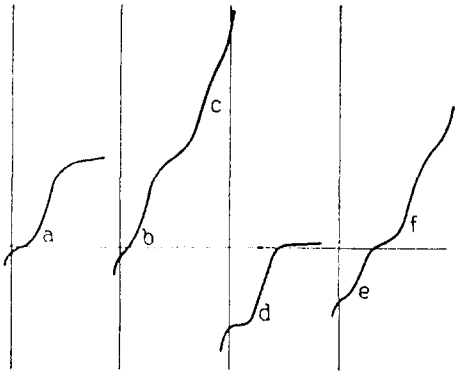

Fig. 1.—(a) $Co\Phi_2^+$; (b), (c), $Co\Phi_2^+ + NO$; (d), $Co\Phi_2$; (e), (f), $Co\Phi_2 + NO$.

havior of $Co\Phi_2^+$ and of $Co\Phi_2$ in the presence of nitric oxide has been followed polarographically.

In phosphate buffer at *p*H 7.5, with histidine concentration 0.1 *F* and at 20°, solutions of $Co\Phi_2^+$ (10^{-3} *F*) free of nitric oxide give (besides the reduction wave $Co\Phi_2 + 2e^- \rightarrow Co^0 + 2\Phi^-$ at $\pi_{1/2} \simeq -1.4$ v. *vs.* S.C.E., which does not interest us here) a polarographic wave at $\pi^{1/2} = -0.21$ v. *vs.* S.C.E. (Fig. 1, a) corresponding to the reduction $Co\Phi_2^+ + e^- \rightarrow Co\Phi_2$. In the presence of nitric oxide, two waves are obtained on the polarogram (Fig. 1b, c), each having practically the same height as the one obtained in the absence of nitric oxide (Fig 1a), the half-wave potentials of which are, respectively, −0.16 and −0.42 v. *vs.* S.C.E. (further indefinite waves, not of interest here, are caused by the second reduction of $Co\Phi_2NO$ by the reduction of nitric oxide and of $Co\Phi_2 \rightarrow Co^0$).

Under the above-mentioned temperature, *p*H and [Φ] conditions, solutions of $Co\Phi_2$ show on the polarograph an oxidation wave with $\pi_{1/2} = -0.20$ v. *vs.* S.C.E. (Fig. 1d). In the presence of nitric oxide, this oxidation wave shifts its half-wave potential to −0.16 v. (Fig. 1e) and a new reduction wave appears with $\pi_{1/2} = -0.40$ v. *vs.* S.C.E. (Fig. 1f), its height being practically equal to that of the oxidation wave of $Co\Phi_2$ (Fig. 1d) in the absence of nitric oxide. The oxidation wave ($\pi_{1/2} = -0.16$ v.) (Fig. 1e) is always smaller, though not quantitatively reproducible, because of uncontrolled oxidation ($Co\Phi_2NO \rightarrow Co\Phi_2^+ + NO^-$) catalyzed by the electrode surface. These results may be explained as follows: the $Co\Phi_2$ oxidation wave and the $Co\Phi_2^+$ reduction wave in the presence of nitric oxide (Fig. 1e, b), both with $\pi_{1/2} \simeq -0.16$ v., are relative to the reaction $Co\Phi_2^+ + NO + e^- \rightleftarrows [Co\Phi_2NO]$. The reduction waves (Fig. 1f, c), obtained from solutions of $Co\Phi_2$ and $Co\Phi_2^+$ in the presence of nitric oxide, are attributed to the reduction $[Co\Phi_2NO] + e^- \rightarrow [Co\Phi_2NO]^-$. In the case of the reduction of $Co\Phi_2^+$ in the presence of nitric oxide, this wave (Fig. 1c) is caused by the reduction of $Co\Phi_2NO$ formed at the electrode surface as a reaction product of nitric oxide contained in the solution, with $Co\Phi_2$ obtained in the first reduction process $Co\Phi_2^+ + e^- \rightarrow Co\Phi_2$. In fact, measurements of the partial pressure of nitic oxide on a solution of $Co\Phi_2^+$, and spectrophotometric measurements on a solution of $Co\Phi_2^+$ in the presence and absence of nitric oxide, exclude interactions between $Co\Phi_2^+$ and nitric oxide.

