyclo*hexanone a maximum at 290 mμ (ε 5,200).

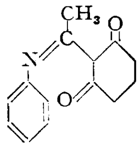
When an ethanolic solution of (I) is shaken with hydrogen at room pressure and temperature over palladium–charcoal, there is an uptake of 2 mols. of hydrogen during several hours and the product consists almost entirely of 2-acetyl*cyclo*hexanone, isolated as the copper derivative (Borsche, *Annalen*, 1910, **377**, 70; Meerwein and Vossen, *J. pr. Chem.*, 1934, **141**, 149), together with a small quantity of 2-ethyl*cyclo*hexane-1 : 3-dione (III; R = Et). Addition of increasing amounts of alkali results in an increased yield of (III; R = Et) which reaches 45% in the presence of one equivalent. Interruption of the hydrogenation after an uptake of 1 mol. of hydrogen gave a mixture of 2-acetyl*cyclo*hexanone and (III; R = Et) together with unchanged (I). The presence of (III; R = Et) in the hydrogenation product of (I) confirms the nature of the carbon skeleton in the latter.

A detailed theoretical interpretation of these and other hydrogenations must be reserved for a later communication, but certain pertinent observations can be made here. The infra-red spectrum of (I) indicates that in solution it exists almost completely as the enol, which at the concentrations employed for catalytic hydrogenation would be ionised to only a small extent. Palladium catalysts do not normally attack carbonyl groups at room temperature and pressure, and so it would appear that (I) is hydrogenated as the enol, *e.g.*, (V), and that an essential stage in the process is the hydrogenolysis of the enolic hydroxyl group. This type of hydrogenation would be closely analogous to the hydrogenation of enol acetates over Adams's catalyst (Inhoffen, Stoeck, Kölling, and Stoeck, *Annalen*, 1950, **568**, 52) which leads to the hydrogenolysis of the acetoxy-group and saturation of the double bond adjacent to it. With the addition of alkali, the enolate anion is formed and this is hydrogenated to a mixture containing the same constituents but a much larger relative proportion of (III; R = Et). Prolonged hydrogenation of (I) during several days resulted in a hydrogen uptake of more than 2 mols., and after removal of alkali-soluble material, treatment of the product with Brady's reagent gave a low yield of the 2 : 4-dinitrophenylhydrazone of 2-ethyl*cyclo*hexanone (Barltrop, King, and Whalley, *J.*, 1945, 277). No evidence for the presence of any other ketone was obtained.

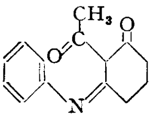
2-Ethyl*cyclo*hexane-1 : 3-dione was first described by Stetter and Dierichs (*Ber.*, 1952, **85**, 61), who prepared it by alkylation of *cyclo*hexane-1 : 3-dione with potassium methoxide and ethyl iodide in methanol. A more convenient method, especially for large-scale preparations, and giving comparable yields, is the one used in these laboratories for the preparation of 2-methyl*cyclo*hexane-1 : 3-dione (Robinson *et al.*, to be published) and is an extension of that used by Sonn (*Ber.*, 1931, **64**, 1847) for the *C*-alkylation of dimedone, in which the β-diketone is refluxed with potassium hydroxide and methyl iodide in aqueous acetone.

Treatment of (I) with an excess of aniline in boiling ethanol gave in high yield a single anil which was soluble in aqueous alkali, being recovered unchanged on neutralisation, and gave no colour with ferric chloride. It must therefore have a *trans*- rather than a *cis*-β-diketonic structure (Birch, *J.*, 1951, 3026), *i.e.*, must be (VIII) rather than (IX); and indeed (VIII) is the structure predicted for the anil on the basis of the above interpretation of the catalytic hydrogenation of (I). Rigorous confirmation for the structure (VIII) was provided by cyclodehydration in a mixture of phosphoric anhydride and phosphoric acid (Birch, Jaeger, and Robinson, *J.*, 1945, 582; Birch and Smith, *J.*, 1951, 1882) to the tetrahydroketomethylphenanthridine (X), lithium aluminium hydride reduction of which gave (XI), converted by heating with palladised charcoal at 250° into the known 9-methylphenanthridine, m. p. 85° (picrate m. p. 233°) (Morgan and Walls, *J.*, 1931, 2450; Pictet and Hubert, *Ber.*, 1896, **29**, 1184). The alternative structure would have given, after the above sequence of operations, the known 5-methylacridine, m. p. 117° (picrate, m. p. 213—214°) (Königs, *Ber.*, 1899, **32**, 3607; Kaufmann and Albertini, *Ber.*, 1911, **44**, 2054). The anil (VIII) is inert to diazomethane in solution in ether–methanol, owing, no doubt, to the presence in (VIII) of a six-membered chelate ring involving nitrogen. In this connection it may be noted that *o*-hydroxyazo-compounds are incapable of methylation by diazomethane (Smith and Mitchell, *J.*, 1908, **93**, 843).

