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THE FORMATION OF A REARRANGED PRODUCT ON DEHYDRATION OF A BICYCLIC NITRONE-HYDROXYLAMINE*

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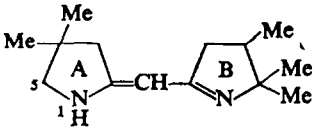
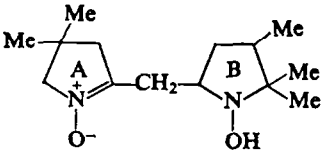
Abstract—Dehydration of the nitrone-hydroxylamine (II) with toluene-*p*-sulphonyl chloride and triethylamine gives the rearranged product. 2,3,4,5-tetrahydro 5,5-dimethyl 3-oxo-2-(4′,5′,5′-trimethylpyrrolidin-2′ ylidene) pyridine (III). The benzoate of (III) undergoes rearrangement in dilute acid to give the pyrrolo-imidazole (XI).

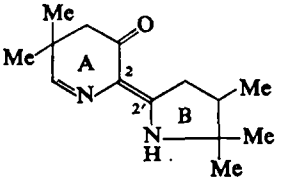
THE 2′(pyrrolidin 2-ylidenemethyl)1′-pyrroline (I) is readily obtained[2] by dehydration of the corresponding *bis*-hydroxylamine using phosphorus oxychloride and triethylamine. Its usefulness for corrin synthesis would be enhanced if a third double bond could be introduced, directly or indirectly, between positions 1 and 5 of the structure (I). In an attempt to obtain this triply-unsaturated compound the nitrone-hydroxylamine (II) was treated with toluene-*p*-sulphonyl chloride and triethylamine in benzene None of the desired product was formed. Instead, a crystalline base $C_{14}H_{22}N_2O$, m.p. 147°, was obtained in 36% yield. Small amounts of the same base were isolated following the decomposition of the copper complex of (I) on standing in methanol, and after treatment of (I) with N-bromosuccinimide followed by ethanolic potassium hydroxide. Evidence for the assignment of structure (III) to this compound is presented below.



I



II



III

* Experiments towards the Synthesis of Corrins. Part X[1].

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[1] Part IX, R. F. C. Brown, V. M. Clark and Lord Todd, *J. Chem. Soc.* 2337 (1965).

[2] R. F. C. Brown, V. M. Clark, I. O. Sutherland and Sir Alexander Todd, *J. Chem. Soc.* 2109 (1959).

The compound was a weak monacidic base, pK'_a 4·0*, and was stable to both acid and alkali. It did not react with 2,4-dinitrophenylhydrazine, nor did it reduce alkaline triphenyl tetrazolium chloride. It gave no ferric chloride test, but with methanolic copper acetate, a deep violet colour developed. Analysis showed the presence of one active hydrogen. The UV spectrum had two maxima, at 287 mμ (ϵ_{max}, 13500) and 332 mμ (ϵ_{max}, 13200); both were unchanged on addition of alkali, but in acid they were moved to 254 mμ (ϵ_{max},10500) and 305 mμ (ϵ_{max}, 26200): C_3H_7·CO·CH=CH·NEt_2 has a long wavelength absorption maximum at 307 mμ (ϵ_{max}, 28000).[3] The IR spectrum contained bands at 3280 (NH group), 1610 (C=N), and 1630 and 1545 cm^{-1} (vinylogous amide).[4] The nuclear magnetic resonance spectrum showed peaks at τ0·55 (1′—NH group; numbering referred to structure III), 3·17 (6—CH=N—), a group of six or more weak lines over the range 6·69–7·52 (3′—CH_2), 7·92 (4—CH_2, adjacent to carbonyl group), and at 8·82 and 9·07 (methyl groups).

On hydrogenation in ethanol over platinum, the base (III) took up the equivalent of two moles of hydrogen to give a solution which was strongly reducing to alkaline triphenyltetrazolium chloride: on working up, autoxidation to the starting material occurred, so that exclusive formation of a tetrahydro-compound could not be assumed. In ethanolic hydrochloric acid, on the other hand, hydrogenation over platinum led to the slow absorption of three moles of hydrogen, and the sparingly soluble dihydrochloride (IV) of a hexahydro-base $C_{14}H_{28}N_2O$ was obtained. This salt, which was not a hydroxylamine (it did not reduce alkaline triphenyltetrazolium chloride), showed no UV absorption in neutral ethanol. Its IR spectrum showed two sharp bands at 1580 and 1545 cm^{-1} which we assign to NH or OH bending modes, since they are not present in the spectrum after evaporation of the salt with deuterium oxide. The UV spectrum of the free base showed only the end absorption attributable to basic nitrogen atoms,[5] and there was no IR absorption in the double bond region; clearly, (IV) is a saturated bicyclic compound. On titration it had p$K'a_1$ 6·8 and p$K'a_2$ 11·0: such a wide separation in a saturated diamine is characteristic of 1,2- but not of 1,3-diamines.[6,7] The difference, (p$K'a_2$–p$K'a_1$) is rather larger in the present case (4·2) than in the case of the 2,2′-bipyrrolidinyl previously reported[7] (3·35), but the presence of the 3-hydroxyl group might well be expected to increase this difference: c.f. ethylamine, pK_a10·63, ethanolamine, pK_a 9·50.[8] As the nitrone-hydroxylamine (II) is formally derived from a 1,3-diamine, a rearrangement must have occurred in the reaction with toluene-*p*-sulphonyl chloride.

Ozonolysis of compound (III) gave 4,5,5-trimethyl-pyrrolidone, derived from ring B, together with the keto-glutarimide (V)[9] which indicated that rearrangement had

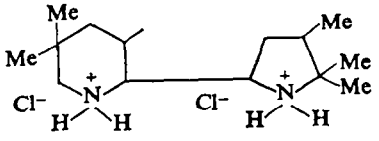
* All pK'_a values quoted were obtained from the half-neutralization point on microtitration of the compound in 50% aqueous methanol with 0·2N-acid or alkali.

