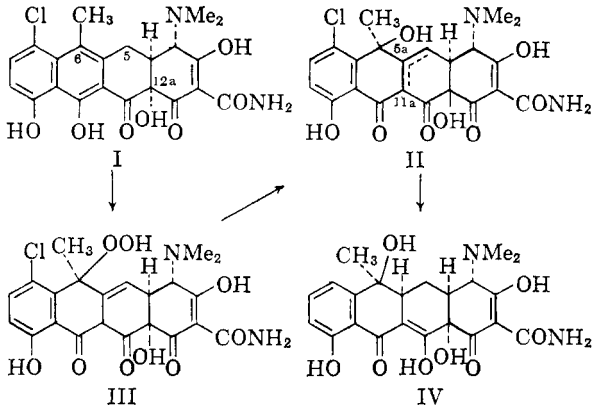
5a(11a)-dehydrotetracycline[3] (II, Δ5a,11a) from a mutant of *Streptomyces aureofaciens* and the demonstration that this metabolite is a precursor of 7-chlorotetracycline.[4] Consideration of structure (II) led us to favor 7-chloroanhydrotetracycline (I) as the biological progenitor of (II)[5]; enzymic oxidation of (I) could produce (II) directly or involve formation of an intermediate 6-hydroperoxide[6] (III).

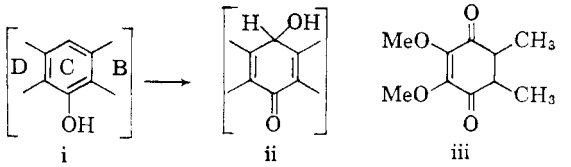


We now have found that this phase of the proposed biosynthesis may be simulated in the laboratory by photo-oxygenation[7] of 7-chloroanhydrotetracycline (I). Thus, after passage of oxygen through a benzene solution (0.25%) of (I) irradiated with light from a fluorescent lamp for 5 days, a yellow crystalline solid (yield, after recycling, 70%) appeared on the walls of the Pyrex vessel. The *major* component of this mixture (crystallized from chloroform) is 7-chloro-6-deoxy-6-hydroperoxy-5,5a-dehydrotetracycline (III) (calcd. for $C_{22}H_{21}N_2ClO_9$: C, 53.64; H, 4.30; N, 5.69. Found: C, 53.38; H, 4.11; N, 5.68) giving a positive ferrous thiocyanate reaction[8] and having light absorption (λ_{max} 249 mμ, ε 24,100; 375–380 mμ, ε 4,500 [in methanolic 0.1 *N* HCl]; γ_{CHCl_3} 3608, 3467, 1707, 1640, 1600 cm.$^{-1}$) virtually identical with that of (II).[9] The stereochemistry of (III) proved to be the "natural" one,[10] for catalytic reduction (1 mole H_2; Pd-C (5%); MeOH) afforded quantitatively the free base of 7-chlorodehydrotetracycline (II), $[\alpha]_D$ + 210° (*c*, 0.4 in $CHCl_3$) identical in every respect (ultraviolet, infrared spectra) with the *S. aureofaciens* metabolite,[11] $[\alpha]_D$ + 212° (*c*, 0.38 in $CHCl_3$). We wish to suggest that the strong carbonyl absorption at 1711 cm.$^{-1}$ in this compound favors the 5,5a- rather than the 5a,11a-location of the double bond. The reduction of (II) to tetracycline (IV) already has been described[3] and completes the partial synthesis. With the impending convergence[12] of the efforts of several laboratories on stereospecific syntheses of diverse anhydrotetracyclines, the present reaction sequence offers a solution[13] to the total stereospecific synthesis of all of the tetracycline antibiotics, as well as providing the impetus for appropriate radiochemical incorporation studies.

(3) J. R. D. McCormick, P. A. Miller, J. A. Growich, N. O. Sjolander and A. P. Doerschuk, *J. Am. Chem. Soc.*, **80**, 5572 (1958).

(4) J. R. D. McCormick, N. O. Sjolander, P. A. Miller, U. Hirsch, N. H. Arnold and A. P. Doerschuk, *ibid.*, **80**, 6460 (1958).