The lithium aluminium hydride reduction recorded above is notable in that the 9 : 10-double bond is unattacked, whereas it has been reported (Wooten and McKee, *J. Amer. Chem. Soc.*, 1949, **71**, 2946) that reduction of phenanthridine with the same reagent but with much longer heating gives 9 : 10-dihydrophenanthridine. The structure of (XI) is proved by the analysis and ultra-violet absorption spectrum, which resembles that of quinoline (Morton and de Gouveia, *J.*, 1934, 916; Johnson and Buell, *J. Amer. Chem. Soc.*, 1952, **74**, 4517) rather than that of *o*-aminostyrene (Pestemer, Langer, and Manchen, *Sitzungsber. Akad. Wiss. Wien*, 1936, **145**, 546). It is noteworthy that the above route, essentially an extension of Borsche's classical method (*loc. cit.*) for the synthesis of tetrahydrophenanthridines, is a convenient one for the synthesis of substituted phenanthridines; all the stages from (I) to (XI) proceed in high yields, and although the final dehydration–dehydrogenation gives only a 40% yield, there is no doubt that a milder and more efficient process could be found. Should a variety of 2-acyl*cyclo*hexane-1 : 3-diones become readily available, then the method would be sufficiently flexible to permit the synthesis of phenanthridines with substituents in ring A, an alkyl group (or hydrogen) in the 9-position, and alkyl groups in ring C



(VIII)



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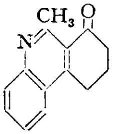

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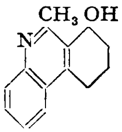
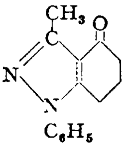
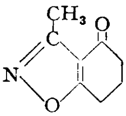


(XI)



(XII)



(XIII)

The establishment of the structure of the anil (VIII) enabled the first attempts at the preparation of (II) to be made, since it appeared that one carbonyl group of the β-diketone system in (VIII) might be protected against reduction by the formation of an enolate anion. It has, for example, been suggested (Brown, " Organic Reactions," Vol. VI, p. 472, Wiley, New York, 1951) that the reduction of α-angelicalactone to 3-acetylpropanol (Hochstein, *J. Amer. Chem. Soc.*, 1949, **71**, 305) involves the protection of the carbonyl group as a lithium aluminium enolate. The latter reducing agent could not be used with (VIII), however, since it reduces anils to the corresponding secondary amines (Nystrom and Brown, *ibid.*, 1948, **70**, 3738). The milder sodium borohydride reagent, in contradistinction to lithium aluminium hydride, does not reduce nitriles (Chaikin and Brown, *ibid.*, 1949, **71**, 122), and so the sodium enolate of (VIII) was reduced with one equivalent of sodium borohydride in aqueous methanol in the expectation of reducing one carbonyl group of (VIII) to a secondary alcoholic group, whilst leaving the azomethine linkage unattacked. The product consisted of (III; R = Et) together with unchanged material. Reduction of the enolate with an excess of borohydride gave (III; R = Et) in 75% yield. Similar results were obtained by direct reduction of (VIII) with an excess of the reagent. The process appears to involve a true hydrogenolysis of the anil linkage rather than to proceed by hydrolysis to (I) followed by reduction, since treatment of (I) with sodium borohydride under closely parallel conditions gave a different, ill-defined product containing much starting material. Sodium borohydride, which fails to reduce the β-diketone system in (VIII), is also without action upon carboxylic acids (Chaikin and Brown, *loc. cit.*). The explanation for this behaviour probably lies in the vinylogy between the enolic form of the β-diketone system and the carboxyl group. There is evidence (Brown, *loc. cit.*) that reduction with lithium aluminium hydride proceeds by a mechanism in which hydrogen is transferred as hydride in a bimolecular nucleophilic displacement reaction, and it seems likely that reduction with sodium borohydride follows a similar path. Accordingly, the reduction of a carboxyl group with the latter reagent will depend on the approach of a borohydride anion to the mesomeric carboxylate anion, and since no reduction occurs it appears that the energy of activation required for the process is so high (owing to the repulsion of like charges) as to be prohibitive. It is therefore not surprising that the energy of activation required for the approach of a borohydride anion to the enolate anion of (VIII) is also prohibitively high. Reduction of (VIII) with lithium aluminium hydride gave a complex product which on treatment with Brady's reagent gave a small quantity of a 2 : 4-dinitrophenylhydrazone which could not be identified.

