change in a_0 in going from water to 80% dioxane is approximately half as large as the difference in a_0 between denatured and native "non-helical" proteins, data for two of which are shown in the table for comparison.

That these results are not due to the presence of a small number of ionized carboxyl groups in the purely aqueous solution, with suppression of the ionization as dioxane is added, was demonstrated by repeating some of the experiments in the presence of 0.1 *M* HCl. No significant change was observed. The general trend of the data is also independent of the choice of λ_0, within narrow limits. With λ_0 = 234 mμ, for example, b_0 = 45° and a_0 goes from −138 to +53°.

Data similar to those shown here have been obtained with N-acetyl-L-leucine, N-benzoyl-L-glutamic acid, and N-benzoyl-L-leucine amide, and with a wide variety of solvents. For each substance, the effect of the solvent is to change a_0 and not b_0. In each case the non-polar solvents lie at one extreme and the more polar ones at the other. The results will be reported in full at a later date. The conclusion to be drawn from all the data is that a change in environment of peptide groups of a protein, such as accompanies denaturation, is likely to make a substantial contribution to the over-all change in optical rotation, and that this contribution is likely to appear as a change in a_0 when the data are analyzed by use of equation 1.

(6) The able technical assistance of Mrs. P. M. Hudson is acknowledged.

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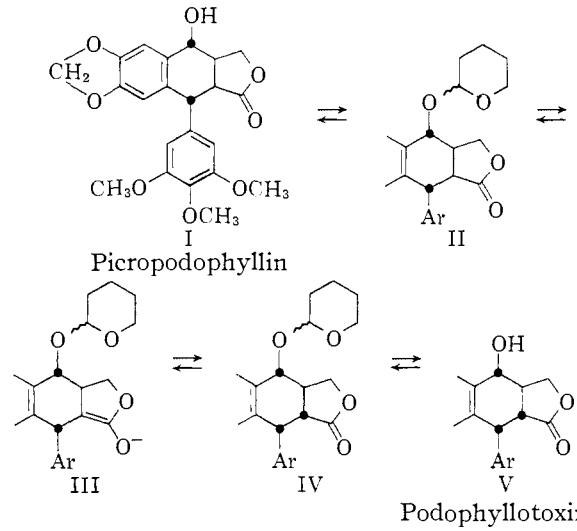
SYNTHESIS OF PODOPHYLLOTOXIN[1]

Sir:

Podophyllotoxin (V), containing a strained lactone system, is easily and essentially completely isomerized with alkaline catalysts to the thermodynamically more stable picropodophyllin (I).[2] We now find that protonation of the enolate[3] of a picropodophyllin derivative makes possible the regeneration of podophyllotoxin (V) from picropodophyllin (I).

Protonation of the enolate of picropodophyllin (as in III) could lead either to podophyllotoxin or to picropodophyllin. Examination of models suggested that the front of the enolate is somewhat more accessible to an approaching proton donor than the back. Conceivably, therefore, frontside protonation, which would give podophyllotoxin, could compete effectively with backside protonation, which would give picropodophyllin.



Test of this possibility required formation of the enolate of picropodophyllin. To avoid complications arising from the presence of hydroxyl hydrogen, picropodophyllin (I) was converted by combination with dihydropyran to O-tetrahydropyranylpicropodophyllin (II). One of the two crystalline diastereoisomers of II[4] was treated at room temperature with just over one molar equivalent of triphenylmethylsodium in ether.[5] Then to neutralize enolate III in the resulting tan mixture, cold acetic acid containing a trace of sulfuric acid was added in one portion. After preliminary fractionation of the protonated material, the tetrahydropyranyl derivative (IV) of podophyllotoxin was treated with hot hydrochloric acid in alcohol to remove the protecting group. Crystallization and chromatography of the product furnished pure podophyllotoxin (V) in 23% yield.[6] Approximately 40% of the protonated product consisted of the tetrahydropyranyl derivative of picropodophyllin (II) mixed with some picropodophyllin. It is expected that proton sources bulkier than acetic acid will increase the ratio of podophyllotoxin to picropodophyllin.

Since picropodophyllin has been synthesized,[7] the work described here completes a total synthesis

(1) This report, describing a portion of the Doctoral research of C. D. Gatsonis, represents paper No. XIII in the series on "Compounds Related to Podophyllotoxin"; the preceding paper is by W. J. Gensler, F. Johnson, and A. D. B. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).