[3] K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weeden, *J. Chem. Soc.* 45, (1946).
[4] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. F. Frank and D. J. Wallace, *J. Amer. Chem. Soc.* **71**, 3337, (1949).
[5] N. J. Leonard and D. M. Locke, *J. Amer. Chem. Soc.* 77, 437 (1955).
[6] G. Schwarzenbach, *Helv. Chim. Acta* **16**, 522 (1933).
[7] R. F. C. Brown, V. M. Clark, M. Lamchen and Sir Alexander Todd, *J. Chem. Soc.* 2116 (1959).
[8] A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen, London (1962).
[9] R. F. C. Brown, *Aust. J. Chem.* 77, 154 (1964).

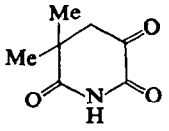
taken place in ring A. Hydrogenation of (III) to a saturated bicyclic system containing a 1,2-diamine structure leads to the unique formulation indicated.

In addition to (V) and the pyrrolidone, small amounts of *as*-dimethylsuccinic acid and an oxidation product $C_{14}H_{22}N_2O_2$ were isolated from the ozonolysis reaction. This last compound is probably (VI) although it is not possible to assign a definite structure on the spectroscopic and analytical evidence available.

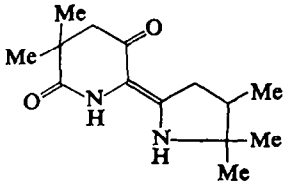
Acylation of III using benzoyl or acetyl chloride in the presence of pyridine gave, in each case, a yellow, mono-acyl derivative having rather complex UV, IR and NMR



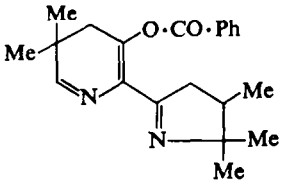
IV



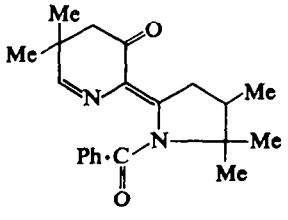
V



VI

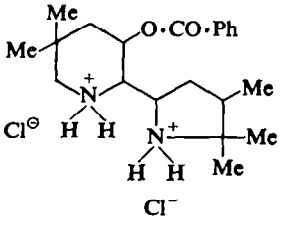


(a)



(b)

VII



VIII

spectra. The solid acetyl compound was pale yellow, (long wavelength maximum in EtOH 330 mμ), whilst the benzoyl compound was bright yellow (long wavelength maxima 332 and 365 mμ); this difference may well be associated with internal charge transfer in certain conformers since there was a marked variation between solid and solution. The mono-benzoyl derivative VII exhibited UV maxima at 225, 250, 332 and 365 mμ, and strong IR bands at 1675 and 1550 cm^{-1} in chloroform solution, and at 1687, 1659 and 1534 cm^{-1} in Nujol mull. The IR bands in solution were significantly broader than in the mull, possibly indicating a mixture of conformers in solution.

This spectral evidence favours[10] the N-benzoyl for mulationVIIb but rearrangement to an O-benzoate VIIa appears possible. Thus, on hydrogenation, the mono-benzoyl derivative absorbed three moles of hydrogen and the product showed the single strong band at 1715 cm^{-1} expected for an O-benzoate.

The crude hexahydro-benzoate, a gum, gave a crystalline dihydrochloride VIII, which, when anhydrous, had no hydroxyl band in its IR spectrum, but again exhibited normal O-benzoate (1712 cm^{-1}) and aromatic ring bands. This salt was very hygroscopic, and analyses were carried out on material approximating to a trihydrate. On titration it had a $pK'a_1$ 4·9 and $pK'a_2$ 8·9 which confirmed that the 1,2-diamine system persisted in the benzoylated series. Alkaline hydrolysis removed the benzoyl group, and the product was again isolated as a hydrochloride. This was similar to, but not identical with, the dihydrochloride IV, although it was expected to have the same gross structure. The difference is presumably stereochemical.

The NMR spectrum (60 Mc/s) of the benzoyl derivative VIIa in carbon tetrachloride was strikingly different from that of its precursor III. The region from τ7·1 to 9·1 was extremely complex, but integration showed that it probably contained signals from the 4-methylene group (τ8·37) and the *gem*-dimethyl groups at C-5 and C-5′ (sharp major peaks at τ8·58, 8·69 and 9·04) superimposed upon the complex pattern to be expected from the ABX system of the 3′ and 4′ hydrogen atoms. These assignments[11] are tentative, since there was considerable overlapping of major peaks, and reliable integration of individual peaks was impossible. The multiplicity of major peaks in the region τ8·5 to 9·1 suggested that either or both of the *gem*-dimethyl groups showed a magnetic non-equivalence of methyl groups. A broad envelope with peaks at τ2·58 and 2·74 (5 protons) was assigned to the benzoyl group, a sharp singlet (1 proton) at τ3·03 to the aldimine proton at C-6, and an asymmetric doublet (3 protons) centred at τ9·62 (J = 5·0 c/s) to the 4′-methyl group.

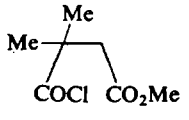
The NMR spectrum (60 Mc/s, CCl_4) of the corresponding acetyl derivative showed peaks due to the methyl groups at τ8·80, 8·90 and 9·01 of approximate intensity 2 : 2½ : ½. The peak at τ9·01 was probably one half of a doublet (J > 6c/s) centred near τ8·95 due to the 4′-methyl group.

Ozonolysis of the yellow benzoyl derivative VII and decomposition of the ozonide with aqueous hydrogen peroxide gave only benzoic acid and a small amount of impure *as*-dimethylsuccinic acid. A much more significant fission of the molecule occurred on brief heating with 1N-sodium hydroxide solution, when an acidic carbonyl compound was formed. This gave an acidic 2,4-dinitrophenylhydrazone $C_{12}H_{14}N_4O_6$, and could be oxidized by potassium permanganate to *as*-dimethylsuccinic acid. The derivative

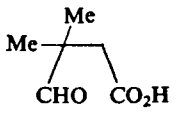
[10] L. B. Bellamy, *The Infra-Red Spectra of Complex Molecules* (2nd Edition). Methuen, London (1958).

[11] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon, London (1959).