The reduction of $Co\Phi_2NO$ (Fig. 1c, f) leads to a complex $[Co\Phi_2NO]^-$ (still including nitric oxide inside). This is confirmed by the coulometry of a solution of $Co\Phi_2NO$ made at −0.50 v. *vs.* S.C.E., which eliminated proportionally both waves, the oxidation one (Fig. 1e) and the reduction one (Fig. 1f). With the coulometry carried out at −0.75 v. *vs.* S.C.E., the polarogram finally shows only the $Co\Phi_2$ oxidation wave (Fig. 1d). This means that at the latter potential, a further reduction of nitric oxide within the complex is obtained and $Co\Phi_2$ is produced again.

The results show that $Co\Phi_2$ exhibits with nitric oxide the same "carrier" property that it shows with oxygen.[1]

(1) J. Z. Hearon, D. Burk and A. L. Schade, *J. Natl. Cancer Inst.*, 9, 337 (1949).

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DEGRADATION OF THIOSTREPTON. DERIVATIVES OF 8-HYDROXYQUINOLINE

Sir:

Earlier communications from these laboratories have described the isolation and general properties of the antibiotic thiostrepton[1,2,3] and more recently, the isolation of three thiazole amino acid derivatives.[4,5] The antibiotic also contains an additional chromophoric system, and we now present evidence from parallel pyrolytic and hydrolytic degradations concerning this part of the molecule.

Pyrolysis of thiostrepton at 250–350° and 0.2 mm. pressure yielded, in addition to the diketopiperazine of alanine and isoleucine, two crystalline phenolic bases characterized by deep green ferric chloride reactions. The first, m.p. 90–95°, λ_{max}^{EtOH} 242 mμ (42,500) and 314–316 mμ (3,500) was not obtained completely pure, but its molecular formula $C_{11}H_{11}ON$ was assured by high resolution mass spectrometry (Found: mol. wt., 173.142; calcd. for $C_{11}H_{11}ON$: mol. wt., 173.139).[6] Its identification as a derivative of 8-hydroxyquinoline was suggested by the characteristic ultraviolet spectrum, solubility in hexane, ferric chloride test, formation of an orange chloroform-soluble copper complex, and a close similarity in infrared spectrum with that of 4-methyl-8-hydroxyquinoline. It was identified as 4-ethyl-8-hydroxyquinoline (I) by comparison with an authentic sample, m.p. 92–93°; *Anal.*

(1) J. Vandeputte and J. D. Dutcher, "Antibiotics Annual, 1955–1956," Medical Encyclopedia, Inc., New York, N. Y., p. 560.

(2) J. F. Pagano, M. J. Weinstein, H. A. Stout and R. Donovick, *ibid.*, 1955–1956, p. 554.

(3) B. A. Steinberg, W. P. Jambor and Lyda O. Suydam, *ibid.*, 1955–1956, p. 562.

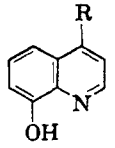
(4) G. W. Kenner, R. C. Sheppard and C. E. Stehr, *Tetrahedron Letters*, 23 (1960).

(5) M. Bodanszky, J. T. Sheehan, J. Fried, N. J. Williams and C. A. Birkhimer, *J. Am. Chem. Soc.*, **82**, 4747 (1960).

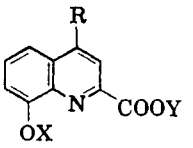
(6) We are grateful to Mr. J. H. Beynon and Mr. A. E. Williams of Dyestuffs Division, Imperial Chemical Industries, Ltd., Blackley, Manchester, England, for this determination.

Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.4; N, 8.09. Found: C, 76.22; H, 6.60; N, 7.89; obtained by reaction between *o*-aminophenol and 1-chloropentanone-3. The second pyrolysis product $C_{11}H_9O_2N$; m.p. 110–113°, λ_{max}^{EtOH} 256 mμ (26,500), 335 mμ (3,500) and 355 mμ (3,000); $\nu_{max}^{CHCl_3}$ 1678 cm.$^{-1}$ (aromatic ketone); *anal.* Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.63; H, 5.13; N, 7.50; formed crystalline dinitrophenylhydrazone and semicarbazone derivatives. Wolff–Kishner reduction of the latter again yielded 4-ethyl-8-hydroxyquinoline (I), and the ketone must therefore be formulated as the corresponding 4-acetyl derivative (II), in agreement with results simultaneously obtained by study of the products of acidic hydrolysis of thiostrepton.