2-Acetylcyclohexane-1 : 3-dione reacts with phenylhydrazine and hydroxylamine to give cyclic condensation products to which the structures (XII) and (XIII) are assigned by analogy with the anil (VIII).

EXPERIMENTAL

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss and Mr. F. Hall. Infra-red spectra were determined for Nujol mulls except where otherwise stated in a Perkin-Elmer Model 21 double-beam instrument, the Nujol bands being omitted. Approximate indications of the intensity of bands are given as follows: s = strong, m = medium, w = weak. All spectra were determined by Dr. F. B. Strauss with the technical assistance of Mr. F. Hastings.

2-*Acetyl*cyclo*hexane*-1 : 3-*dione* (I).—*cyclo*Hexane-1 : 3-dione (49·6 g.) (Thompson, *loc. cit.*) was refluxed in acetic anhydride (266 g.) containing sodium acetate (fused, 7·18 g.) for 5 hours. After cooling, most of the acetic anhydride was removed under reduced pressure, and the dark residue extracted with ether. The ethereal extracts were combined, filtered if necessary, and extracted with successive 100-c.c. portions of 10% aqueous sodium hydroxide. The alkaline extracts on acidification gave initially oils and then resins. The oils were taken up in ether, and the combined ethereal solutions washed with water (2 × 100 c.c.), shaken with an excess of aqueous cupric acetate solution for 15 minutes, and left overnight. The copper complex (36 g.) was filtered off and decomposed by shaking it with 3N-hydrochloric acid (200 c.c.) and ether (200 c.c.). The ethereal layer was separated, washed with water (4 × 50 c.c.), and dried (Na_2SO_4), and the ether removed under reduced pressure. The residue was distilled to give the 2-*acetyl*cyclo*hexane*-1 : 3-*dione* as a colourless oil (25 g.), b. p. 126—127°/22 mm., which rapidly set in the receiver to a mass of crystals, m. p. 29·5° (Found : C, 62·8; H, 6·3. $C_8H_{10}O_3$ requires C, 62·4; H, 6·5%). The triketone dissolves in aqueous sodium hydrogen carbonate with evolution of carbon dioxide, and is insoluble in light petroleum but soluble in most other organic solvents. The infra-red absorption bands are at the following wave-lengths (μ) : 3·80 (diffuse) m, 4·25m, 5·96s, 6·39s, 7·03s, 7·40s, 7·50s, 7·76m, 7·97m, 8·13m, 8·41s, 8·79m, 9·37m, 9·52m, 9·73m, 9·93s, 10·50m, 10·84m, 11·88m, 13·93w. In solution in chloroform the hydroxyl band occurred at 2·87 and carbonyl bands at 6·01 and 6·40 μ.