(2) A comprehensive review is given by J. L. Hartwell and A. W. Schrecker, *Fortschr. Chem. Org. Naturstoffe*, **17**, 83 (1958).

(3) The rate controlled protonation of enols has been studied carefully by Zimmerman and his associates. Pertinent references may be found in a paper by H. E. Zimmerman and T. W. Cutshall, *J. Am. Chem. Soc.*, **81**, 4305 (1959). In the present note, we have made no distinction between enol and enolate; the same stereochemical arguments apply to both.

(4) Some of the properties of this form are: m.p. 203–204°; $[\alpha]^{25}D$ +103 (c = 1 in chloroform); ultraviolet absorption maximum as a 10^{-4} *M* solution in alcohol, 291 mμ (log ε 3.51); no infrared absorption for hydroxyl at 3700–3125 cm.$^{-1}$; *Anal.* Calcd. for $C_{27}H_{30}O_9$: C, 65.05; H, 6.07. Found: C, 65.31; H, 6.10. Exploratory work by Dr. S. C. Chakravarti showed that the reaction of podophyllotoxin with dihydropyran and hydrochloric acid catalyst gave the crude tetrahydropyranylpodophyllotoxin in low yield. Later, R. G. McInnes obtained the tetrahydropyranyl derivatives of podophyllotoxin and of picropodophyllin, as mixtures, by using dihydropyran as solvent and a trace of phosphorus oxychloride as catalyst. In the present work, the tetrahydropyranyl derivatives of picropodophyllin were prepared with dihydropyran in chloroform solvent with *p*-toluenesulfonic acid as catalyst.

(5) W. B. Renfrew, Jr., and C. R. Hauser, "*Org. Syntheses*," Collective Volume 2, 607 (1943); C. R. Hauser and B. E. Judson, Jr., *Org. Reactions*, **1**, 286 (1942).

(6) Some of the data are: m.p. 160–161°; the synthetic podophyllotoxin showed m.p. 156–157° when mixed with authentic material (m.p. 156–157°); $[\alpha]^{25}D$ −132° (c = 1 in chloroform); the infrared absorption curves of synthetic and authentic podophyllotoxin are the same; treatment of synthetic podophyllotoxin with piperidine causes isomerization to picropodophyllin.

(7) W. J. Gensler, C. M. Samour, Shih Yi Wang and F. Johnson, *J. Am. Chem. Soc.*, **82**, 1714 (1960).

of podophyllotoxin. The method also indicates the feasibility of synthesizing base-sensitive podophyllotoxin derivatives, of interest in connection with cancer chemotherapy, *via* the stereochemically stable picropodophyllin forms.

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POLY-[DI-μ-DIPHENYLPHOSPHINATO-ACETYLACETONATOCHROMIUM(III)]. A COÖRDINATION POLYMER WITH AN INORGANIC BACKBONE

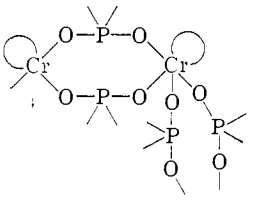
Sir:

Much of the recent activity directed toward the synthesis of coördination polymers has involved the investigation of systems in which metallic ions are catenated by bis-chelating agents.[1-11] Such catenating groups are, *perforce*, organic in nature, with the result that the backbone of the polymer contains organic linkages. At this time we wish to report the preparation of a new kind of coördination polymer with a completely inorganic backbone.

By a substitution–addition polymerization,[12] we have made a series of products with the basic composition $Cr(AcCHAc)(OPPh_2O)_2$. Although we have produced such products by several techniques, the most satisfactory has been the direct reaction between chromium(III) acetylacetonate and diphenylphosphinic acid at temperatures from 175 to 250° under a slow sweep of nitrogen. Heating is continued until acetylacetone can no longer be detected in the exit gas by reaction with ferric ion. The residue then is separated into fractions by extracting successively with ethanol, benzene, and chloroform in a Soxhlet extractor. After these extractions the amount of insoluble residue from the reaction between 10.5 g. of $Cr(AcCHAc)_3$ and 13.1 g. of $Ph_2P(O)OH$ was 2.7 g. at 175°, 5.8 g. at 200°, and 9.4 g. at 250°, a marked increase with increasing temperature. A fraction insoluble in ethanol but soluble in benzene contained 9.4% Cr, 9.3% P, 58.5% C, and 4.9% H; a fraction insoluble in ethanol and benzene but soluble in chloroform 8.6% Cr, 10.8% P, 59.6% C, and 4.8% H; a fraction insoluble in all three 8.6% Cr, 10.3% P, 59.1% C, and 4.9% H. The latter two agree well with 8.88% Cr, 10.58% P, 59.49% C, and 4.65% H, the values calculated for $[Cr(AcCHAc)(OPPh_2O)_2]_n$; the former with the values 9.66% Cr, 9.21% P, 58.46% C, and 4.83% H calculated for $(AcCHAc)[Cr(AcCHAc)(OPPh_2O)_2]_4Cr(AcCHAc)_2$.