Hydrolysis of thiostrepton with boiling *N* HCl for 24 hours followed by extraction with ether furnished in the ether extract a phenolic acid (III)[7] m.p. 190–200 (dec.), λ_{max}^{EtOH} 265 mμ (32,000); 375 mμ (3,500); ν_{max}^{Nujol} 1730, 1700 cm.$^{-1}$. *Anal.* Calcd. for $C_{12}H_9O_4N$: C, 62.34; H, 3.92; N, 6.06; mol. wt., 231. Found: C, 62.61; H, 4.03; N, 6.10; neut. equiv., 225 (alkali, not titrable with anhydrous $HClO_4$). The ultraviolet spectrum again is similar to those of 8-hydroxyquinoline derivatives, and the infrared spectrum resembles that of a methylated xanthurenic acid.[8] The acid formed a dinitrophenylhydrazone



I, R = CH_3CH_2
II, R = CH_3CO



III, R = CH_3CO, X = Y = H
IV, R = CH_3CO, X = Y = CH_3
V, R = CH_3CO, X = CH_3, Y = H
VI, R = CH_3CH_2, X = Y = H
VII, R = $CH_3CH(OH)$, X = Y = CH_3
VIII, R = $CH_3CH(OH)$, X = Y = H

(m.p. 233° dec.) and gave a positive iodoform test indicating the presence of a CH_3CO- grouping. This was confirmed by the n.m.r. spectrum[9] of its methyl ester methyl ether (IV), which showed a band at 7.45 τ (CH_3CO-) but no bands in the aldehyde region.[10] IV was prepared by methylation of III with diazomethane, m.p. 165–167°; λ_{max}^{alc} 263 mμ (30,000); 366 mμ (2,700). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40; OCH_3, 23.95; mol. wt., 259. Found: C, 65.09; H, 5.43; N, 5.58; OCH_3, 24.16; mol. wt. (Rast), 270. Dinitrophenylhydrazone, m.p. 243° (dec.). Saponification of IV with dilute alkali gave the methyl ether (V), m.p. 128–130°. *Anal.* Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.86; H, 4.68; N, 5.70. The acid III is decarboxylated smoothly at 180°, yielding 4-acetyl-8-hydroxyquinoline (II) identical in all respects with the product obtained by pyrolysis. The above data strongly support the formulation of III as 4-acetyl-8-hydroxyquinaldic acid. Confirmation was obtained by synthesis of the methyl ester methyl ether (IV), as described below.

From the mother liquors of III a second crystalline phenolic acid (VI), m.p. 190–200° (dec.) was obtained. *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.82; H, 4.67; N, 6.47; λ_{max}^{alc} 255 mμ (36,000); 357 mμ (3,400). Compound VI had properties very similar to those of III except that the ketone function was missing (only one carbonyl band at 1740 cm.$^{-1}$). On heating, decarboxylation occurred leading to 4-ethyl-8-hydroxyquinoline (I), and the parent acid therefore was formulated as 4-ethyl-8-hydroxyquinaldic acid (VI), analogous to the acetyl acid (III).

The phenolic acids VI and III (the latter as its dimethyl derivative (IV)) were synthesized: 2-methyl-4-ethyl-8-methoxyquinoline, m.p. 69.5° [*anal.* Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.47; H, 7.42; N, 7.12] prepared by reaction between *o*-anisidine and hex-2-en-4-one, was condensed with 2.5 equivalents of formaldehyde. Oxidation of the crude methylol derivative with potassium permanganate yielded, after esterification with diazomethane and chromatography on silica gel, 4-ethyl-8-methoxyquinaldic acid methyl ester, m.p. 97.5–98° [*anal.* Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.44; H, 6.3; N, 5.8] and also 4-acetyl-8-methoxyquinaldic acid methyl ester [*anal.* Found: C, 64.66; H, 4.91; N, 5.37]. The latter was identical with the product (IV) derived from thiostrepton. The 4-ethyl-8-methoxyquinaldic acid methyl ester was demethylated by potassium iodide in refluxing phosphoric acid and yielded the phenolic acid (VI), m.p. 189–199° (dec.) [*anal.* Found: C, 66.41; H, 5.17; N, 6.17; λ_{max}^{alc} 256 mμ (41,000); 358 mμ (2,600)], the infrared spectrum of which was very similar to but not identical with that of the acid VI derived from thiostrepton.[11]