The *copper* salt was prepared by shaking an ethereal solution of (I) with saturated aqueous cupric acetate, and was obtained from chloroform as blue needles, m. p. 263—265° (rapid heating, decomp.) (Found : C, 51·8; H, 4·4. $C_{16}H_{18}O_6Cu$ requires C, 52·0; H, 4·9%). The *sodium* salt, prepared by adding (I) in ethanol to ethanolic sodium ethoxide (1 equiv.) followed by removal of the solvent, was obtained as needles, m. p 266° (decomp.), by partial evaporation of its solution in ethanol and retained water tenaciously (Found, in material dried at 15 mm. for 5 hours over P_2O_5 : C, 53·3; H, 5·3. $C_8H_9O_3Na,\frac{1}{4}H_2O$ requires C, 53·3; H, 5·3%).

3-*Acetoxy*-2-*methyl*cyclo*hex*-2-*en*-1-*one* (IV).—2-Methyl*cyclo*hexane-1 : 3-dione (9·75 g.) was heated under reflux in acetic anhydride (35 g.) containing sodium acetate (2 g.) for 7 hours. Next day most of the acetic anhydride was removed under reduced pressure, the residue treated with ether, and the sodium acetate filtered off. The ether was removed under reduced pressure, and the residue distilled to give 3-*acetoxy*-2-*methyl*cyclo*hex*-2-*en*-1-*one* as an oil, b. p. 143—145°/20 mm. (Found : C, 63·9; H, 7·4. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%). The ultra-violet absorption spectrum (methanol) shows a band at 237·5 mμ (ε 8,500). The infra-red absorption bands were at the following wave-lengths (μ) : 5·68s, 5·98s, 6·99m, 7·40s, 7·51m, 7·66m, 8·03w, 8·35s, 8·61s, 8·97s, 9·25s, 9·60m, 9·92m, 10·88m, 11·34w, 11·91m, 12·06m, 13·88m. These spectra are in accord with the structure (IV).

*Catalytic Hydrogenation of 2-Acetyl*cyclo*hexane*-1 : 3-*dione*.—(i) The trione (1 g.) in ethanol (25 c.c.) was shaken with hydrogen at atmospheric pressure over 30% palladium–charcoal (100 mg.) for 20 hours; the hydrogen uptake had then become very slow, the total absorbed being 440 c.c. (Calc. for 2 mols. : 430 c.c.). The catalyst was filtered off, and the solvent evaporated under reduced pressure, affording an oil which had a characteristic penetrating odour and gave a very dark colour with ferric chloride. During several hours, the oil deposited a small quantity of crystalline material which was removed and washed with a little pure ether. The crystals had m. p. 173—175°, undepressed by 2-ethyl*cyclo*hexane-1 : 3-dione (III; R = Et) obtained as described in (ii). The oil was shaken with an excess of saturated aqueous cupric acetate for 15 minutes, and the mixture heated on the steam-bath for 20 minutes and left overnight. The greyish-green precipitate was filtered off and recrystallised from aqueous alcohol to give the copper salt of 2-acetyl*cyclo*hexanone (880 mg., 80%), m. p. 160—161° alone or admixed with an authentic sample prepared by Meerwein and Vossen's method (*loc. cit.*) (Found : C, 56·4; H, 6·45. Calc. for $C_{16}H_{22}O_4Cu$: C, 56·2; H, 6·4%).

(ii) The triketone (I) (300 mg.) in ethanol (7·5 c.c.) containing aqueous sodium hydroxide (0·6 c.c. of 0·4N, 0·125 equiv.) was hydrogenated over 30% palladium–charcoal (30 mg.). After an uptake of 2 mol. (7 hours) the hydrogenation was interrupted, the catalyst filtered off, and the solution concentrated to small bulk at 15°. Ethyl acetate (25 c.c.) and hydrochloric acid (2 c.c. of 3N) were added, and the organic layer removed, washed with water (3 × 10 c.c.), dried (Na_2SO_4), and evaporated under reduced pressure to an oil. Addition of pure ether precipitated crystals, which were filtered off and recrystallised from benzene to give 2-ethyl*cyclo*hexane-1 : 3-dione (III; R = Et) as needles (90 mg., 33%), m. p. 173—175°. A portion sublimed for analysis at 110°/8 × 10^{-3} mm. had m. p. 176—177° (Stetter and Dierichs, *loc. cit.*, give 178°), undepressed by a sample prepared from *cyclo*hexane-1 : 3-dione as described below (Found : C, 68·4; H, 8·4. Calc. for $C_8H_{12}O_2$: C, 68·55; H, 8·6%). The infra-red absorption bands are at the following wave-lengths (μ) : 3·68s, 5·5w, 6·13m, 6·38s, 7·03s, 7·30s, 7·87s, 8·36s, 9·07s, 9·41s, 10·37m, 10·60s, 10·74m, 11·70m, 13·07w, 13·87m. The *bis*-2 : 4-*dinitrophenylhydrazone* was obtained from tetrahydrofuran–ethanol as a brick-red, microcrystalline powder, m. p. 207—209° (Found : C, 48·2; H, 4·2. $C_{20}H_{20}O_8N_8$ requires C, 48·0; H, 4·0%). Its ultra-violet absorption spectrum (chloroform) exhibits maxima at 260 (ε 23,700) and 365 mμ (ε 45,200). The ethereal mother-liquors from (III; R = Et) were evaporated to an oil, from which the copper salt of 2-acetyl*cyclo*hexanone (252 mg., 37%) was obtained.