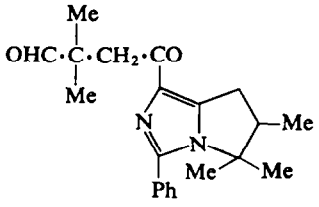
seemed likely to be the dinitrophenylhydrazone of either β-formylpivalic acid or β-formylisovaleric acid, reported by Clarke and Ramage[12] to have m.p.'s 173° and 260° respectively. However, the m.p. of the latter, β-formylisovaleric acid 2,4-dinitrophenylhydrazone, seemed rather high, and their method of preparation, by Rosenmund reduction of the half-ester half-acid chloride IX at 100°, open to doubt. Acid chlorides of this type are very susceptible to rearrangement, particularly when prepared by the action of thionyl chloride containing traces of impurities.[13] This uncertainty in the preparation of the acid chloride IX was overcome by using oxalyl chloride, which is known not to promote rearrangement.[14] The acid chloride was kept below 10° before reduction to the aldehyde by lithium tri-(*tert*-butoxy) aluminium hydride[15] at −70°. The crude aldehyde, after acid hydrolysis, gave the 2,4-dinitrophenylhydrazone of β-formylisovaleric acid, m.p. 192°, which was identical in all respects with that obtained from the cleaveage of compound VIIa. Identity was further established by comparison of the methyl esters. The formation of β-formylisovaleric acid X confirms the presence of a potential aldehyde group (C-6) in the benzoyl derivative VII, and indeed, on treatment with acid, the latter rearranges to a compound, XI, containing a free aldehyde group.



IX



X



XI

The benzoyl derivative VII, a rather weak base, is rapidly and quantitatively converted in dilute acidic solution to a colourless isomeric base of pK_a' 6·4. To this isomer, we assign the pyrroloimidazole structure XI. The presence of a tertiary aldehyde group was shown by IR maxima at 2830, 2700 and 1724 cm^{-1}, and by the presence of a sharp peak at $\tau = 0{\cdot}32$ in the nuclear magnetic resonance spectrum. A second conjugated carbonyl group showed IR absorption at 1658 cm^{-1}, and the compound readily formed a dioxime. The aldehyde group was reduced by sodium borohydride, but the IR and UV spectra of the resulting dihydro compound showed the conjugated carbonyl group to be unaffected. However, with lithium aluminium hydride in tetrahydrofuran both carbonyl groups of XI were reduced and a tetrahydro compound was obtained.

The NMR spectrum of XI showed sharp peaks at τ2·57 (phenyl hydrogens), 6·67 (methylene adjacent to carbonyl group), and at 8·82 and 8·92 (methyl groups). The UV

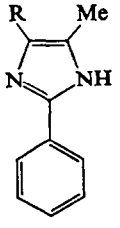
[12] P. Clarke and G. R. Ramage, *J. Chem. Soc.* 4345 (1954).
[13] J. Cason, *J. Amer. Chem. Soc.* **69**, 1548 (1947).
[14] S. Ställberg-Stenhagen, *J. Amer. Chem. Soc.* **69**, 2568 (1947).
[15] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **80**, 5377 (168).

spectrum of XI showed a maximum at 271 mμ, but none near 230 mμ, indicating that the benzoyl group of VII had been incorporated into a heterocyclic ring.

UV SPECTRA OF BASE XI AND MODEL COMPOUNDS

Compound	EtOH		EtOH + HCl	
	λ max (mμ)	ε max	λ max (mμ)	ε max
Base (XI)	271	14100	255	14500
Tetrahydro deriv of (XI)	263	7100	247	8700
N-Phenyl-Imidazole-CHO (XII)	297	17400	277	17600
N-Phenyl-Imidazole-CH_2OH(XIII)	283	16100	277	17300

In the Table the spectra of the phenylimidazoles XII and XIII[16] are compared with those of XI and its tetrahydro derivative. Although the positions of the absorption maxima vary, the shifts λ_{max}(EtOH) − λ_{max}(EtOH + HCl) and λ_{max}(carbonyl compound) − λ_{max}(derived alcohol) are comparable, and suggest that the two groups of compounds may be closely related. The discrepancies in wavelengths and ε values are probably attributable to the non-planarity of the absorbing system in compound XI, which is formally a hindered diaryl with a bulky ortho-substituent, c.f. diphenyl (λ_{max}249 mμ, ε17000) and 2-isopropyldiphenyl (λ_{max}233 mμ, ϵ_{max}11000)[17].

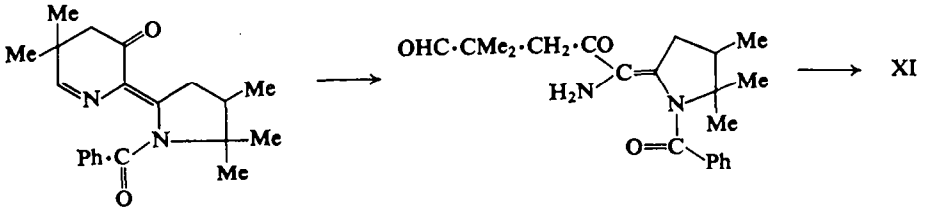


XII: R = —CHO
XIII: R = —CH_2·OH

More direct though not decisive evidence supporting structure XI was obtained by permanganate oxidation under mildly alkaline conditions, which gave the neutral products benzamide (30%) and 1-benzoyl-4,5,5-trimethylpyrrolid-2-one (14%). It is likely that these products are derived from the same potential benzoyl group but from different nitrogen atoms, and that their formation is in accord with the pyrrolo-imidazole structure. Dimethylmalonic and benzoic acids were isolated from the acidic products, and the probable presence of *as*-dimethyl-succinic acid was demonstrated by paper chromatography.