In a subsequent experiment, thiostrepton was hydrolyzed with a mixture of equal volumes of formic and hydrochloric acids for 24 hours at 105°. After evaporation of the acids the product was extracted into ether and methylated with diazomethane. Crystallization afforded an optically active dimethyl derivative (VII), m.p. 175–177°, $[\alpha]_D^{25}$ −78° (*c*, 1.6 in ethanol), λ_{max}^{alc} 254 mμ (39,000); 347 mμ (3,000). *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.50; H, 6.09; N, 5.58. The infrared spectrum of VII showed only one carbonyl band (1750 cm.$^{-1}$) but in addition a sharp band at 3370 cm.$^{-1}$ indicating the presence of a hydroxyl group. VII was identified as the methyl ether methyl ester of 4-(α-hydroxyethyl)-8-hydroxyquinaldic acid (VIII), by its chromic acid oxidation to IV. Catalytic hydrogenation of IV with the uptake of one mole of hydrogen also yielded racemic VII.

(7) Acid III was mentioned in footnote 15 of ref. 5. Its presumed volatility refers to the decarboxylation product II.

(8) A. Butenandt, U. Schiedt and E. Biekert, *Ann.*, **586**, 229 (1954).

(9) For the n.m.r. spectrum and its interpretation we are indebted to Dr. Harold Conroy of the Mellon Institute. The spectrum also shows that three of the four aromatic hydrogens are vicinal, the fourth is separated from them.

(10) Evidence for substitution in position 4 was obtained by nitric acid oxidation of II, III and V, which yielded, after decarboxylation, a mixture shown by paper chromatography to be composed of nicotinic, isonicotinic and cinchomeronic acids. An identical mixture (infrared and paper chromatography) was obtained by pyrolysis of cinchomeronic acid.

(11) The discrepancies in the two spectra are most likely due to contamination of the acid from thiostrepton by the keto acid III, which is difficult to remove by crystallization.

No positive evidence is yet available to indicate whether the 4-acetyl and 4-ethylquinaldic acids, III and IV, are genuine constituents of the antibiotic, or are formed from VIII during the process of hydrolysis and isolation.

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RECEIVED AUGUST 10, 1961

PARTIAL CHROMATOGRAPHIC RESOLUTION, ROTATORY DISPERSION, AND ABSOLUTE CONFIGURATION OF OCTAHEDRAL COMPLEXES CONTAINING THREE IDENTICAL BIDENTATE LIGANDS

Sir:

We have obtained a partial resolution of the acetylacetonates of chromium(III) and cobalt(III) by chromatography[1] on *d*-quartz or alumina treated with *d*-tartaric acid.[2] The rotatory dispersion shows a strong Cotton effect associated with the spin-allowed transitions near 600 mμ. For both compounds the rotational strength[3] R is negative for the enantiomer less strongly adsorbed on alumina–*d*-tartaric acid. We have attempted to establish the absolute configurations of the acetylacetonates and corresponding oxalates[4] as well by referring them to the known absolute configuration[5] of the ethylenediamine derivative $(+)_D$-$Coen_3^{+3}$ (see Fig. 1)—but first some pedagogy concerning sign conventions.

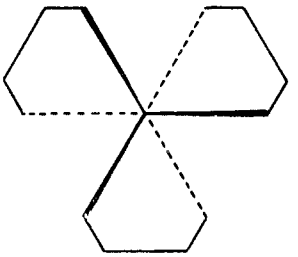

Fig. 1.—The absolute configuration of $(+)_D$-$Coen_3^{+3}$.

It has been customary to label the enantiomers D or L (*d* or *l*) depending on the sign of the rotation at the sodium D-line. This is unsatisfactory in that the letter designation should refer to the geometry of the molecule. If the absolute configuration is not known, then the isomers should be designated either with the sign of the rotation at some wave length, say $(+)_D$ or $(+)_{589\ m\mu}$ as is customary or alternatively with the sign of the net rotational strength associated with some excited state, say $(+)_T$. On the other hand, if the absolute configuration is known, there is a geometrical method of identifying the enantiomers based on accepted conventions which consists in associating with the chelate ring a segment of a helix or screw. In this way the enantiomer depicted in Fig. 1 is associated with a left-handed helix. Therefore, we propose that this enantiomer be designated Λ-$Coen_3^{+3}$ rather than D-$Coen_3^{+3}$. We use the Greek letters Λ and Δ to avoid confusion with the earlier convention.