(5) In an alternative hypothesis (ref. 1) the 5a,11a-double bond marks the site of an aldol condensation implying that 6-hydroxylation occurs without involvement of an aromatic ring C. In the case of 6-demethyltetracycline this may seem at first sight preferable to quinol formation from a phenol unsubstituted in the *para*-position (i) → (ii). However, the isolation of the keto-form of a phenol is not without precedent, *e.g.*, gliorosein (iii) (E. B. Vischer, *J. Chem. Soc.*, 815 (1953)).

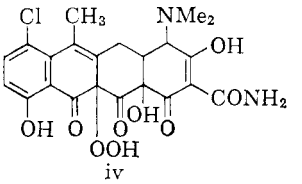


(6) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957), have suggested the possible intervention of a quinol hydroperoxide in homogentisic acid biosynthesis.

(7) See A. G. Davies, "Organic Peroxides," Butterworths, London, 1961.

(8) F. Feigl, "Spots Tests in Organic Analysis," 6th Edn., Elsevier, London, 1960, p. 535.

(9) The intact nature of the *enolizable* (but not fully enolized) 10,11,12-trioxygenated B-C-D-chromophore was revealed by a characteristic bathochromic shift of the long wave length band of the spectrum of (III) to 410 mμ in the presence of Ni^{2+} ion [see L. H. Conover, *Chem. Soc. Special Publications*, 5, 48 (1956)]. This served to eliminate alternatives such as (iv)



iv

(10) The nature of the minor product and of the stereoselectivity of this reaction will be discussed in the publication.

(11) We are indebted to Drs. J. R. D. McCormick and S. Kushner (Lederle Laboratories, Pearl River, N. Y.) for a sample of 7-chlorodehydrotetracycline.

(12) See *e.g.*, H. Muxfeldt, *Chem. Ber.*, **92**, 3122 (1959); A. S. Kende, T. L. Fields, J. H. Boothe and S. Kushner, *J. Am. Chem. Soc.*, **83**, 439 (1961).

(13) Studies of the photo-oxygenation of other anhydrotetracyclines are in progress.

(14) Pfizer Ltd. Predoctoral Fellow, 1960–1962.

CHEMISTRY DEPARTMENT
THE UNIVERSITY
GLASGOW W. 2, SCOTLAND
A. I. SCOTT
C. T. BEDFORD[14]

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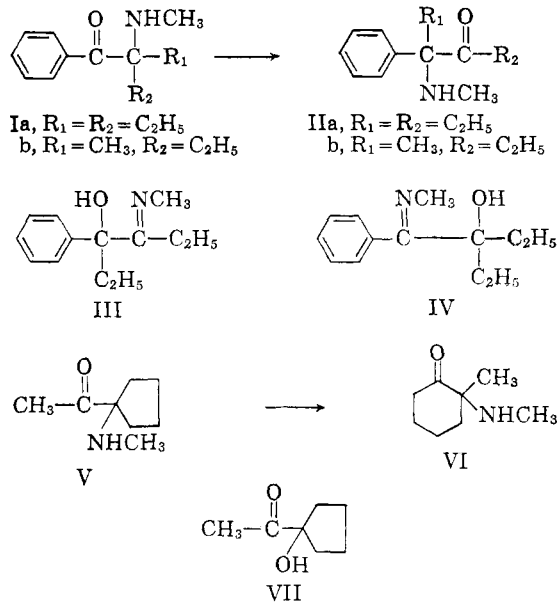
A NEW REARRANGEMENT OF α-AMINOKETONES

Sir:

We wish to report the discovery of a novel skeletal rearrangement of α-aminoketones. An example of this rearrangement is the conversion of 2-ethyl-2-methylaminobutyrophenone (Ia) to 3-methylamino-3-phenyl-4-hexanone (IIa) in 35% yield at 240°. Similarly, Ib could be rearranged to IIb in 32% yield. The scope of the reaction was shown to include aliphatic aminoketones by the 32% conversion of α-methylaminocyclopentyl methyl ketone (V) to 2-methyl-2-methylaminocyclohexanone (VI), which rearrangement involved ring enlargement.

A mechanism for this rearrangement is proposed which involves two carbon skeleton migrations. In the rearrangement of Ia, for example, the iminoalcohol III is considered to be an intermediate resulting from the migration of an ethyl group.