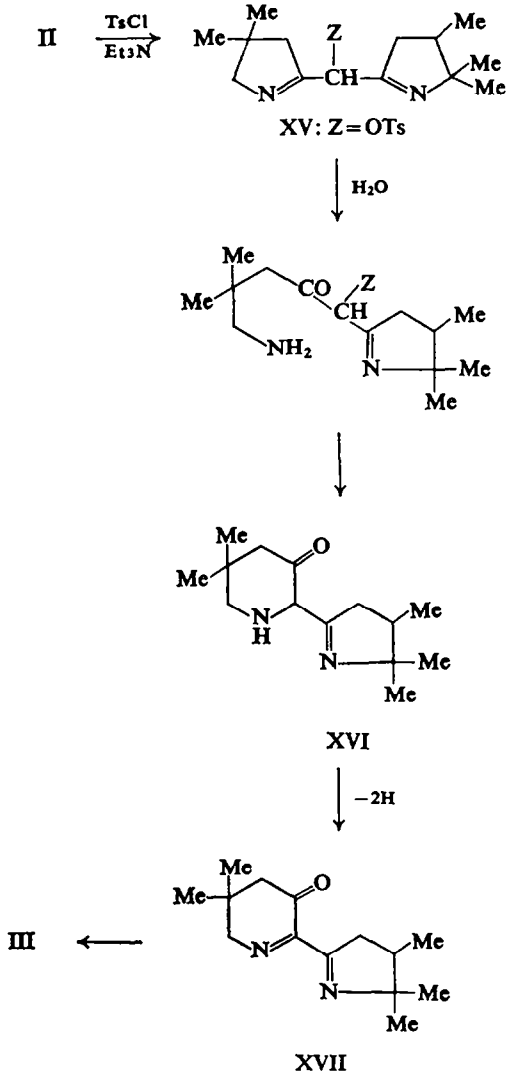
The course of the acid-catalysed isomerisations of VII to the pyrrolo-imidazole XI remains to be considered. Acyl migration in the neutral molecule is not favoured since VII was recovered unchanged after heating in xylene for 10 hr. Assuming that III undergoes benzoylation on nitrogen, to give VIIb, hydrolytic opening of ring A would give XIV, cyclization of which would yield the pyrrolo-imidazole XI.

[16] J. W. Cornforth and H. T. Huang, *J. Chem. Soc.* 731 (1948).
[17] E. A. Braude and W. F. Forbes, *J. Chem. Soc.* 3776 (1955).



VII,b XIV

The details of the formation of the original base III from the nitrone-hydroxylamine II are also unclear. The product differs from the starting material by loss of the elements of water and one molecule of hydrogen. It seems likely that an intermolecular redox reaction or the dehydrogenation of an intermediate by atmospheric oxygen (which was



not excluded) occurs. We propose that, in the initial steps, the hydroxylamine undergoes dehydration and the nitrone suffers a migration of oxygen (via a toluene-*p*-sulphonyloxy group) to the adjacent methylene group by a cyclic process.[18] On treatment of the reaction mixture with water the product XV could undergo hydrolysis and ring expansion to the intermediate XVI. Dehydrogenation of this would give the cross-conjugated triketone-analogue XVII, which, following prototropy, would give the more highly conjugated vinylogous amide III. The formation of the base III from the dipyrrolinylmethane I can be explained in the same way, since oxidation at the meso-carbon atom of structure I would result in the formation of an intermediate of type XV with, for example, Z=Br. Such a meso-brominated base has been isolated from the products of direct bromination of the dipyrrolinylmethane I.[19]

EXPERIMENTAL

Unless otherwise stated IR data refer to Nujol mulls. UV spectral shifts on addition of acid or alkali were observed by adding concentrated hydrochloric acid or ethanolic potassium hydroxide (1 drop) directly to a 1 cm cell (of volume ~ 4 ml) containing a ~ 10^{-4}M solution of the compound. Most nuclear magnetic resonance measurements were made on chloroform or carbon tetrachloride solutions at 40 Mc (Varian instrument) and calibrated against tetramethysilane as internal standard. The spectrum of compound (VII) was also measured at 60 Mc/sec (Varian A-60 instrument). Band positions are given as τ values[10]. Light petroleum refers to the fraction of b.p. 60–80°.

2,3,4,5-*Tetrahydro*-5,5-*dimethyl*-3-*oxo*-2-(4′,5′,5′-*trimethylpyrrolidin*-2′-*ylidene*) *pyridine* (III).—(a) Toluene-*p*-sulphonyl chloride (22·5 g) in benzene (50 ml) was added during 15 min to an ice-cold, stirred solution of the nitrone-hydroxylamine (II, 15·0 g) in benzene (100 ml) and triethylamine (30 ml). Further cooling in ice was maintained for 1 hr, after which the stirring and cooling were stopped and the reaction mixture allowed to stand for five days with exclusion of moisture, but not of air. Triethylammonium salts were removed by filtration and washed with ether (150 ml). The filtrate and washings were evaporated to leave a syrup which was separated by shaking with ether and dilute sulphuric acid into a basic (8·4 g) and a neutral fraction (3·7 g).

The basic fraction, a dark syrup, was dissolved in ether and passed through a column of basic alumina (15 cm long × 3 cm diameter). Elution with ether (500 ml) gave an amber oil (7·1 g) which partly crystallized. Crystallization from light petroleum, and further chromatography of the mother liquors on alumina using light petroleum, gave the *tetrahydropyridine* as very pale yellow needles (4·84 g, 36%), m.p. 147°. Further crystallization from pentane afforded colourless needles of unchanged m.p. (Found: C, 71·9; H, 9·8; N, 11·9; active H, 0·44; M (thermistor method),[20] 232. $C_{14}H_{22}N_2O$ requires: C, 71·8; H, 9·5; N, 12·0; 1 active H, 0·43%; M, 243), λ_{max}(EtOH) 287 mμ (ϵ_{max} 13500) and 332 mμ (ϵ_{max}, 13200), unchanged on addition of ethanolic sodium hydroxide; λ_{max}(EtOH + HCl) 254 mμ (ϵ_{max}, 10500) and 305 mμ (ϵ_{max}, 26200), ν_{max}($CHCl_3$) 3280, 1630, 1610, and 1545 cm^{-1}, apparent pK_a 4·0. It gave a deep violet colour with methanolic copper acetate, but no colour with ferric chloride, and could be recovered after several hours' heating with 3N ethanolic sodium hydroxide, 3N sulphuric acid, or 2,4-dinitrophenylhydrazine in ethanolic sulphuric acid. It did not reduce alkaline triphenyl tetrazolium chloride.[21]

The *hydrochloride* formed needles from ethanol and ether, m.p. 227–229° (decomp) (Found: C, 62·3; H, 8·8; equiv, 276. $C_{14}H_{23}ClN_2O$ requires: C, 62·1; H, 8·6%; equiv, 271), ν_{max}3250, 2470, 2090, 1632, 1575, and 1507 cm^{-1}.