The triketone was hydrogenated by the above method in the presence of increasing amounts of aqueous alkali. The results may be summarised as follows : (*a*) (I) (220 mg.) with palladium–charcoal (30 mg.) in ethanol (5 c.c.) containing aqueous sodium hydroxide (1·78 c.c. of 0·4N, 0·5 equiv.) gave (III; R = Et) (80 mg., 40%); (*b*) (I) (200 mg.) and palladium–charcoal (30 mg.) in ethanol (5 c.c.) containing aqueous sodium hydroxide (3·25 c.c. of 0·4N, 1 equiv.) gave (III; R = Et) (81 mg., 45%)

(iii) The triketone (I) (230 mg.) was hydrogenated in ethanol (10 c.c.) over 30% palladium–charcoal (30 mg.). After 3 days the hydrogen uptake was 130 c.c. (Calc. for 4 mols. : 143 c.c.). The catalyst was filtered off and the solvent removed to give an oil which was taken up in ether, thoroughly extracted with aqueous alkali, washed with brine, and evaporated to yield a small quantity of pleasant-smelling oil, treatment of which with Brady's reagent gave a 2 : 4-dinitrophenylhydrazone separating from ethanol as orange-red needles (22 mg.), m. p. 159—161° alone or admixed with a specimen of the same derivative of 2-ethyl*cyclo*hexanone (Barltrop, King, and Whalley, *loc. cit.*) prepared by catalytic hydrogenation of a sample of 2-ethyl*cyclo*hex-2-en-1-one kindly supplied by Dr. J. A. Barltrop (Found : C, 55·1; H, 5·9. Calc. for $C_{14}H_{18}O_4N_4$: C, 54·9; H, 5·9%). Concentration of the alcoholic filtrates yielded no further 2 : 4-dinitrophenylhydrazone.

2-*Ethyl*cyclo*hexane*-1 : 3-*dione* (III; R = Et).—*cyclo*Hexane-1 : 3-dione (5·6 g.) in acetone (3·5 c.c.)–water (14 c.c.) containing potassium hydroxide (2·8 g.) was refluxed with ethyl iodide (10 c.c.) for 10 hours. After cooling, the organic solvents were removed, and the crystalline precipitate was recrystallised from ethyl acetate to give 2-ethyl*cyclo*hexane-1 : 3-dione as needles (1·5 g.), m. p. 173—175°. A portion sublimed for analysis at 110°/5 × 10^{-3} mm. had m. p. 177—178° (Found : C, 68·8; H, 8·9. Calc. for $C_8H_{12}O_2$: C, 68·55; H, 8·6%).