Further rearrangement of III with migration of a phenyl group would result in formation of the product, IIa. The hydroxyimine III or a mixture of the corresponding hydroxyketone and methylamine, when placed under the conditions of the original rearrangement reaction, gave the product in comparable yield. The isomeric iminoalcohol IV was eliminated as an intermediate, since it gave significantly lower yields (7%) of product IIa when subjected to comparable reaction conditions.

In the aliphatic series the isomeric iminoalcohols, although not considered as intermediates in the rearrangement, nevertheless can be used as starting materials for the synthesis of α-aminoketones which would otherwise be difficult to prepare. For example, the α-hydroxyketone VII in the presence of methylamine gave a 22% yield of the α-aminocyclohexanone VI.

The proposed mechanism predicts that an α-tertiary aminoketone would be much more difficult, if not impossible, to rearrange, since the first rearrangement product would involve a zwitter-ion. The validity of this prediction was demonstrated in an attempted rearrangement of the tertiary aminoketone 2-ethyl-2-dimethylaminobutyrophenone at 265°. The absence of unconjugated carbonyl in the infrared spectrum and the recovery of the starting aminoketone in 70% yield indicated that no rearrangement had occurred.

The generality of the rearrangement of hydroxyimines was further demonstrated by the similar conversions of 3-hydroxy-3-phenyl-2-butanone and 1,1-diphenyl-1-hydroxy-2-propanone to 3-methylamino-3-phenyl-2-butanone (39%) and 2-methylamino-2-phenylpropiophenone (36%), respectively.

A mechanism involving direct displacement of the hydroxyl group of 1,1-diphenyl-1-hydroxy-2-propanone by methylamine, followed by rearrangement of the resulting aminoketone, 1,1-diphenyl-1-methylamino-2-propanone *via* its iminoamine was eliminated. This aminoketone was synthesized independently and then subjected to the conditions of the rearrangement. The only isolable product, N-methylbenzhydrylamine, was obtained in 82% yield. Thus, the α-aminoketone could not be an intermediate in the rearrangement.

2-Ethyl-2-methylaminobutyrophenone (Ia) had b.p. 74–6°(0.12 mm.), $n^{25}D$ 1.5227; Ia HCl salt, m.p. 204.5–205°. The structure of Ia was established by sodium borohydride reduction to 1-(1-ethyl-1-methylaminopropyl)-benzyl alcohol (HCl salt, m.p. 259°) with subsequent N-methylation according to the Eschweiler–Clark procedure to give 1-(1-dimethylamino-1-ethylpropyl)-benzyl alcohol (m.p. 81–82°; HCl salt, m.p. 233° dec). The dimethylamino alcohol was synthesized independently.

The rearranged product from Ia, namely, 3-methylamino-3-phenyl-4-hexanone, IIa, had b.p. 60–65°(0.03 mm.), $n^{28.5}D$ 1.5135, d^{25} 0.9972; HCl salt, m.p. 210.5–211°.

The structure of IIa was established by sodium borohydride reduction to 3-methylamino-3-phenyl-4-hexanol (m.p. 120–121°), then periodate cleavage of the amino alcohol and isolation of propiophenone as its 2,4-dinitrophenylhydrazone derivative.

When 2-methyl-2-methylaminobutyrophenone, Ib [b.p. 79°(0.4 mm.), $n^{25}D$ 1.5243], was heated in a sealed tube at 200° for ten hours, 2-methylamino-2-phenyl-3-pentanone, IIb, could be isolated (HCl salt m.p. 192–193°). Sodium borohydride reduction of IIb gave diastereoisomeric 2-methylamino-2-phenyl-3-pentanols (m.p. 115–116° and m.p. 75–76°) which, upon periodate cleavage, gave acetophenone and propionaldehyde, both isolated as their 2,4-dinitrophenylhydrazone derivatives.

The structure of the starting aliphatic aminoketone, α-methylaminocyclopentyl methyl ketone, V [b.p. 49–50°(1.5 mm.), $n^{25}D$ 1.4642; HCl salt, m.p. 118–120°] was established by sodium borohydride reduction to 1-(1-methylaminocyclopentyl)-ethanol (HCl salt, m.p. 113–114°), then periodate cleavage and isolation of cyclopentanone as its 2,4-dinitrophenylhydrazone derivative. The structure of the rearranged product, 2-methyl-2-methylaminocyclohexanone, VI [b.p. 55–57°(2 mm.), $n^{25}D$ 1.4710; HCl salt, m.p. 191–192°] was established by its independent synthesis from 2-bromo-2-methylcyclohexanone and methylamine.