The *picrate* formed bright yellow needles from ethanol, m.p. 197° (decomp). (Found: C, 51·7; H, 5·4; N, 15·0. $C_{20}H_{25}N_5O_8$ requires: C, 51·8; H, 5·4; N, 15·1%).

[18] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and Sir Alexander Todd, *J. Chem. Soc.* 2094 (1959).

[19] H. Moncure and C. B. Morgan, unpublished observations.

[20] B. R. Y. Iyengar, *Rec. Trav. Chim.* 73, 789 (1954).

[21] G. A. Snow, *J. Chem. Soc.* 2588 (1954).

(b) The dipyrrolinylmethane (I) (0·5 g) was converted to the copper complex,[2] which was dissolved in methanol (20 ml) and allowed to stand for 2 days in the presence of air. When the deep blue colour of the complex had faded, the methanol was evaporated, and the basic fraction isolated as a dark gum. Sublimation of this gum at 100°/20 mm gave a small quantity of partly crystalline sublimate, which with ethanolic picric acid formed a crystalline picrate. Recrystallization from ethanol afforded the tetrahydropyridine picrate (32 mg), identified by its m.p. and mixed m.p. with the above picrate, 197° (decomp), and by conversion to the base and comparison of UV and IR spectra.

(c) The dipyrrolinylmethane (I) (50 mg) and N-bromosuccinimide (50 mg) in carbon tetrachloride (5 ml) were heated under reflux for 45 min. The solvent was evaporated, and the residue heated under reflux for 1 hr with potassium hydroxide (100 mg) in methanol (3 ml). After evaporation of the methanol and addition of water, the products were extracted with ether. The ethereal solution was shaken with aqueous potassium hydrogen phthalate to remove the strongly basic starting material, and then evaporated to give a pale yellow gum. Treatment of this with ethanolic picric acid and repeated crystallization of the precipitated picrate from ethanol gave the tetrahydropyridine picrate (5 mg), identified by m.p. and mixed m.p. with the above picrate, 196–7°.

Hydrogenation of the oxo-tetrahydropyridine (III)—(a) The oxo-tetrahydropyridine (90 mg) in ethyl acetate (10 ml) and acetic acid (1 ml) was hydrogenated over pre-reduced platinum oxide (10 mg). Absorption of hydrogen ceased after 25 min (uptake 18·5 ml, 2·0 mole), and after filtration, the resultant solution was strongly reducing as evidenced by the alkaline triphenyltetrazolium chloride reagent.[21] Isolation of the product following addition of dilute ammonia and extraction with ether gave a gum which was distinctly less powerful as a reducing agent. Chromatography in light petroleum b.p. 40–60° on a magnesium carbonate column (10 × 1 cm), followed by repeated crystallization, from light petroleum, of the solid product from the feebly-reducing eluate, gave the starting material as colourless needles, identified by m.p. and mixed m.p., 147°.

(b) The oxo-tetrahydropyridine (300 mg) in ethanol (100 ml) containing 10N-hydrochloric acid (1 ml) was hydrogenated over pre-reduced platinum oxide (100 mg). Hydrogen was absorbed rapidly during 10 min (*ca* 1 mole); after 5 hr absorption ceased (uptake 98 ml, 3·1 mole). Catalyst was removed, and the filtrate evaporated to give a semi-crystalline residue which after repeated crystallization from ethanol afforded *5,5-dimethyl-3-hydroxy-2-(4,5,5-trimethyl-2′-pyrrolidinyl) piperidine dihydrochloride* (IV) (155 mg) as needles which sublimed and decomposed above 300°. (Found: C, 53·5; H, 9·9; Cl, 22·8; N, 9·3. $C_{14}H_{30}Cl_2N_2O$ requires: C, 53·7; H, 9·7; Cl, 22·6; N, 9·0%). The product had no UV absorption in neutral ethanol; on the other hand in the IR $\nu_{max} = 3280$, 2700 and 2485 (two peaks in complex band), 1580, and 1545 cm^{-1}. Following deuteration by evaporating with deuterium oxide the salt had ν_{max} 2420 and 2130, 2070 and 1900 (three peaks in complex band) cm^{-1}.

The *base* crystallized from a small volume of pentane in rosettes of needles, m.p. 109°, which were quite hygroscopic (Found: C, 69·7; H, 11·3; N, 11·3. $C_{14}H_{28}N_2O$ requires: C, 70·0; H, 11·7; N, 11·7%) and showed only UV end absorption in EtOH, ν_{max} 3300 cm^{-1}, pKa_1 6·8 and pKa_2 11·0. It did not reduce alkaline triphenyltetrazolium chloride.

Ozonoylsis of the oxo-tetrahydropyridine (III)—The base (200 mg) in ethyl acetate (10 ml) was treated with oxonized oxygen for 20 min at 0°. The ozonide was decomposed by hydrogenation over 10% palladium on strontium carbonate, and the resulting gum distributed (in three separating funnels) between ether and water (3 × 10 ml of each).

Evaporation of the ethereal layers gave a yellow gum (85 mg) which was further separated into basic and neutral/acidic fractions. The basic fraction, when stirred with benzene, gave crystals which were recrystallized from acetone–pentane to give an *oxidation product* (4 mg) as needles, m.p. 233°. (Found: C, 66·9; H, 9·1; N, 11·5. $C_{14}H_{22}N_2O_2$ requires: C, 67·2; H, 8·9; N, 11·2%), λ_{max}(EtOH) 259 mμ (ϵ_{max} 8100) and 341 mμ (ϵ_{max} 14900), λ_{max}(EtOH + HCl) 254 mμ (ϵ_{max}, 7100) and 340 mμ (ϵ_{max} 15100) ν_{max}3260, 1668, 1652, 1552 and 1532 cm^{-1}.