1-(2 : 6-*Diketo*cyclo*hexyl*)*ethylideneaniline* (VIII).—2-Acetyl*cyclo*hexane-1 : 3-dione (2·60 g.) and aniline (2·09 g.) were refluxed in ethanol (12·5 c.c.) for 4 hours, the mixture was cooled and added to water (150 c.c.), and the crystalline precipitate (3·51 g.) filtered off, dried in a desiccator, and recrystallised from light petroleum (b. p. 60—80°) to yield the *anil* (VIII) as needles (3·35 g.), m. p. 87° (Found : C, 73·6; H, 6·9; N, 5·9. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%). The ultra-violet absorption spectrum (methanol) shows bands at 255 (ε 15,800) and 310 mμ (ε 19,400). The infra-red absorption spectrum was typical of that for an enolic β-diketone, with bands at the following wave-lengths (μ) : 3·75 (diffuse) w, 6·15s, 6·38s, 7·05m, 7·10m, 7·40m, 7·50m, 7·79m, 7·97w, 8·14m, 8·48m, 8·57w, 8·82w, 9·37w, 9·47w, 9·75w, 10·07w, 10·50w, 10·70w, 10·88w, 11·17w, 11·60w, 11·95w, 12·20w, 13·08m, 13·87w.

5 : 6 : 7 : 8-*Tetrahydro*-8-*keto*-9-*methylphenanthridine* (X).—A mixture of phosphoric anhydride (9 g.) and phosphoric acid (*d* 1·75, 7 c.c.) at 120° was added to the above anil (1·2 g.), and the temperature raised to 170° and kept thereat for 30 minutes. On cooling to 90° the green fluorescent solution was added to water, and the aqueous solution made alkaline to litmus. The crystalline precipitate was taken up in ether, and the ethereal solution washed with water, dried (Na_2SO_4), and evaporated. The crystalline residue was recrystallised from light petroleum (b. p. 60—80°) to give the *phenanthridine* (X) as needles (1·01 g.), m. p. 118° (Found : C, 79·6; H, 6·2; N, 6·7. $C_{14}H_{13}ON$ requires C, 79·65; H, 6·2; N, 6·7%). The ultra-violet absorption spectrum (methanol) shows bands at 245 (ε 54,000) and 285 mμ (ε 12,400). The infra-red absorption spectrum shows bands at the following wave-lengths (μ) : 5·95s, 6·19m, 6·39m, 6·70m, 7·03m, 7·14m, 7·32m, 7·38m, 7·48m, 7·81m, 8·25w, 8·43w, 8·66w, 8·79w, 8·93w, 9·27w, 9·81w, 10·17w, 11·13w, 11·36w, 11·76w, 12·32w, 12·77w, 13·13w, 13·90w.

The hydrochloride, formed by passing dry hydrogen chloride into a solution of (X) in pure ether, had m. p. 234—235° (decomp., rapid heating). The 2 : 4-dinitrophenylhydrazone, obtained by adding Brady's reagent together with a little concentrated hydrochloric acid to an alcoholic solution of (X), had m. p. 254° (decomp., rapid heating).

5 : 6 : 7 : 8-*Tetrahydro*-8-*hydroxy*-9-*methylphenanthridine* (XI).—The above phenanthridone (0·875 g.) in pure ether (60 c.c.) was added to a solution of lithium aluminium hydride (0·318 g.) in pure ether (80 c.c.) and refluxed for 30 minutes. On cooling, a little " Hyflosupercel " was added, followed by damp ether (5 c.c.) and water (15 c.c.), and the mixture was filtered. The ethereal layer was separated, and the aqueous layer extracted with ether (4 × 50 c.c.). The ethereal solutions were combined, washed with water (4 × 25 c.c.), dried (Na_2SO_4), and evaporated under reduced pressure, giving a partly crystalline residue, which was recrystallised from ethyl acetate to give the *hydroxyphenanthridine* (XI) as clusters of needles (0·555 g.), m. p. 167° (Found : C, 78·9; H, 7·0; N, 6·5. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0; N, 6·6%). The ultra-violet absorption spectrum shows bands at 225 (ε 23,000), 275 (ε 4,200), 304 (ε 2,900), and 316 mμ (ε 3,100). For quinoline, Morton and de Gouveia (*loc. cit.*) give maxima at 275 (ε 4,500) and 311 mμ (ε 6,300), and Johnson and Buell (*loc. cit.*) at 226 (ε 32,400), 230 (ε 28,800), 277 (ε 3,500), 299·5 (ε 3,000), and 312·5 mμ (ε 3,400). For *o*-aminostyrene, Pestemer, Langer, and Manchen (*loc. cit.*) give maxima at 238 (ε 10,000) and 332 mμ (ε 2,200). The infra-red absorption spectrum shows bands at 3·18s, 3·72 (diffuse) m, 6·20w, 6·28m, 6·36m, 6·66m 6·99m, 7·15w, 7·27s, 7·43m, 7·85m, 7·97w, 8·41w, 8·54w, 8·62m, 9·02w, 9·22m, 9·30w, 9·64w, 9·73w, 9·82m, 10·09w, 10·55w, 10·72m, 11·30w, 11·55w, 11·67w, 12·15w, 12·75w, 13·23s, 13·42m μ.