The structure of the product (3-methylamino-3-phenyl-2-butanone; HCl salt, m.p. 213°) obtained from the reaction of 3-hydroxy-3-phenyl-2-butanone with methylamine was established by ultraviolet and infrared spectra.

The structure proof used for the product (2-methylamino-2-phenyl-propiophenone; HCl salt, m.p. 215.5–216°) obtained from the reaction of 1,1-diphenyl-1-hydroxy-2-propanone with methylamine comprised sodium borohydride reduction of the aminoketone to diastereoisomeric 1-(1-methylamino-1-phenyl-ethyl)-benzyl alcohols (m.p. 122° and m.p. 91°) and then periodate cleavage and isolation of acetophenone as its 2,4-dinitrophenylhydrazone derivative.

The structure of 1,1-diphenyl-1-methylamino-2-propanone (HCl salt, m.p. 214–215°) was established by infrared analysis as well as by sodium

borohydride reduction to 1,1-diphenyl-1-methylamino-2-propanol (m.p. 76–76.5°), with periodate cleavage to give benzophenone and acetaldehyde, both isolated as their respective 2,4-dinitrophenylhydrazone derivatives.

All new compounds reported above had acceptable carbon, hydrogen and nitrogen analyses.

CALVIN L. STEVENS
ROBERT D. ELLIOTT
BRADLEY L. WINCH
IRWIN L. KLUNDT
CHEMISTRY DEPARTMENT
WAYNE STATE UNIVERSITY
DETROIT 2, MICHIGAN

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Fe^{57} MÖSSBAUER RESONANCE AND COMPARISON OF BONDING IN $C_8H_8Fe_2(CO)_6$ AND $C_8H_8Fe(CO)_3$

Sir:

Since the initial[1] reported isolation of the compound $(COT)[Fe(CO)_3]_2$ (COT = cycloöctatetraene), a number of speculations regarding the structure of this compound[2] and its relationship to the compound $(COT)Fe(CO)_3$ have been published. As Cotton has pointed out,[3] all of the proposed structures ranging from nearly planar rings to the well-known tub form will give nearly identical nuclear magnetic resonance spectra. Manuel and Stone[2] have examined the infrared spectra of $COT[Fe(CO)_3]_2$ in $CHCl_3$ and CS_2 and have considered both the planar and the tub configuration of the COT ring as possible structures. As pointed out by them (as well as by Cotton[3], but only for the binuclear compound) the definitive data with respect to the structure of these compounds must be sought in X-ray scattering studies.

Such investigations have been carried out by Lipscomb and Dickens both on $(COT)Fe(CO)_3$[4] and $(COT)[Fe(CO)_3]_2$,[5] and the pertinent parameters are summarized in the first three lines of Table I.

TABLE I

COMPARISON OF STRUCTURAL PARAMETERS[4,5] AND RESONANT GAMMA ABSORPTION PARAMETERS FOR $(COT)Fe(CO)_3$ AND $(COT)[Fe(CO)_3]_2$

	$(COT)Fe(CO)_3$	$(COT)(Fe(CO)_3)_2$
$Fe-C_{end}$[a]	2.05	2.06
$Fe-C_{centr}$[a]	2.18	2.15
$Fe-C\equiv$[a]	1.80	1.78
ΔE[b]	1.23	1.32
δE[b]	0.23	0.18
$\Gamma_{1/2}$[b]	0.32	0.33

[a] Values in A. ±0.3. [b] Values in mm. sec.$^{-1}$ ±0.01 at 78°K.

We have used both of these compounds as thin absorbers in a Mössbauer resonance experiment[6,7] using Co^{57} diffused into metallic chromium as a source. The results of these measurements are summarized in the last three lines of Table I, in which ΔE is the quadrupole splitting, δE is the isomer shift[8,9] and $\Gamma_{1/2}$ is the full width at half height of the resonance line. Both compounds show essentially no resonant absorption at room temperature. At liquid nitrogen temperature, on the other hand, the resonance effect of a 0.25 mm. thick absorber is on the order of 15 to 20% and thus easily measurable with considerable precision. The velocity scale was calibrated using a value of 3.95 mm. sec.$^{-1}$ for the ground state splitting of Fe^{57} in soft iron.[10]