The neutral/acidic fraction gave crystals on stirring with ether–light petroleum, and a further quantity was obtained by chromatography of the mother liquors on silica. Recrystallization from acetone–pentane gave 5,5-dimethyl-2,3,6-trioxopiperidine (7 mg) (V)[9], as leaflets, m.p. 169°. (Found: C, 54·7; H, 6·4; N, 9·9. Calc for $C_7H_9NO_3$. C, 54·2; H, 5·9; N, 9·0%) λ_{max}(EtOH) 262 mμ (ϵ_{max}3600) λ_{max}(EtOH + KOH) 308 mμ (ϵ_{max}1200), ν_{max}3350, 3190, 3050, 1705 and 1670 cm^{-1}. It was soluble in aqueous sodium hydrogen carbonate solution and gave a weak red colour with ferric chloride.

Evaporation of the original aqueous layers gave a syrup (*ca* 100 mg) which on repeated extraction with boiling light petroleum gave a crude pyrrolidone fraction which was further purified by filtration

through alumina in methylene chloride. followed by crystallization from pentane, and sublimation at 80°/0·5 mm. 4,5,5-Trimethylpyrrolidone (23 mg) was obtained as a crytalline mass, m.p. 40–42°. (Found: C, 66·0; H, 10·6. Calc for $C_7H_{13}NO$: C, 66·1; H, 10·3%), and identified by comparison of its IR and nuclear magnetic resonance spectra with those of an authentic specimen.[22]

The petroleum-insoluble residue from the aqueous layers was dissolved in 2N-hydrochloric acid and the solution continuously extracted with ether. In a parallel experiment starting from 1·0 g of the oxo-tetrahydropyridine (III) this extraction yielded an acidic gum (96 mg) which was chromatographed on silica (10 × 1 cm) in ether–light petroleum (1:1). The column was eluted with solvent containing increasing proportions of ether, 25 ml fractions being collected. Fractions 3 and 4 crystallized on evaporation. Repeated recrystallization from ether–pentane gave *as*-dimethylsuccinic acid (6 mg), m.p. and mixed m.p. with an authentic sample 141–142°, further identified by comparison of IR spectra.

Acylation of the oxo-tetrahydropyridine (III): (a) Benzoyl chloride (350 mg) in ether (5 ml) was added to the oxo-tetrahydropyridine (500 mg) in ether (5 ml) and pyridine (3 ml). After 10 min crystals began to separate from the bright yellow solution. The solution was allowed to stand for 12 hr, then water (200 ml) was added, the product extracted with ether (5 × 40 ml), and the extract washed with water and evaporated to dryness. The solid residue was repeatedly crystallized from ether–pentane to give a *benzoyl deriv.* (VIIa/b), (201 mg) as fine yellow needles, m.p. 166°. (Found: C, 74·4; H 7·7; N, 7·9. $C_{21}H_{26}N_2O_2$ requires: C, 74·5; H, 7·7; N 8·3%), λ_{max}(EtOH) 225 (ϵ_{max} 10800), 260(ϵ_{max}, 10000), 332 (ϵ_{max}, 6000), and 365 (ϵ_{max} 5300) mμ, ν_{max} (mull) 3045 1687, 1659, 1608, 1588 and 1534 cm^{-1}, ν_{max}($CHCl_3$) 1675 (very broad), 1615 and 1550 cm^{-1}.

The mother liquors from this crystallization were warmed with 2N-hydrochloric acid, and the resulting colourless solution made alkaline with ammonia. The precipitated base was crystallized from ether–pentane to give the imidazole (XI) (179 mg), m.p. 142–143°, described below.

(b) Acylation of the oxo-tetrahydropyridine (250 mg) with acetyl chloride (140 mg) in ether and pyridine by the method described in (a) gave an *acetyl deriv.* (112 mg) as long pale yellow needles, m.p. 118–119°. (Found: C, 66·8; H, 9·8; N, 10·8. $C_{16}H_{24}N_2O_2$ requires: C, 66·6; H, 9·6; N, 11·1%), λ_{max} (EtOH) 265 (ϵ_{max} 5000) and 330 (ϵ_{max} 12,300) mμ, λ_{max}EtOH + HCl) 253 mμ (ϵ_{max} 10900), ν_{max}(mull) 1705, 1648, 1612 and 1535 cm^{-1}, ν_{max}($CHCl_3$) 1690, 1640, 1620 and 1550 cm^{-1} (all bands very broad; approximate band centres given). The NMR spectrum (60 Mc/sec, CCl_4) showed sharp singlets at 2·86 (one proton at C–6), 7·82 (2 protons, 4-methylene group), and 8·09 (3 protons of acetoxy group). Peaks due to the methyl groups appeared at τ 8·80, 8·90 and 9·01, and a complex pattern attributable to the hydrogens at C-3′ and C-4′ was present in the region τ 7·3 to 8·7.

Hydrogenation of the Benzoyl Derivative (VIIa/b)—The benzoyl derivative (102 mg) in ethanol (20 mg) was hydrogenated over pre-reduced platinum oxide (20 mg). Absorption of hydrogen ceased after 3 hr (uptake 21·5, 2·9 mole). The product, a pale gum, had ν_{max}3300 and 1715 cm^{-1}. Treatment of the gum with ethanolic hydrogen chloride and ether precipitated a salt which, on repeated precipitation from ethanol–ether, gave *3-benzoyloxy-5,5-dimethyl-2-(4′,5′,5′-trimethyl-2′-pyrrolidinyl) piperidine dihydrochloride* (VIII) (75 mg), m.p. 250° (decomp). After drying at 90°/1 mm the compound showed no hydroxyl band in its IR spectrum (mull), but the dry material was extremely hygroscopic, and a strong band at 3425 cm^{-1} was present after brief exposure to air. The compound was analysed after equilibration with air. (Found: C, 52·3; H, 8·6; Cl, 15·4; N, 6·2; equiv, from pK_{a1}, 472. $C_{21}H_{34}Cl_2N_2O_2$, 3 H_2O requires: C, 53·5; H, 8·6; Cl, 15·4; N, 5·9%; first equiv, 472), and had λ_{max}(EtOH) 228 mμ (ϵ_{max} calc for trihydrate, 11700), ν_{max}3425 (H_2O), 1712, 1602 and 1589 cm^{-1}, pK_{a1} 4·9 and pK_{a2} 8·9.