The *methiodide*, prepared by refluxing (XI) in acetone with an excess of methyl iodide for 4 hours, separated from acetone as slightly yellow prismatic needles, m. p. 242° (decomp.) (Found : C, 50·6; H, 5·3. $C_{15}H_{18}ONI$ requires C, 50·7; H, 5·1%).

9-*Methylphenanthridine*.—The above tetrahydrohydroxymethylphenanthridine (150 mg.) was heated with 30% palladium–charcoal (20 mg.) at 250° for 30 minutes. On cooling, the residue was extracted with ethanol (10 c.c.) and ether (total 50 c.c.) and the extracts were combined and filtered. Removal of the solvents gave an oil which was extracted with successive portions of boiling light petroleum (b. p. 40—60°) until only a little dark resin remained. The extracts were combined, concentrated to small bulk, and percolated in light petroleum (b. p. 40—60°) through a short column of alumina. Evaporation of the eluate gave a crystalline residue which was recrystallised from light petroleum (b. p. 40—60°), giving 9-methylphenanthridine as needles (55 mg.), m. p. 84° (Morgan and Walls, *loc. cit.*, give m. p. 84°) (Found : C, 87·0; H, 5·7; N, 7·3. Calc. for $C_{14}H_{11}N$: C, 87·1; H, 5·7; N, 7·3%). The picrate had m. p. 233—235° (decomp.) (Pictet and Hubert, *loc. cit.*, give 233°). The ultra-violet absorption spectrum shows bands at 250 (ε 29,500), 330 (ε 2000), and 345 mμ (ε 2000).

Reduction of (VIII) *with Sodium Borohydride*.—(i) A solution of the anil (VIII) in methanol (10 c.c.) was brought to pH 10 by addition of 10% aqueous sodium hydroxide, sodium borohydride (50 mg. of 82%, 1 equiv.) in methanol (2 c.c.) was added, and the mixture refluxed for 40 minutes, cooled, acidified, left for 2 hours, poured into brine (70 c.c.), and thoroughly extracted with chloroform. The extracts were combined, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to an oil, which was taken up in ether and extracted with aqueous sodium hydroxide. Acidification of the alkaline extracts precipitated unchanged material (340 mg.), m. p. 84°, raised to 87° and undepressed by (VIII), after recrystallisation from light petroleum (b. p. 40—60°). The aqueous mother-liquors were continuously extracted with ether overnight. Evaporation of the dried extract gave a crystalline residue, which recrystallised from benzene, giving 2-ethyl*cyclo*hexane-1 : 3-dione (III; R = Et) as needles (270 mg.), m. p. 173—175° undepressed by an authentic specimen, and possessing an identical infra-red absorption spectrum.

(ii) The anil (VIII) (1 g.) in methanol (7 c.c.) containing aqueous sodium hydroxide (1·6 c.c. of 10%, pH of solution *ca.* 10) was added to sodium borohydride (600 mg.) in methanol (2 c.c.). The solution was gently warmed to initiate the reaction and, when gas evolution had moderated, was refluxed for 80 minutes. On cooling, the mixture was acidified to precipitate 2-ethyl*cyclo*hexane-1 : 3-dione (III; R = Et) (280 mg.), m. p. after recrystallisation from benzene, 174—176°. Chloroform extraction of the aqueous mother-liquors gave a further quantity of (III; R = Et) (230 mg.); total yield was 510 mg. (76%).

(iii) The anil (VIII) (250 mg.) was reduced with sodium borohydride (250 mg.) in methanol (8 c.c.). The product after working up in the usual manner was (III; R = Et), m. p. 173—175° (120 mg., 71%).