In a study of the rotatory dispersion of these complexes Moffitt[3] assumed that the rotation is due to an admixture of 4p orbitals with the 3d orbitals involved in the transition under the asymmetric trigonal field in $Y_3^{\pm 3}$. He predicted that the rotation should take its sign from the asymmetric potential. However Sugano[6] has shown that this first-order theory cannot account for the rotational strength on symmetry grounds; Moffitt's error lay in the phase. While the exact mechanism of the rotation remains unknown, we may expect that the sign of the rotation should correlate to the sign of the trigonal field since this is based on symmetry.[7] Our studies of crystal spectra of acetylacetonates[8] and oxalates[9] have afforded values of the trigonal field parameter[10] K. These are recorded in Table I. Notice that for every Cr–Co pair the signs of the trigonal field parameter correlate to the signs of the rotation as expected.

TABLE I

Complex ion or compound	Method of resolution	Sign of R (600 mμ band)	K (cm.$^{-1}$)	Δb
$Cren_3^{+3}$	Less soluble	+	+ 67[b]	$< -2.6°$[f]
$Coen_3^{+3}$	Chlorotartrate[a]	+	+ 45[b]	$-2.6°$[g]
$Cr(C_2O_4)_3^{-3}$	Less soluble	+	+270[c]	$-8°$[h]
$Co(C_2O_4)_3^{-3}$	Strychnine salt[a]	−	−100[c]	$> -8°$[f]
$Cr(O_2C_5H_9)_3$	Less readily adsorbed	−	+600[d]	+3°[i]
$Co(O_2C_5H_9)_3$	On Al_2O_3–$C_4O_6H_6$	−	+600[e]	$> +3°$[f]

[a] See reference 4. [b] Calculated from spectra reported by S. Yamada and R. Tsuchida, *Bull. Chem. Soc. Japan*, **33**, 98 (1960). [c] From reference 9. [d] From reference 8. [e] T. S. Piper, *J. Chem. Phys.*, in press. [f] These values have been inferred from the fact that the radius of Cr(III) is larger than that of Co(III). [g] From reference 5. [h] J. N. van Niekerk and F. R. L. Schoening, *Acta Cryst.*, **5**, 196, 499 (1952). [i] L. M. Shkolnikova and E. A. Shugam, *Kristallografiya*, **5**, 32 (1960).

Of course there is no necessary correlation between the sign of K and the absolute configuration. This is readily understood in terms of the ionic model. An asymmetric potential (point group D_3) may be generated by representing the ligands

(1) These compounds also have been resolved partially on lactose. See T. Moeller and E. Gulyas, *J. Inorg. Nucl. Chem.*, **5**, 245 (1958). Our dispersion curves agree with their rotations measured at single wave lengths.

(2) G. Karagounis, E. Charbonnier and E. Flöss, *J. Chromatog.*, **2**, 84 (1959). These authors provide experimental details and a bibliography of such chromatographic separations.

(3) For a definition of this term and a summary of the theory of optical activity see W. Moffitt, *J. Chem. Phys.*, **25**, 1189 (1956).

(4) For a review of previous work on rotatory dispersion of oxalates and ethylenediamine derivatives see J. P. Mathieu, *J. chim. phys.*, **33**, 78 (1936).

(5) Y. Saito, K. Nakatsu, M. Shiro and H. Kuroya, *Acta cryst.*, **8**, 729 (1955).

(6) S. Sugano, *J. Chem. Phys.*, **33**, 1883 (1960).

(7) In this note we suppress the splittings of the excited states in the trigonal field since they are considerably smaller than the width of the rotational dispersion curves. In some cases the components are known to have opposite signs (see ref. 3). Indeed our dispersion curves for the cobalt acetylacetonate become slightly positive at longer wave lengths, indicating the A_1 component of R is positive while the E component is negative. We will deal with this in a later publication.

(8) R. L. Carlin and T. S. Piper, to be published in *Inorg. Chem.*

(9) T. S. Piper and R. L. Carlin, *J. Chem. Phys.*, in press.

(10) T. S. Piper and R. L. Carlin, *ibid.*, **33**, 1006 (1959).