The near identity of the two sets of values for ΔE, δE and $\Gamma_{1/2}$ for the two compounds leaves little doubt concerning the close similarity of the environment of the iron atoms in these substances. Clearly the near planarity of the C_4 residue in the mono-iron compound[3,4] is essentially preserved in the bis-iron compound, and a structure such as IV of ref. 3 can be ruled out. While the difference in the Fe–C bond distances reported[4,5] for the two compounds is within the quoted experimental error of ±0.02Å., the larger quadrupole splitting in $(COT)[Fe(CO)_3]_2$, which arises from the interaction between the electric field gradient at the iron nucleus and the nuclear quadrupole moment of the 14.4 Kev. level in Fe^{57}, is consistent with the shorter $Fe-C_{centr.}$ and Fe–C (carbonyl) distance in the hexacarbonyl compound. That the quadrupole splitting observed for these compounds is sensitive to the molecular structure and bonding—in the present case specifically to charge delocalization—is clearly indicated by the fact that the ΔE values reported in Table I are appreciably different from those which we have measured for related compounds, *e.g.*, $(COT)_2Fe(CO)_3$ (1.60 mm. sec.$^{-1}$),[11] and $(COT)[C_2(CN)_4)]\ FeCO_3$ (0.86 mm. sec.$^{-1}$)[11].

Moreover, the near identity of the parameter $\Gamma_{1/2}$ for the two compounds precludes any appreciable difference in the environments of the two iron atoms in $(COT)[Fe(CO)_3]_2$, since such a difference would be observed as line broadening of one of the two peaks of the quadrupole split pair with respect to the other (which is not observed), or with respect to $\Gamma_{1/2}$ for $(COT)Fe(CO)_3$. Although much of the line broadening arises from effects in the source, it is worthwhile noting that $\Gamma_{1/2} = 0.33 \pm 0.01$ mm. sec.$^{-1}$ is essentially identical with the value we have observed[12] for $Fe(CO)_5$ and $(COT)_2Fe(CO)_3$ at 78°K., but substantially smaller than the line width observed for other iron carbonyl compounds[13] which do not contain the (COT) ring, at the same temperature.

Finally, it may be noted that the very small isomer shifts in Table I are consistent with the values

(1) T. A. Manuel and F. G. A. Stone, *Proc. Chem. Soc.*, 60 (1959); M. Rausch and G. N. Schrauzer, *Chem. and Ind.*, 957 (1959); A. Nakamura and N. Hagihara, *Bull. Chem. Soc. Japan*, **32**, 880 (1959); G. N. Schrauzer, *J. Am. Chem. Soc.*, **83**, 2966 (1961).

(2) T. A. Manuel and F. G. A. Stone, *J. Am. Chem. Soc.*, **82**, 366 (1960); D. A. Brown, *J. Inorg. Nuclear Chdm.*, **10**, 39 (1959); **10**, 49 (1959).

(3) F. A. Cotton, *J. Chem. Soc.*, 400 (1960).

(4) B. Dickens and W. N. Lipscomb, *J. Am. Chem. Soc.*, **83**, 4862 (1961).

(5) B. Dickens and W. N. Lipscomb, *ibid.*, **83**, 489 (1961).

(6) R. L. Mössbauer, *Z. Physik*, **151**, 124 (1958).

(7) For a review of this technique, see "The Mössbauer Effect," H. Fraunfelder, W. A. Benjamin Co., New York, N. Y., 1962.

(8) O. C. Kistner and A. W. Sunyar, *Phys. Rev. Letters*, **4**, 412 (1960); S. De Benedetti, G. Lang, and R. Ingalls, *ibid.*, **6**, 60 (1961).

(9) L. R. Walker, G. K. Wertheim and V. Jaccarino, *ibid.*, **6**, 98 (1961).

(10) S. S. Hanna, J. Heberle, C. Littlejohn, G. J. Perlow, R. S. Preston and D. H. Vincent, *Phys. Rev. Letters*, **4**, 28 (1960).

(11) G. K. Wertheim and R. H. Herber (to be published). We are indebted to Dr. G. N. Schrauzer for generous samples of these compounds.

(12) G. K. Wertheim and R. H. Herber, to be published.

(13) R. H. Herber, W. Robinson and G. K. Wertheim, *J. Chem. Phys.*, in press.