Reduction of (VIII) *with Lithium Aluminium Hydride.*—The anil (VIII) (250 mg.) was refluxed with lithium aluminium hydride (250 mg.) in tetrahydrofuran (25 c.c.) for 45 minutes. The product, worked up in the usual manner, was an oil (200 mg.) which was thoroughly extracted with alkali. The residue was treated with Brady's reagent overnight, to give a 2 : 4-dinitrophenylhydrazone which separated from ethanol as needles (18 mg.), m. p. 192—193° (Found : C, 54·95; H, 5·4; N, 17·0%; *M*, 266). The ultra-violet absorption spectrum showed a principal absorption maximum at 380 mμ (ε 32,300). In a similar experiment the oil obtained after removal of alkali-soluble material was treated with dioxan (1 vol.)–3N-sulphuric acid (1 vol.) for 24 hours at room temperature. Chromatography of the product on alumina yielded no pure material.

4 : 5 : 6 : 7-*Tetrahydro*-4-*keto*-3-*methyl*-1-*phenyl*iso*indazole* (XII).—2-Acetyl*cyclo*hexane-1 : 3-dione (I) (500 mg.) was refluxed with phenylhydrazine (350 mg.) in ethanol (10 c.c.) for 2 hours. On cooling, water (30 c.c.) was added, and the crystalline precipitate filtered off and recrystallised from aqueous ethanol to yield the iso*indazole* (XII) as long needles (690 mg.), m. p. 129° (Found : C, 74·6; H, 6·2; N, 12·2. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%). The infra-red absorption spectrum shows bands at the following wave-lengths (μ) : 5·98s, 6·25w, 6·45w, 6·64m, 6·73m, 6·98m, 7·08m, 7·13w, 7·56w, 7·70w, 7·76w, 8·38w, 8·62w, 9·07w, 9·38w, 9·42w, 9·62w, 9·70w, 9·80w, 9·93w, 10·24w, 10·82w, 10·92w, 11·11w, 11·50w, 11·78w, 12·56w, 12·88m, 13·83w.

4 : 5 : 6 : 7-*Tetrahydro*-4-*keto*-3-*methylbenz*iso*oxazole* (XIII).—2-Acetyl*cyclo*hexane-1 : 3-dione (590 mg.) was added to hydroxylamine hydrochloride (266 mg.) in water (10 c.c.), and the mixture neutralised with aqueous sodium hydroxide, left for 3 days, poured into water (100 c.c.), and extracted with ether (4 × 25 c.c.). The extracts were combined, extracted with 10% aqueous sodium hydroxide (total 25 c.c.), washed with water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crystalline residue, which, recrystallised from light petroleum (b. p. 40—60°), gave the iso*oxazole* (XIII) as long, hair-like needles (173 mg.), m. p. 66—67° (Found : C, 63·8; H, 6·1; N, 8·9. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). The infra-red absorption spectrum shows bands at the following wave-lengths (μ) : 5·92s, 5·98s, 6·25s, 6·69w, 6·83s, 7·03m, 7·12m, 7·27s, 7·40m, 7·47w, 7·60w, 7·75w, 7·92s, 8·45w, 8·75w, 9·33m, 9·42w, 9·61w, 9·85m, 11·31w, 11·72w, 12·08w, 13·38w.

The alkaline extracts from the above were combined, acidified, and extracted with chloroform. The crystalline product was recrystallised from ethyl acetate to give what is probably 2 : 6-*diketo*cyclo*hexyl methyl ketoxime* as colourless prisms (165 mg.), m. p. 121° (evolution of gas) (Found : C, 56·6; H, 6·5; N, 8·2. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·5; N, 8·3%). On cooling, the melt solidifies and remelts at 64—65°. The ultra-violet absorption spectrum shows a band at 255 mμ (ε 13,200). The infra-red absorption bands are at the following wave-lengths (μ) : 3·18m, 6·13s, 6·26s, 7·35s, 7·50s, 8·33m, 8·75w, 9·28w, 9·57w, 10·28s, 10·51m, 10·83m, 11·71w, 11·95w, 12·65w, 13·53w.

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