Ebullioscopic measurements in benzene have yielded number-average molecular weights of 1940 to 2633 for benzene-soluble fractions and up to 10,870 for chloroform-soluble fractions. The benzene-soluble fraction thus contains on the average four to five chromium-containing units per polymer segment assuming either acetylacetonate or diphenylphosphinate end groups, the chloroform-soluble, about eighteen. We have not been able to determine the molecular weight of the insoluble fractions yet, but, since some of the soluble as well as the insoluble fractions have compositions agreeing with the infinite polymer, the difference between them presumably is one of molecular weight, the less soluble fractions having higher molecular weights. It thus appears that we have succeeded in forming a polymer with degree of polymerization dependent upon reaction conditions, substantially greater amounts of higher molecular weight species forming at higher reaction temperatures.

The structure of these polymers probably involves double diphenylphosphinate bridges[13] between chromium atoms in the backbone, *i.e.*



Strong evidence for such an assumption is afforded by the isolation and characterization of the first member of the series, the dimer $(AcCHAc)_2Cr(OPPh_2O)_2Cr(AcCHAc)_2$. It is readily produced in high yield by the reaction of diphenylphosphinic acid with excess chromium(III) acetylacetonate at 240°, gives proper analysis for the formula given (found 11.0% Cr, 6.5% P, 56.7% C, and 5.2% H; calcd. 11.13% Cr, 6.63% P, 56.54% C, and 5.16% H), and gives an ebulliometric molecular weight of 917 in benzene (calcd. 934.8). Increasing the relative amount of diphenylphosphinic acid results in the continuation of the chain started in the dimer, building up a polymer of $Cr(AcCHAc)(OPPh_2O)_2$ units. An alternate technique we have used for the preparation of the polymer is the reaction of the dimer with diphenylphosphinic acid in 1:2 ratio.

An examination of the structure of the polymer with Stuart–Briegleb models shows that closure of a ring requires several units and is unlikely.

(1) D. N. Chakravarty and W. C. Drinkard, Jr., *J. Indian Chem. Soc.*, **37**, 517 (1960).

(2) W. C. Drinkard, Jr., D. Ross, and J. Wiesner, *J. Org. Chem.*, **26**, 619 (1961).

(3) N. A. Glukhov, M. M. Koton, and Y. V. Mitin, *Vysokomolekulyarnye Soedineniya*, **2**, 791 (1960).

(4) R. N. Hurd, G. DeLaMater, G. C. McElheny, and L. V. Pfeiffer, *J. Am. Chem. Soc.*, **82**, 4454 (1960).

(5) C. N. Kenney, *Chem. & Ind.*, 880 (1960).

(6) R. W. Kluiber and J. W. Lewis, *J. Am. Chem. Soc.*, **82**, 5777 (1960).

(7) V. V. Korshak, *et al.*, *Vysokomolekulyarne Soedineniya*, **2**, 498 and 662 (1960).

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(9) L. E. Mattison, M. S. Phipps, J. Kazan, and L. Alfred, *J. Polymer Sci.*, **54**, 117 (1961).

(10) A. N. Nesmeyanov, M. I. Rybinskaya, and G. L. Slonimskii, *Vysokomolekulyarne Soedineniya*, **2**, 526 (1960).

(11) H. L. Schäfer and O. Kling, *Z. anorg. u. allgem. Chem.*, **309**, 245 (1961).

(12) B. P. Block and G. Barth-Wehrenalp, *J. Inorg. & Nuclear Chem.*, in press.

(13) Similar bridges have been postulated to be present in $UO_2(OP(OBu)_2O)_2$: C. F. Baes, Jr., R. A. Zingaro, and C. F. Coleman, *J. Phys. Chem.*, **62**, 129 (1958).