Ozonolysis of the Benzoyl Derivative (VIIab)—This compound (50 mg) in ethyl acetate (15 ml) was treated with ozonized oxygen for 10 min at 0°. The solvent was evaporated *in vacuo*, and the residue warmed with 5% hydrogen peroxide solution for 2 hr. Excess peroxide was decomposed by shaking with a little platinum black, and the filtered solution made alkaline with sodium bicarbonate. Neutral and basic materials (10 mg) were removed by extraction with ether. Acidification and extraction with pentane (3 × 10 ml) yielded crystalline benzoic acid (9 mg), identified by its IR spectrum and by paper chromatography in the propanol–ammonia (70:30) system.[23] Continuous extraction with ether gave a second acidic fraction which when stirred with pentane deposited a semi-solid mass (18 mg). This was dissolved in ether–light petroleum (1:1) and chromatographed on silica (8 × 1 cm). The

[22] R. B. Moffett and J. L. White, *J. Org. Chem.* **17**, 407 (1952).
[23] F. A. Isherwood and C. S. Hanes, *Biochem. J.* **55**, 824 (1953).

column was eluted with the same solvent, containing increasing proportions of ether, and 25 ml fractions were collected. Fractions 3 and 4 (5 mg) crystallized on evaporation: several recrystallizations from ether–pentane gave impure *as*-dimethyl succinc acid (1 mg), m.p. *ca* 130° (authentic sample m.p. 142°), identified by its IR spectrum in thin crystalline film and by paper chromatography in the propanol–ammonia (70:30) system.

Alkaline Fission of the Benzoyl Derivative (VIIa/b)—The benzoyl derivative (50 mg) was heated at 90° for 6 min with 1N-sodium hydroxide (3 ml). Extraction with ether yielded a gum (29 mg), from which was separated a neutral fraction (15 mg) which deposited crystals on stirring with benzene. Repeated crystallization from benzene gave a small quantity of off-white prisms, m.p. 125–126°, mixed m.p. with benzamide (m.p. 128°) 125–127°. This was probably impure benzamide, its IR spectra being almost identical with that of benzamide.

The alkaline aqueous solution was brought to pH 2 with dilute sulphuric acid and again extracted with ether (5 × 10 ml). Evaporation of the extract gave a colourless oil (10 mg) which had ν_{max}(film) 3300 and 1769 cm^{-1}. With 2,4-dinitrophenyl hydrazine in aqueous perchloric acid a solid was precipitated which, on crystallization from ethanol, gave yellow needles of *β-formylisovaleric acid 2,4-dinitrophenylhydrazone*, m.p. 192°. (Found: C, 46·6; H, 4·6; N, 17·7. $C_{12}H_{14}N_4O_6$ requires: C, 46·5; H, 4·6; N, 18·1%), λ_{max}(EtOH) 364 mμ (ϵ_{max}, 19200), ν_{max}3290, 3100, 1713, 1617, 1592, 1542 and 1519 cm^{-1}, shown to be identical with a synthetic sample by m.p., mixed m.p. and comparison of IR spectra.

On brief treatment with excess ethereal diazomethane the above dinitrophenylhydrazone was converted to the methyl ester, m.p. 155°, undepressed in admixture with the synthetic sample, m.p. 156°, described below, and which had an IR spectrum identical with that of the synthetic ester.

In a parallel experiment the crude oily β-formylisovaleric acid (10 mg), on oxidation with potassium permanganate (7 mg) in water, was converted to *as*-dimethylsuccinic acid (5 mg), identified by m.p. and mixed m.p., 141–142°, and by comparison of IR spectra.

Synthesis of β-Formylisovaleric Acid 2,4-Dinitrophenylhydrazone—β-Carboxyisovaleric methyl ester[24] (1·0 g) in benzene (15 ml) was treated with oxalyl chloride (1·5 ml) with cooling in ice. After 1 hr, benzene and excess reagent were removed by freeze-drying, and the crude acid chloride which remained was dissolved in anhydrous tetrahydrofuran (10 ml). This solution was cooled to −70°, and a solution of lithium tri-(*tert*-butoxy)-aluminium hydride,[15] prepared from lithium aluminium hydride (0·24 g) and *t*-butanol (1·40 g) in tetrahydrofuran (10 ml), was added with stirring. After 30 min water was added and the product isolated as an oil, which was divided into two equal parts.

One part was heated under reflux with 3N-hydrochloric acid for 3 hr and then treated with 2,4-dinitrophenylhydrazine. An acidic derivative was separated from the resulting crude precipitate, and crystallized from ethanol to give yellow needles of the above *acid dinitrophenylhydrazone* (69 mg), m.p. 192°. (Found: C, 46·3; H, 4·5; N, 18·0. Calc for $C_{12}H_{14}N_4O_6$: C, 46·5; H, 4·6; N, 18·1%), identical with the substance obtained by degradation.

The other part was treated directly with 2,4-dinitrophenylhydrazine in hydrochloric acid, and the precipitate crystallized repeatedly from ethyl acetate–light petroleum to give the *methyl ester* (64 mg) as yellow needles, m.p. 156°. (Found: C, 48·2; H, 4·9; N, 17·5. $C_{13}H_{16}N_4O_6$ requires: C, 48·2; H, 5·0; N, 17·3%, ν_{max}3255, 3115, 1707, 1628, 1593, 1539, 1527, and 1502 cm^{-1}.

Acid Isomerization of the Benzoyl Derivative (VIIab) *to the Imidazole* (XI)—The benzoyl derivative (33 mg) was added to 1N-hydrochloric acid (2 ml); the yellow crystals dissolved within 3 min to give a colourless solution. Addition of aqueous sodium hydroxide and extraction with ether yielded colourless crystals (31 mg), m.p. 140–141°. Recrystallization from ether–pentane gave 1-(3,3-*Dimethyl*-1,4-*dioxobutyl*)-6,7-*dihydro*-5,5,6-*trimethyl*-3-*phenyl*-5H-*pyrrolo*[1,2-*c*] *imidazole* (XI) as needles, m.p.143°. (Found: C, 74·2; H, 7·7; N, 8·3. $C_{21}H_{26}N_2O_2$ requires: C 74·5; H, 7·7; N, 8·3%), λ_{max}(EtOH) 27·1 mμ (ϵ_{max} 14100), λ_{max}(EtOH + HCl) 255 mμ (ϵ_{max} 14500), ν_{max}($CHCl_3$) 2830, 2700, 1724, 1658, and 1757 cm^{-1}, apparent pK_a 6·4.

The titration curve of the benzoyl drivative (7 mg) in 50% methanol (4 ml) with 0·1N-hydrochloric acid showed no inflection from pH 8·3 to 2·5, indicating the benzoyl derivative to be a very weak base, whereas back-titration of the colourless acidic solution with 0·1N-sodium hydroxide showed marked hysteresis, with an inflection at pH 6–7 corresponding to the pK_a of the imidazole. Comparison of the UV spectra of the benzoyl derivative in ethanol, and in ethanolic hydrochloric acid, with those of the imidazole, showed that the isomerization was quantitative in dilute solution.

[24] W. A. Bone, J. J. Sudborough and C. H. G. Sprankling, *J. Chem. Soc.* **85**, 534 (1904).

The *dioxime* formed readily in pyridine, and crystallized from aqueous methanol in needles, m.p. 218°. (Found: C, 68·4; H, 7·9; N, 15·3. $C_{21}H_{28}N_4O_2$ requires: C, 68·5; H, 7·7; N 15·2%) λ_{max}(EtOH) 264 mμ (ϵ_{max}, 11700), λ_{max}(EtOH+HCl) 257 mμ (ϵ_{max} 13200), ν_{max}3200, 3090, 1649 and 1607 cm^{-1}.

Hydride Reductions of the Imidazole (XI)—(a) The imidazole (50 mg) on reduction with sodium borohydride (15 mg) in cold methanol gave a dihydro-derivative 1-(3,3-*dimethyl*-4-*hydroxy*-1-*oxobutyl*)-6,7-*dihydro*-5,5,6-*trimethyl*-3-*phenyl*-5H-*pyrrolo*[1,2-*c*]*imidazole* which formed colourless needles from aqueous methanol, m.p. 127–128°. (Found: C, 74·0; H, 8·5; N, 8·4. $C_{21}H_{28}N_2O_2$ requires: C, 74·1; H, 8·3; N, 8·2%), λ_{max}(EtOH) 272 mμ (ϵ_{max} 13200), λ_{max}(EtOH+HCl) 249 mμ (ϵ11200) ν_{max}3230, 1655 and 1575 cm^{-1}.

(b) Reduction of the compound (50 mg) with lithium aluminium hydride (100 mg) in boiling tetrahydrofuran (20 ml) during 4 hr gave a tetrahydro-derivative 1-(1,4-*dihydroxy*-3,3-*dimethylbutyl*)-6,7-*dihydro*-5,5,6-*trimethyl*-3-*phenyl*-5H-*pyrrolo*[1,2-*c*]*imidazole* as prisms from ethanol, m.p. 238°. (Found: C, 73·4; H, 9·2; N, 8·2. $C_{21}H_{30}N_2O_2$ requires: C, 73·6; H, 8·8; N, 8·2%), λ_{max}(EtOH) 263 mμ (ϵ_{max}7100), λ_{max}(EtOH+HCl) 247 mμ (ϵ_{max} 8700), ν_{max}3280, 3100–3050 (broad band), and 1605 cm^{-1}.

Permanganate Oxidation of the Imidazole (XI)—This compound (150 mg) in acetone (4 ml) was added to a solution of potassium permanganate (50 mg) and sodium hydrogen carbonate (50 mg) in water (5 ml) with stirring. After 1 hr most of the acetone was evaporated, water (15 ml) added, and more potassium permanganate (500 mg) introduced in small portions over 36 hr. The solution was made just acid with dilute sulphuric acid, solid sodium bisulphite was added to dissolve the manganese dioxide, and the white precipitate which remained was collected and recrystallized from aqueous methanol to give 1-*benzoyl*-4,5,5-*trimethylpyrrolid*-2-*one* (14 mg, 14%) as colourless leaflets, m.p. 99°. (Found: C, 72·6; H, 7·7. $C_{14}H_{17}NO_2$ requires: C, 72·7; H, 7·4%), λ_{max}(EtOH) 231 (ϵ_{max}9400) and 244 (ϵ_{max}8900) mμ, ν_{max}($CHCl_3$) 1727 and 1679 cm^{-1}. This was identical, (m.p. mixed m.p., and IR spectra) with the compound, m.p. 99°, obtained on hearing 4,5,5-trimethyl-pyrrolidone[21] (75 mg) with benzoyl chloride (125 mg) and triethylamine (0·2 ml) in benzene for 12 hr. (Found: C, 72·5; H, 7·4; N, 6·1. Calc for $C_{14}H_{17}NO_2$: C, 72·7; H, 7·4; N, 6·1%).

The aqueous filtrate from the oxidation was extracted with methylene chloride (5 × 10 ml) to give a gum which crystallized on trituration with ether. The crystals were sublimed at 70°/0·5 mm, and recrystallized twice from ether, and then methanol, to give benzamide (16 mg, 30%), m.p. 128°, undepressed in admixture with authentic benzamide.

Further continuous extraction of the aqueous filtrate with ether gave a neutral (20 mg) and an acidic (107 mg) fraction. The acidic fraction was dissolved in ether–light petroleum (1:1, 10 ml) and chromatographed on a column of silica (10 × 1 cm). The column was eluted with the same solvent pair, the ratio ether:light petroleum being increased to 2:1 during the collection of 10 fractions of 20 ml. Fraction 2 (95 mg) crystallized on evaporation, and had m.p. 118–119°, undepressed in admixture with benzoic acid. Fractions 3–6 (39 mg) were partly crystalline, and, after six recrystallizations from ether–pentane, dimethylmalonic acid (6 mg), m.p. and mixed m.p. with an authentic sample 190–194° (decomp), was obtained and further identified by comparison of IR spectra and by paper chromatography. The mother liquors from the purification of this acid were examined by paper chromatography in the propanol–ammonia (70:30) system, which showed two acidic spots having the same R_f values as dimethylmalonic acid (0·15) and *as*-dimethylsuccinic acid (0·19).

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